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On launching a new journal '*Perioperative Precision Medicine*': a rapidly evolving discipline

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Anesthesia is indispensable for most types of surgery and a key factor to ensure the safety and to improve the prognosis of patients. With the rapid development of science and technology and the persistent enhancement of anesthesiology expertise, it is no longer sufficient to put a singular emphasis on anesthesia during surgery. Anesthesiology is now evolving towards perioperative medicine, which involves patient-centered care and value-based multidisciplinary management of surgical patients in the perioperative period.

The majority of fatalities occur during the perioperative period due to major organ injuries and associated complications after surgery. Therefore, the aim of perioperative medicine should focus on minimizing the occurrence of major postoperative adverse effects, promoting high-quality recovery for patients, and reducing mortality, especially for critically ill patients.

The modern medicine has evolved from empirical medicine, evidence-based medicine to precision medicine. Precision medicine aims to prevent or treat disease based on a patient's genetic, living environment and lifestyle. In the perioperative period, personalized medical care would ensure the safety of patient and improve treatment efficacy. Precision medicine has developed with the rapid progress in gene sequencing technology and cross-application of bioinformatics and big data analysis. Recently, great achievements of big data analysis and artificial intelligence technologies, especially in image recognition and diagnosis, are leading perioperative precision medicine to a new era.

In light of this, we have launched *Perioperative Precision Medicine* (PPM), with the aims to deepen the understanding of perioperative medicine in the new era and to advance personalized diagnosis, treatment and prognosis. PPM serves as a platform to share the cutting-edge research findings in the field, and welcomes research studies, reviews, brief communications, perspectives, comments, etc.

This inaugural issue of PPM highlights the advancements made in ultrasound-guided radial artery catheterization and end-tidal carbon dioxide monitoring in non-intubated patients. Additionally, it summarizes the interaction between C-type lectin receptors and Candida albicans and the treatment prospects, and reviews the role and significance of miRNAs as regulators of the host antifungal immune response in fungal infections which are an important part of perioperative infections that contributes to decreased patient survival.

We hope to provide new impetus to the scientific research and clinical practice in perioperative medicine. Also, we invite like-minded researchers, scientists, and clinicians from around the world to join us.

Editor-in-Chief of Perioperative Precision Medicine

Lize Xiong

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Review Article https://doi.org/10.61189/298294zwziab

Advances on ultrasound-guided radial artery catheterization

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Highlights

- Ultrasound-guided radial artery catheterization can effectively improve the success rate of first-time puncture and reduce the total puncture time and the incidence of complications.
- Ultrasound-guided radial artery catheterization methods should be selected based on the specific characteristics of individual patients.

Abstract

A higher success rate in ultrasound-guided radial artery catheterization has been demonstrated by numerous studies when comparing to traditional puncture catheterization, because it significantly shortens the overall puncture time and reduces the incidence of related complications. This review summarizes the methods, influencing factors, related complications and clinical application of ultrasound-guided radial artery catheterization in the perioperative period.

Keywords: Ultrasound-guided radial artery puncture, catheterization, complications, influencing factors, research progress

Introduction

Arterial puncture catheterization is an invasive procedure that involves puncturing and catheterizing the major arteries in the limbs of the human body. It is commonly used in clinical practice to dynamically monitor vital signs, such as blood pressure changes, and perform blood gas analysis to provide guidance for clinical treatment accordingly. The radial artery is often preferred as the first choice for arterial puncture in clinical practice due to its shallow location, obvious pulsation, absence of accompanying veins and rich collateral circulation. Because of less limb exposure, puncture at radial artery usually has lower incidence of post-puncture complications and facilitates better postoperative recovery. However, traditional radial artery puncture catheterization, i.e., palpation guided puncture, mainly relies on the surgeon's experience, with an unstable puncture efficacy. Additionally, owing to the diversity and complexity of clinical patients, such as pediatric patients, shock patients, obese patients, and critically ill patients, puncture failures are often encountered. Ultrasound (US)-guided radial artery puncture and catheterization, as a new type of puncture method, can effectively improve the success rate of first-time puncture and shorten the total puncture time, with a lower incidence of complications [1, 2]. Research has shown that US-guided puncture and catheterization has little effect on the distal blood flow of the puncture site, with minimal damage and faster recovery of the radial artery. Distal radial artery puncture can also reduce radial artery occlusion in the wrist and prevent other complications [3]. Furthermore, US-guided radial artery puncture and catheterization has shown significant advantages in standardizing training for resident doctors [4]. This review comprehensively describes the methods, influencing factors, related complications and clinical applications of US-guided radial artery catheterization.

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Table 1. Comparison of the advantages and disadvantages of common puncture methods

Methods	Advantages	Disadvantages
Short-axis out-of-plane method	i. Clearly determining the relative position of the puncture needle and the vessel lumen ii. Short puncture time iii. Fully displaying the radial artery and adjacent tissues and structures, which is beneficial for adjusting the puncture needle iv. Higher success rate of first puncture	i. Difficult to determine the position of the needle tip ii. Easily penetrating the vessel wall iii. Difficult to operate: lacking guidance after puncturing into the vessel and requiring operator's experience
Long-axis in-plane method	i. Clear visualization of the puncture needle tip position i. Higher success rate of initial puncture compared to out-of-plane in the short axis [10] ii. More precise determination of the relative position of the puncture needle to the vessel	i. Difficulty in establishing the relative position of the puncture needle to the vessel lumen ii. Lengthy puncture times iii. Difficult to manipulate: challengingly maintaining the puncture needle, radial artery, and ultrasound beam in the same plane at all times during the operation
Short-axis out-of-plane combined with Long-axis in-plane method	i. Ensuring the needle tip remaining within the ultrasound visual field at all times ii. Shorter puncture time iii. Significant improvement in the success rate of initial puncture iv. Reduced incidence of complications	i. Time needed to become proficient in operating the ultrasound machine and precisely locating the needle [11]
Dynamic needle tip positioning method	i. Same advantages as the short-axis plane approach ii. Significantly improving the success rate of puncture catheterization iii. Clearly observing the direction of progress of the needle from penetrating the skin to entering the blood vessel iv. Helping operators determine the optimal puncture site i. Timely adjusting and re-puncturing if the initial puncture fails [12]	i. Difficult to operate: requiring the probe to be accurately moved multiple times, and the operator to practice multiple times and have certain experience ii. Repeatedly pushing the puncture needle into the artery after the puncture, which may require more time compared to other ultrasound-guided methods
Developing lines-guided localization method	i. Shortening the surgical time: both the time for puncture point positioning and the puncture time ii. Accurately and quickly locating the puncture site iii. Reducing the difficulty of hand-eye coordination iv. Improving the first puncture success rate and overall puncture success rate	i. A certain level of difficulty in requiring visual confirmation of the midpoint for puncture, and certain experience of the operator

US-guided radial artery puncture methods

Unlike traditional radial artery puncture and catheterization, US-guided radial artery puncture and catheterization initially utilizes the short-axis out-of-plane method and long-axis in-plane method. Based on the methods, many other advanced methods with increasing advantages have emerged, e.g., the short-axis out-of-plane combined with long-axis in-plane method, oblique plane method, dynamic needle tip positioning method and developing lines-guided localization method. The advantages and disadvantages of each method are shown in **Table 1**.

Short-axis out-of-plane method

When performing radial artery puncture and catheterization using the short-axis out-of-plane method, the operator first locates the radial artery by US technology to determine the appropriate puncture site. Once the puncture point is identified, the surgeon holds the US probe in left hand and adjusts it to the center of the cross-sectional image of the radial artery on the screen. Meanwhile, the right hand holds the needle and punctures the skin at an angle of 30-45° at the puncture point. If blood return is observed, the needle tail was pressed down and continued to advance at an angle of 10-15° relative to the skin. After that, the

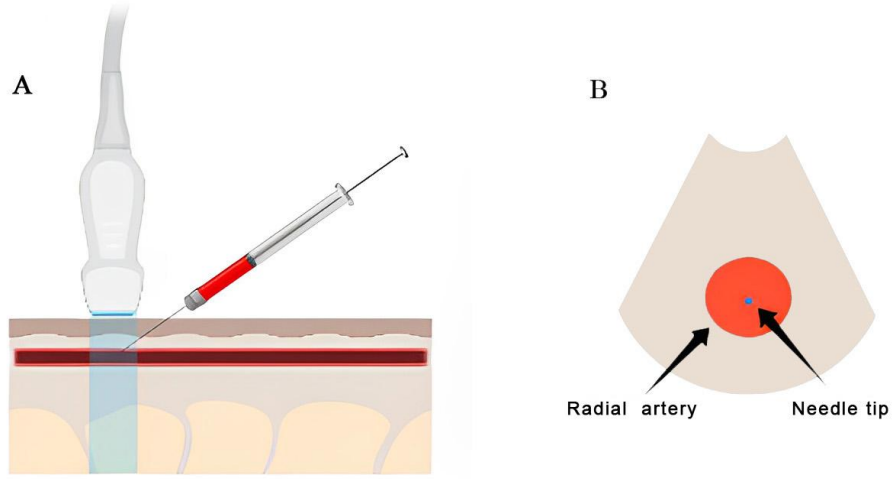

Figure 1. Schematic diagram of the short-axis out-of-plane method. (A) Position of ultrasound probe and puncture needle; (B) Schematic ultrasound image of the radial artery when the short-axis out-of-plane technique is used.

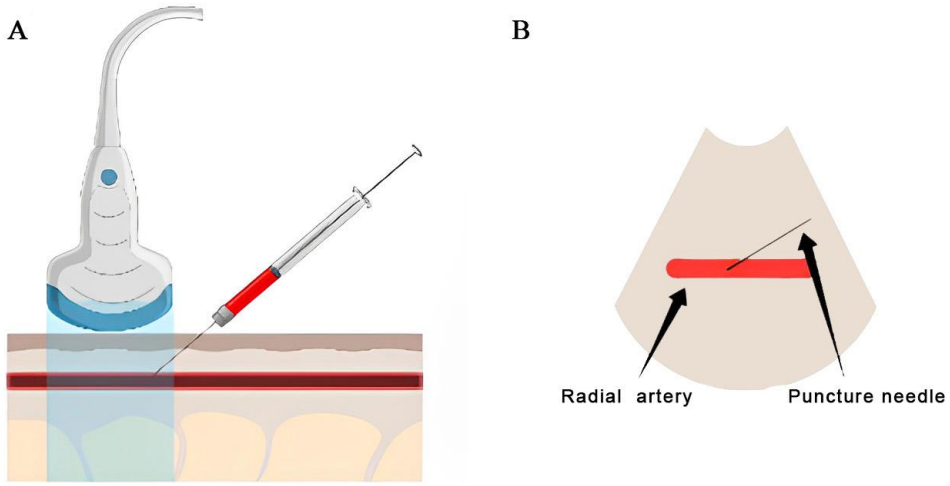

Figure 2. Schematic diagram of the long-axis in-plane method. (A) Position of the ultrasound probe and puncture needle; (B) Schematic ultrasound image of the radial artery using the long-axis in-plane technique.

needle core is slowly withdrawn, and the catheter sheath is inserted into the radial artery. If there is no blood return, the needle tail can be pressed down and continued to advance until blood flow returns to normal. Throughout the process, special attention should be paid to continuously adjusting the probe to keep the needle tip visible during the needle insertion (**Figure 1**).

Long-axis in-plane method

The long-axis in-plane method involves the operator holding the US probe with their left hand and placing it at the puncture point, with the long-axis of the probe parallel to the long-axis of the radial artery to obtain longitudinal imaging of the radial artery. The right hand of the operator holds the puncture needle, which is inserted in from the side of the US probe to make sure the direction of the needle is parallel to the blood vessel. At this point, the puncture needle can be observed on the image. When advancing the puncture needle to the lumen of the radial artery, it is important to observe for any blood return as it is difficult to ensure that the puncture needle is in the same plane as the radial artery. If there is backflow of blood, the operator can continue advancing the needle, and then insert catheter and remove the stylet. If there is no blood return, the short-axis out-of-plane method can be used for repositioning (**Figure 2**).

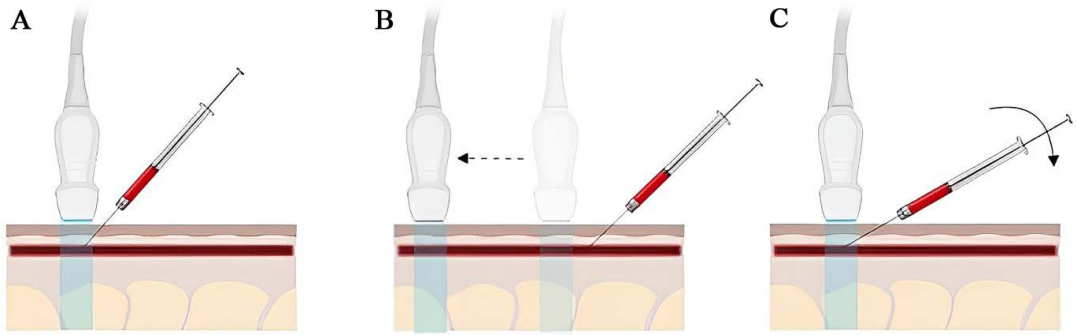

Figure 3. Schematic diagram of radial artery puncture and catheterization using the dynamic needle tip localization method. (A) Needle advancement based on the short-axis out-of-plane puncture method. (B) The ultrasound probe is moved towards the proximal end until the hyperechoic bright spot of needle tip disappears. (C) The puncture needle is further advanced until the hyperechoic bright spot of needle tip reappears on the image.

Short-axis out-of-plane combined with long-axis in-plane method

Short-axis out-of-plane combined with long-axis in-plane puncture method is generally divided into two types: "in-plane first and out-of-plane later" and "out-of-plane first and in-plane later". The first type is usually used as a remedy after the failure of the long-axis in-plane method. The operator uses the long-axis in-plane method at first. If the puncture fails or there is no blood return, the US probe is rotated 90°, and the short-axis out-of-plane method is adopted. This involves adjusting the needle tip above the short-axis of the radial artery and then proceeding with the puncture and catheter placement. The second method is more common. First, the short-axis out-of-plane method is used to measure the diameter of the radial artery and the distance between the skin, and then the long-axis in-plane method is used to determine the direction of the radial artery course to accurately locate the radial artery. Then the operator uses the long-axis in-plane method to puncture and place the catheter. Wang et al. found that compared with traditional palpation, using the short-axis out-of-plane combined with long-axis in-plane method for radial artery puncture and catheterization can achieve higher first-time success rate (91.6%) and overall success rate (97.9%), while shortening the puncture time [5].

Oblique plane method

The oblique plane method can be considered as a special case of the short-axis out-of-plane combined with long-axis in-plane method. When using the oblique plane method for puncture, the operator holds the US probe with the left hand and the puncture needle with the right hand. First, the location of the radial artery should be evaluated using the short-axis out-of-plane method. Then, the US probe is rotated 30-60° based on the evaluation to make the radial artery appearing as an elliptical structure in the image. Puncture is performed when the elliptical area is the largest.

Dynamic needle tip positioning method

To some extent, dynamic needle tip localization is an improved method based on the short-axis out-of-plane method. Under the guidance of short-axis out-of-plane method, the needle tip appears as a hyperechoic bright spot between the skin and the vessel on the image. While keeping the puncture needle immobile, the US probe is moved about 2 mm towards the proximal end until the hyperechoic bright spot of needle tip disappears from image. Then, while ensuring that the probe immobile, the puncture needle is further advanced until the hyperechoic bright spot of the needle tip reappears on the image. The above procedures were repeated until the sheath needle is inserted into the radial artery lumen for over 0.5cm, and the insertion cannula is pulled out. Studies by Kiberenge et al. found that dynamic needle tip localization exhibited a higher first-time success rate than traditional palpation techniques, and shortened the puncture and placement time, regardless of the experience of physicians (**Figure 3**) [6].

Developing lines-guided localization method

The developing lines-guided localization method can also be considered a modified method of the short-axis out-of-plane method. It is now a commonly used to assist in the localization of the radial artery. This method includes two types, single developing line and double developing lines. In the single developing line-guided localization method, a developing line is fixed to the US probe, with the direction of the developing line perpendicular to the long axis of the probe. The probe is then adjusted to align the

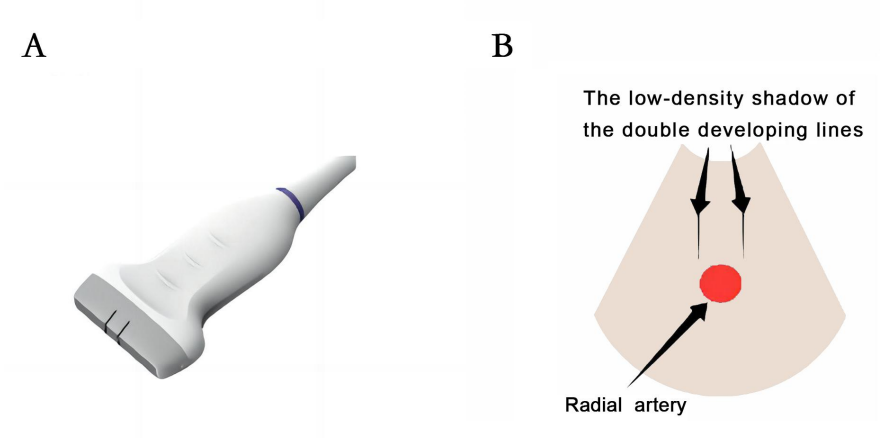

Figure 4. Schematic diagram of radial artery puncture and catheterization using the developing lines-guided localization method. (A) Double developing lines ultrasound probe; (B) Schematic ultrasound image of the radial artery using the developing lines-guided localization technique.

low-density sound shadow with the radial artery on the image, and the intersection point of the developing line and the skin is the puncture point. In the double developing lines-guided localization technique, two developing lines are fixed perpendicular to the long axis of the US probe, and then the probe is adjusted to observe the radial artery between the two low-density sound shadows on the image. The puncture needle is then placed between the two developing lines for puncture and catheterization. It should be noted that during the operation, the long axis of the US probe should always be perpendicular to the developing lines (**Figure 4**).

In addition to the commonly used US methods mentioned above, there are now various emerging methods being utilized in clinical practice, such as modified dynamic needle tip positioning method, modified long-axis in-plane method, and puncture method using a novel electromagnetic guidance US system [7-9].

Related complications

Regardless of whether traditional puncture methods or US-guided methods are used, various complications often occur during radial artery puncture and catheterization, such as hematoma, spasm, infection, embolism, and nerve injury. Understanding these complications is crucial for performing clinical radial artery puncture and ensuring safe and successful outcomes. This article summarizes the clinical manifestations, common causes, treatment, and preventive measures of common complications in US-guided radial artery puncture and catheterization, as shown in **Table 2**.

Compared with traditional puncture methods, US-guided puncture and catheterization have more advantages. Studies have shown that using US to guide radial artery puncture and catheterization can effectively reduce the incidence of complications. Therefore, when encountering patients who are not suitable for traditional radial artery puncture and catheterization, US-guided methods, such as dynamic needle tip positioning technique, should be considered, because it is more suitable for patients with coagulation dysfunction and those who are prone to hematoma [19]. In addition, Hadjivassiliou et al. proposed a guideline for US-guided catheterization of the distal radial artery via the anatomical snuffbox [20]. Their study found that using the anatomical snuffbox radial artery for puncture and catheterization could reduce the risk of radial artery occlusion, minimize the risk of hand ischemia and, prevent injury to adjacent structures. Therefore, in order to reduce the incidence of complications, the anatomical snuffbox radial artery is also an option for puncture and catheterization under US guidance.

Clinical application of US-guided radial artery puncture and catheterization

Radial artery puncture and catheterization, as an invasive operation, can directly and accurately reflect the fluctuation of the patient's blood pressure in real-time. Being more accurate and effective than non-invasive arterial pressure monitoring, it is commonly used in clinical practice for dynamic monitoring of vital signs and for blood gas analysis. Especially for patients with hemodynamic instability such as those with cardiovascular and cerebrovascular diseases, shock, complicated surgeries, and critically ill patients in intensive care units (ICU), accurate and real-time data have great clinical

Table 2. Common complications

Complications	Hematoma	Spasticity	Localized infections	Embolism [18]
Clinical manifestations	-Bruising, pain, swelling of the skin at the puncture site -Local subcutaneous petechiae, ecchymosis, purpura	-Ischemic pain and numbness in the forearm -Difficulty in pushing or rotating the catheter -Radial artery stenosis seen on radial arteriogram	-Redness, swelling and -Pain at the puncture site, -Localized dark skin color and high temperature	-Arm discomfort, pallor, cyanosis -Low hand temperature -Weak radial artery pulsations -Ischemic symptoms rarely present (if these symptoms present, it may be necrotic)
Common causes	-Injury to the radial artery due to more punctures -Low pressure and insufficient time, causing blood to penetrate subcutaneously -Penetration of the radial artery during puncture -Abnormal coagulation of the patient	-Small radial artery diameter -High level of mental stress in the patient -Having one of the following characteristics: female, light weight, hypertension, diabetes, smoking, taking beta-blockers, etc. -Too many long-time operations -Use of non-hydrophilic coated catheters or guidewires -Excessive pressure after bleeding	-Improper handling -Repeated punctures at one puncture site -Patient immunocompromised -Longer hospital stay for the patient	-Smaller radial artery diameter -Longer and stronger post-operative compressions -Female diabetic patient with history of previous transradial coronary intervention procedures, etc. -Repeated punctures -Large diameter of arterial sheath compared to radial artery diameter
Treatment	-Continuous and effective compression to stop bleeding -Cold compresses for a short period of time (<24h) to relieve pain and inflammation, and hot compresses for a longer period of time (>24h) to relieve blood stasis For patients with massive bleeding: -Use of hydrocolloid excipients to accelerate the absorption of oozing blood [13] -Heparin neutralization by intravenous fisetin -Severe cases requiring incision and drainage	-Suspend the puncture, sedate the patient and provide pain relief, apply local heat -Removing the sheath under local anesthesia -Injecting vasodilators such as nitroglycerin or verapamil -May perform a contralateral radial artery or ipsilateral femoral artery puncture if the spasm is severe and prolonged -Using for radial artery spasm [15] -Sheathless technique to relieve spasticity [16]	-Examination of wounds by methods such as wound swab culture -Proper wound management -Blood sampling for bacterial culture testing to select appropriate antibiotics	-Treatment with low molecular heparin drugs -Thrombolytic therapy with drugs such as urokinase -Transient compression of the ulnar artery -Thrombus retrieval by intervention
Preventive measures	-Carefully puncturing, stopping immediately when resistance is encountered and observed -Securing with adhesive tape and using a special hemostat after puncture if necessary [14] -Advising the patient to be less active with a light diet -Continuously and effectively compressing to stop bleeding -Enhancing post-operative observation care	-Advanced communication to keep patient informed and sedated -Pre-operative adequate anesthesia at the puncture site and local injection of 200μg of nitroglycerin to dilate the radial artery -Intraoperative intravenous injection of midazolam and fentanyl [17] -Use of a small hydrophilic coated catheter and a long ultra-smooth guidewire -Gentle intraoperative movements; if puncture fails, waiting for spasm to resolve before re-puncturing -Post-operative prophylaxis with cocktail[1] therapy	-Strict aseptic procedures before surgery -Advising the patient to pay attention to temperature changes after surgery and to consult their doctor immediately if they develop fever and chills -Immune enhancement by improving the diet after surgery	-Pre-operative Allen test -Use of smaller sized sheaths and catheters -Prompt postoperative sheath removal and reasonable control of duration of compression -Anticoagulation with higher doses of heparin -Pre-operative evaluation of radial artery patency and radial artery flow by oximetry-plethysmography test or ultrasound Doppler assessment

[1]Cocktail: commonly used medications and 200μg nitroglycerin, 2.5-5.0mg verapamil, 50U/kg or 5000U heparin. FMD, flow-mediated vasodilation.

guiding significance.

Although US-guided radial artery puncture has become increasingly popular along with the development of visualization technology, many hospitals are not equipped to use US guidance for every puncture operation due to the high cost of US equipment. Therefore, traditional blind puncture method is still the most common puncture method in clinical practice. However, due to its high dependence on operator's experience as well as the complicity of patient conditions and variations of individual in radial artery anatomy, the failure rate of traditional radial artery puncture is relatively high. For operators who cannot routinely use US, US-guided puncture can usually be used as a salvage method after traditional puncture and catheterization have failed. Liu et al. found in their research that after a failed traditional puncture, US guidance could be used as a salvage measure to reduce puncture time and the incidence of complications [21]. Dong et al. found that for patients in need of secondary radial artery puncture and catheterization, US guidance could increase the success rate and reduce the incidence of complications [22].

However, arterial puncture and catheterization operations are somewhat difficult. In clinical work, inexperienced surgeons usually consider catheterization to be more difficult than puncture. Even experienced physicians often encounter challenges such as observing obvious blood return from the puncture needle but facing difficulty in catheter insertion. Since the diameter of the puncture needle is smaller than the diameter of the sheath, which is thinner than the radial artery, the puncture needle may not locate at the center of the artery despite successful puncture and blood return observed. Therefore, although there is blood backflow, difficulties may arise in catheterization. US guidance has the advantage of being intuitive, displaying the images in real-time, which can help the operator clearly observe the structures around the radial artery and instantaneously track the needle tip during the puncture process. These can effectively improve the success rate of puncture. Therefore, it is suitable for widespread use in medical education.

Several studies on US-guided radial artery puncture and catheterization in intern training have shown that the US-guided method helps interns to quickly and accurately acquire the puncture techniques. Chen et al. found that dynamic needle tip positioning method can improve the success rate of puncture and catheterization in interns compared with the traditional blind probing method [23]. Dong et al. randomly divided 116 residents into a new US-guided teaching group (double developing lines-guided localization method) and a traditional US-guided teaching group (short-axis out-of-plane method), and found that radial artery puncture and catheterization under the sound shadow-assisted US guidance significantly improved the first-time success rate (78.43% vs. 58.00%, odds ratio=0.380; 95% CI=0.159 - 0.908; P=0.027), shortened the catheterization time (14.36±3.31 vs. 18.02±4.95, p<0.001), and facilitated standardized teaching for residents [24].

For beginners, it is recommended to start with the simpler one, short-axis out-of-plane method, followed by the long-axis in-plane method and short-axis out-of-plane combined with long-axis in-plane method. By combining basic exercises with training, beginners can solidify their proficiency in this skill. With the development of visual technology, US-guided radial artery puncture teaching can not only improve the efficiency of learning for beginners, but also effectively increase the success rate of the operation compared to traditional teaching methods. Additionally, simulation training with some auxiliary devices can be used during training. Studies have shown that using vascular models for simulation training can effectively improve the first-time success rate of US-guided radial artery catheterization in actual patients, and help beginners to better acquire the dynamic needle tip positioning method [25].

Application of US-guided radial artery puncture in special patient groups

Studies have shown that for some special patient groups, such as those with septic shock, US-guided radial artery puncture can improve the success rate of puncture, shorten the duration of the procedure, and reduce the incidence of complications compared to traditional puncture methods [26]. In addition, US guidance should be considered with priority for infants, obese patients, elderly patients, patients with weak pulses, severe hypotension, or abnormal coagulation function, and critically ill patients that require special attention during radial artery puncture.

Infants

The radial artery of infants is narrow and straight with weak pulsations and is easily displaced during puncture. Additionally, the small

size of the radial artery poses a challenge in visualizing the hyperechoic spot of the needle tip on US images, especially when it is near the radial artery, making it difficult to control the position of the needle tip in real-time during puncture [27]. Furthermore, infants in the perioperative period often have organ deformities and other issues, which significantly increases the difficulty of puncture. However, ordinary US-guided puncture techniques can hardly address these difficulties effectively, so modified US-guided puncture techniques are commonly used in clinical practice.

Quan et al. randomly divided infant patients into two groups, a new US group (double developing lines-guided localization method) and a traditional US group (short-axis out-of-plane method), and found that the first attempt success rate of intubation in the new US group (90%) was significantly higher than that in the traditional US group (60%) [28]. Wang et al. randomized 72 infants aged 1-12 months into a long-axis in-plane combined with short-axis out-of-plane (LAX-IP-SAX-OOP) group and a modified dynamic needle tip positioning (MDNTP) group, and found that the first attempt success rate of intubation in the LAX-IP-SAX-OOP group was significantly higher than that in the MDNTP group (75.0% vs. 36.1%), and the intubation time was significantly shorter in the LAX-IP-SAX-OOP group [29]. Yang et al. found that by adding a scale to the US screen and probe, the correlation to the radial artery positions displayed by both could provide accurate arterial localization and guidance for the operator, thereby helping them locate the needle tip faster and improving the success rate of infant puncture [30]. In addition, there is a new method of single-operator laser-assisted US-guided puncture, which can improve the first attempt success rate of radial artery insertion in children under 2 years old and make the US probe more stable [31].

Here are some tips for radial artery puncture in infants, including: i) for pediatric radial artery puncture, the success rate is the highest when the depth of the radial artery is about 2-4mm [32]; ii) puncture can cause some degree of pain, which is a significant issue to be addressed for infant puncture. It is necessary to use child-friendly language to keep their emotions stable before puncture, and appropriate needles can also alleviate the pain of infants; iii) studies have shown that a puncture angle of 30-45° can increase the first-attempt success rate of radial artery puncture and reduce the incidence of related complications; the needle insertion angle increases with the body weight of the infant and the diameter of the radial artery [33]; iv) puncture can be combined with the subcutaneous injection of 2ml of 0.9% NaCl to deepen the depth of the radial artery and thereby increase the success rate of puncture [34].

Considering the characteristics of infant radial artery and the advantages and disadvantages of conventional US methods (short-axis and long-axis), we found that the short-axis method is more suitable for infants. This is because the infants have thinner blood vessels and the proximity of the target blood vessels to the surrounding anatomical structures. The thinner blood vessels of infants make it difficult to obtain images using the long-axis method.

Elderly patients

Elderly patients often have underlying diseases and hemodynamic instability, so continuous arterial blood pressure monitoring is often required in clinical practice. However, due to weak radial artery pulsation, arterial wall sclerosis, poor elasticity, and loose subcutaneous tissue, the puncture is easy to fail, which may directly lead to the occurrence of complications such as hematoma. Therefore, US-guided puncture is often used in clinic. In addition, due to the frequent occurrence of cognitive dysfunction in elderly patients after surgery, the clinical compliance is also compromised. Therefore, faster and more convenient puncture methods, such as oblique plane puncture and developing lines-guided localization technique, are more suitable.

Chen et al. compared the oblique plane puncture method, short-axis out-of-plane and long-axis in-plane in elderly patients and found that the oblique plane puncture method not only shortened the puncture time but also increased the success rate of puncture [35]. Ye et al. found that double developing lines-guided localization technique shortened the time of positioning and puncture, and improved the success rate of initial puncture in elderly patients [36]. Shim et al. randomized elderly patients into a dynamic needle tip positioning group (group D) and a short-axis out-of-plane group (group C), and their results showed that the first attempt success rate in group D (89%) was significantly higher than that in group C (72%), and the incidence of hematoma in group D (16%) was significantly lower than that in group C (47%) [37]. For elderly patients over 70 years old, the use of dynamic needle tip positioning method can improve the success rate of

initial radial artery catheterization and reduce the incidence of complications.

In addition, it should also be noted that due to the loose subcutaneous tissue in elderly patients, the position of the catheter may be affected during needle withdrawal. Operators should withdraw the needle gently and slowly, and also maintain constant vigilance on the position of the catheter [38].

Obese patients

With the increasing living standard, the number of obese patients is gradually increasing. For obese patients, the large accumulation of subcutaneous fat makes it difficult to palpate arterial pulsations, thus bringing great challenges in traditional blind probing procedures. In addition, repeated punctures can cause discomfort to patients and may lead to various complications.

Zou et al. randomly divided 240 obese patients into a control group, a single developing line-guided localization technique group, and a double developing lines-guided localization technique group, and compared the first attempt success rate, operation time and incidence of complications among the three groups [39]. They found that both single and double developing lines-guided localization techniques improved the first attempt success rate of radial artery catheterization under US guidance in obese patients (control group vs. single developing line vs. double developing lines = 71% vs. 90% vs. 91%), while reducing the incidence of complications (control group vs. single developing line vs. double developing lines = 29% vs. 10% vs. 9%).

One of the difficulties in performing radial artery puncture on obese patients is to maintain the extension of the wrist joint. A study reported improved the success rate of radial artery puncture and catheterization in obese patients and alleviated pain with the clinical use of inflatable radial artery puncture fixation device [40].

Factors affecting the success rate of radial artery puncture

"Hit the nail on the head" during radial artery puncture is a widely accepted approach among anesthesiologists, because it can reduce the incidence of radial artery spasm, alleviate patient pain and shorten operation time. Therefore, to achieve a successful radial artery puncture with "one-shot", it is necessary to understand the factors that affect the puncture success rate, and then to achieve better radial artery catheterization placement with US guidance.

Radial artery anatomy

The diameter, vertical depth, associated variation of artery and whether the vessel is filled are main factors that directly affect the success rate of puncture.

Filled vessels are easier to palpate and visualize. Lee et al. found that the average diameter of the radial artery was 2.2 ± 0.4 mm, and the larger the diameter of the radial artery, the higher the success rate of puncture, and vice versa [41]. Besides, appropriate radial artery depth is also a guarantee of successful puncture. When the radial artery is located deep within the tissue, puncturing it at a small angle would require a longer needle path. To shorten the needle path and improve the chances of success, a larger angle of entry may be attempted. However, a larger angle reduces the contact area between the puncture needle and the blood vessel, making the procedure more challenging. Nakayama et al. found that when the depth of the radial artery was 2-4 mm during radial artery puncture and catheterization in children, the puncture time was reduced and the success rate was improved, and for radial arteries with a depth of less than 2 mm, saline can be subcutaneously injected to increase the depth to 2-4 mm [32]. Nie et al. reported a 20.3% anatomical variation rate of radial artery in Chinese people [42]. This is the primary reason for the failure of puncture.

Operator experience

From the perspective of the operator, their long-term experience and solid skills play a crucial role in the success of the operation.Relevant studies have shown that anesthesiologists with more experience in radial artery puncture and catheterization have a higher success rate than those with less experience [43]. In particular, experienced doctors often use the advantages of US-guided radial artery puncture to improve the success rate [7]. Wang et al. compared the total success rate of US-guided radial artery puncture and catheterization among three anesthesiologists with different clinical training durations, and found that anesthesiologists with longer training time showed an obvious better performance during US-guided radial artery puncture and catheterization [5].

Both the operator's technical level and famil-

Table 3. Radial artery diameter

Classification	Crowd	Mean diameter of the radial artery
Ethnicity	Chinese	2.38±0.56mm
	Japanese	2.4±0.4mm
	Korean	2.60±0.4mm
Age	Adults	2.2±0.4 mm
	Pediatric	1.2±0.3mm [48]
Sex [49]	Men	2.69±0.40mm
	Women	2.43±0.38mm

iarity with the US equipment affect the success rate of puncture and the incidence of complications. Before operation, operators need to perform the Allen test on the patient, and during the operation, the puncture should be performed accurately and in a sterile environment. In addition, patients, especially for pediatric patients, may experience pain and discomfort during radial artery puncture, which can easily lead to puncture failure. Therefore, how to better manage pain in patients is a factor affecting the success of radial artery puncture. Before the operation, operators should fully communicate with the patients. During the puncture, lidocaine can be applied to the puncture site to reduce vascular constriction caused by pain. Zeng et al. found that using a compound lidocaine cream on ICU patients could alleviate the pain of radial artery puncture [44]. In addition, multiple training sessions are helpful in improving the operator's ability. Research has shown that the more a physician knows about the puncture site and technique, the less time and number of attempts they need for puncture [45].

Patient factors

Considering factors related to the patient, sex, age, race, and physical condition are all relevant factors affecting the success rate of puncture.

A study has shown that the radial artery diameter is larger in males than in females, and the thinner vessels in females make puncture more difficult [46]. However, for female patients, the radial artery diameter can be enlarged by subcutaneously injecting 50 ug nitroglycerin in combination with 10 mg lidocaine [47]. As shown in **Table 3**, there are various factors that can lead to differences in radial artery diameter reported by existing studies.

From the data in the table, it can be seen that age also has a certain impact on radial artery puncture. Pediatric patients are more prone to puncture failure and a variety of complications due to their smaller radial artery diameter. Puncture in elderly patients are another challenge due to their fragile and less elastic blood vessels. In addition, patients with pathological obesity tend to have thick subcutaneous fat and tissue dispersal, which can also affect the radial artery puncture and catheterization outcome.

Puncture techniques

As an invasive operation technique, radial artery puncture involves many operative techniques in practical applications, which can help increase the success rate of radial artery puncture. The operative techniques lie in the angle of needle insertion, the angle of the wrist, the position of puncture, and the selection of puncture needle and probing device.

Studies have shown that comparing with the approach of the US probe perpendicular to the radial artery, the approach of the US probe perpendicular to the puncture needle can significantly reduce the first radial artery catheterization time and total puncture time [50]. Zhang et al. found that compared with a 90° needle insertion angle, a 30-45° needle insertion angle increases the contact area between the puncture needle and blood vessel, improves the success rate of the first puncture, and reduced the incidence of hematoma [33]. Existing publications indicate that when performing radial artery puncture in adult patients, inserting the catheter at a wrist angle of 45° can significantly shorten the catheterization time and increase the first success rate [51, 52]. The superficial and most pronounced pulsation is 2-3 cm proximal to the transverse wrist, which is usually the site chosen for the puncture. Study has reported that the distal quarter of the forearm can be considered as the "best insertion site" for radial artery catheterization under US guidance [53]. High-frequency probes, with greater image resolution, can clearly distinguish adjacent nerve and small arterial branches and are suitable for patients with shallow vascular lumina, such as infants and young children. Low-frequency probes, however, are mainly suitable for patients with deeper target vessels, such as obese patients. Saima et al. measured a "safe" segment (the length between the styloid process and the distal edge of the "parallel" segment) using an US device. It was found to be approximately 6.8-11.6 cm in males, with an average of about 9.4 cm, and 5.4-11.0 cm in females, with an average of about 8.2 cm [54].

Conclusion

Due to its advantage of visualization, US is currently a hot topic in clinical practice. The use of US-guided radial artery puncture and catheterization has resolved many disadvantages of traditional blind probing methods, reduced the operator's stress, and improved the success rate of puncture and catheterization. However, due to the high cost of US equipment and the high level of technical difficulty, this method poses new requirements for operators to use US technology.

It can also be observed that many of the newly developed US methods are modifications of basic methods, which laid a foundation for innovations and improvements of better puncture methods. However, US is still in a two-dimensional space, so there are unavoidable limitations. It is conceivable that three-dimensional visualization technology, if applied to the preoperative evaluation or guidance of radial artery puncture and catheterization, may further improve the success rate of puncture.

In addition, most of the reports on physician training of US-guided arterial puncture only focus on the application effects of a certain US method. There is limited comprehensive analysis available to determine which US method is more suitable for beginners to master. Based on theoretical analysis, we proposed that comparing with traditional methods, US-guided radial artery catheterization may help beginners master radial artery puncture more effectively, but the specific utility still needs to be verified by further research.

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Progress of end-tidal carbon dioxide monitoring in non-intubated patients

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Highlights

- This review focuses on literature regarding end-tidal carbon dioxide monitoring for non-intubated patients.
- Partial pressure of carbon dioxide monitoring can benefit non-intubated patients.
- As carbon dioxide detection technology continues to improve, end-tidal carbon dioxide monitoring is expected to be used in more medical scenarios.

Abstract

End-tidal carbon dioxide ($ETCO_2$) monitoring is an important tool for assessing respiratory and circulatory status of patients. It has become an integral component of perioperative anesthesia care in patients undergoing general anesthesia with endotracheal intubation. $ETCO_2$ monitoring can also benefit non-intubated patients. This review covers the basics of $ETCO_2$ and methods of partial pressure of $ETCO_2$ ($P_{ET}CO_2$) monitoring and focuses on the literature regarding $P_{ET}CO_2$ monitoring for non-intubated patients. Most studies explored the superiority of $P_{ET}CO_2$ monitoring in patients under sedation outside operating room, while others investigated the potential advantages of $P_{ET}CO_2$ monitoring in other scenarios such as post-anesthesia care unit, cardiopulmonary resuscitation, and patient-controlled analgesia. As carbon dioxide detection technology and sampling circuits continue to improve, $P_{ET}CO_2$ monitoring is expected to be used in more medical scenarios.

Keywords: End-tidal carbon dioxide, monitoring, non-intubated patients, airway management, anesthesia

Introduction

End-tidal carbon dioxide ($ETCO_2$) monitoring measures the partial pressure of $ETCO_2$ ($P_{ET}CO_2$) or concentration of $ETCO_2$ ($C_{ET}CO_2$) at the end of an exhaled breath. $ETCO_2$ monitoring often relies on capnography, which measures carbon dioxide concentrations over time. Due to its simplicity, non-invasiveness, continuous monitoring capability, and strong timeliness, $ETCO_2$ monitoring has been widely used for evaluating patients' respiratory and circulatory conditions in clinical practice [1]. In clinical anesthesia, $ETCO_2$ monitoring can indicate the respiratory and circulatory conditions of patients, and can help detect respiratory failure, pulmonary embolism, and other conditions during surgery [2, 3]. With the progress of technology and social advancements, the application of $ETCO_2$ monitoring has expanded to non-intubated patients, such as those in endoscopy rooms, catheterization labs, intensive care units (ICU), post-anesthesia care units (PACU), and emergency departments, with $P_{ET}CO_2$ monitoring being the most common [4]. This article primarily reviews the clinical applications of $ETCO_2$ monitoring in non-intubated patients.

$P_{ET}CO_2$ monitoring

Pathophysiology of $P_{ET}CO_2$

Carbon dioxide (CO_2) is present in the blood, with one-third being carried by red blood cells and the remaining two-thirds in plasma. CO_2 produced in the tissues diffuses into the blood

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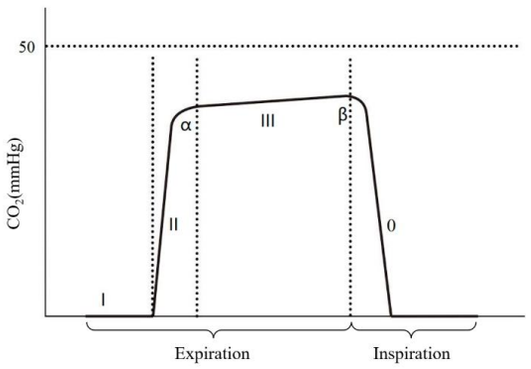

Figure 1. Time capnogram displays segments, phases and angles. Inspiratory segment is phase 0, and expiratory segment is divided into three phases: I, II, and III. Maximum value of CO_2 at the end of the breath is designated as $P_{ET}CO_2$. The angle between phase II and phase III is angle α, and between phase III and inspiratory downstroke is angle β. $P_{ET}CO_2$, partial pressure of end-tidal carbon dioxide.

through tissue cells, is carried by red blood cells through the bloodstream to the lungs, and undergoes diffusion in the pulmonary capillaries to be exhaled from the body via the alveolar air. Therefore, $P_{ET}CO_2$ is typically measured at the peak of the respiratory cycle and is affected by three factors, namely CO_2 production, lung gas exchange, and alveolar ventilation.

In healthy adults, $P_{ET}CO_2$ ranges between 35 and 45 mmHg, and arterial to endtidal partial pressure CO_2 ($P_{(a\text{-}ET)}CO_2$) is between 2 and 5 mmHg due to matching of alveolar ventilation and perfusion [5]. For patients without apparent cardio-pulmonary dysfunction, $P_{ET}CO_2$ values can be used to estimate $PaCO_2$. When the ratio of ventilation to perfusion ($\dot{V}_A/\dot{Q}$) is imbalanced, $P_{(a\text{-}ET)}CO_2$ increases [6]. At this point, arterial blood gas analysis is necessary to obtain a more accurate $PaCO_2$ value. A stable $P_{(a\text{-}ET)}CO_2$ usually indicates relative stability of alveolar ventilation and perfusion, while an increased $P_{(a\text{-}ET)}CO_2$ gradient may hold clinical value in the diagnosis of pulmonary embolism [7].

$P_{ET}CO_2$ values increase in conditions characterized by high CO_2 production and transportation to the lungs, such as high metabolic crises, malignant hyperthermia, thyrotoxic crisis, sodium bicarbonate infusion, venous CO_2 embolism, and increased cardiac output. On the other hand, $P_{ET}CO_2$ values decrease in conditions characterized by low CO_2 production and transportation to the lungs, such as in hypothermia, inadequate pulmonary perfusion, cardiac arrest, pulmonary embolism, and hypotension. When there is inadequate alveolar ventilation, such as in chronic obstructive pulmonary disease or partial airway obstruction, $\dot{V}_A/\dot{Q}$ decreases, and $PaCO_2$ increases, leading to a corresponding increase in $P_{ET}CO_2$. Conversely, when there is excessive ventilation, $\dot{V}_A/\dot{Q}$ increases, and $PaCO_2$ decreases, leading to a corresponding decrease in $P_{ET}CO_2$.

Waveforms of $P_{ET}CO_2$

The time capnogram of $P_{ET}CO_2$ can be divided into two phases: the inspiratory phase (phase 0) and the expiratory phase [8, 9]. The $P_{ET}CO_2$ waveform during the expiratory phase can be further divided into three phases: phase I corresponds to dead space gas; phase II corresponds to alveolar gas elimination, where the PCO_2 rises rapidly to a plateau; phase III corresponds to the plateau period (**Figure 1**). Typically, the CO_2 concentration during phase III shows a slight upward slope over time, as the latest emptied or smallest alveoli contain relatively more CO_2, resulting in a higher PCO_2 level. Therefore, the height and slope of the alveolar plateau can provide information about ventilation and perfusion. The maximum PCO_2 obtained during phase III is known as $P_{ET}CO_2$. When there is a significant change in airway caliber, such as under asthma or chronic obstructive pulmonary disease (COPD), the rising of phase III becomes steeper, and the α angle between phases II and III increases. At the end of phase III, the inspiration begins, and the $P_{ET}CO_2$ drops rapidly to 0. The angle between phase III and the inspiratory phase is usually 90° (β angle), which increases with each subsequent breath.

Under normal conditions, mechanical ventilation waveforms have a trapezoidal appearance, as shown in **Figure 1** [10]. A decrease in airway diameter, such as in cases of asthma, COPD, or partial obstruction of the respiratory circuit, can result in an increase in the slope of the III phase. At the end of exhalation, the decrease to zero flow and the influence of cardiac pulsations can cause oscillations between emptying of different lung regions and the movement of exhaled and fresh gases, resulting in a wave pattern of cardiac origin. The presence of gaps in phase III waveform indicates spontaneous breathing during mechanical ventilation. In the event of an endotracheal tube misplacement into the esophagus, the concentration of CO_2 drops rapidly, causing a decrease in the waveform. Additionally, if CO_2 is repeatedly inhaled, the baseline value will not be zero. A sudden shortening of the plateau period in phase III indicates air leakage from the endotracheal tube

Table 1. The characteristics of three methods of the partial pressure of carbon dioxide monitoring

Types	Location of sensor	Methods of quantifying CO_2 concentration	Spectral range	Characteristics
Mainstream	In breathing circuits	Infrared radiation	Around 4.26 μm, filter required	Potential increase in dead space, generally faster rise time
Sidestream	Away from breathing circuits	Infrared radiation	Around 4.26 μm, filter required	Gas withdrawal rate of 30-500ml/min, long response time, large sample cell
Microstream	Away from breathing circuits	Molecular correlation spectroscopy	4.2 - 4.35 μm, no filter required	Gas withdrawal rate of 50ml/min, short response time, 15ul sample cell

cuff during mechanical ventilation.

Methods of $P_{ET}CO_2$ monitoring

In 1864, John Tyndall first proposed the use of infrared absorption spectroscopy to measure CO_2. According to Beer-Lambert law, the amount of infrared radiation (IR) absorbed by a sensor during IR detection is directly proportional to the concentration of CO_2 absorbed in the sample. With advances in CO_2 monitoring technology in the 1980s, $P_{ET}CO_2$ monitoring gradually became common in clinical practice. **Table 1** shows the characteristics of three methods of $P_{ET}CO_2$ monitoring: mainstream, sidestream and microstream [11].

Mainstream monitoring involves placing an infrared sensor directly in the patient's breathing circuit. Its advantages include fast response time, high accuracy, and minimal waveform distortion. However, the drawback is that it can only be used in relatively closed breathing circuits. Currently, a new type of tube-based mainstream capnography is available for non-intubated patients (cap-ONE; Nihon Kohden, Tokyo, Japan). It is small in size and weighs only 10g, making it suitable for nasal cannula channel [12].

Sidestream monitoring involves connecting a gas sampling tube to the patient's breathing circuit and using a suction pump to draw gas from the breathing circuit into the infrared measurement chamber for analysis. It can be used in both closed and non-closed breathing circuits, making it suitable for patients with spontaneous breathing [5]. The sidestream $P_{ET}CO_2$ sensors generally use conventional infrared radiation techniques, which have a wide absorption spectrum and require filtering, resulting in a low accuracy. Additionally, a large gas sampling volume and flow rate are required, which lead to a longer response time. Although it can be used for patients with spontaneous breathing, it has a higher loss of tidal volume during sampling, making it difficult to be used in newborns [13, 14]. To prevent water vapor blockage, a water trap must be installed, but it is easily damaged.

Currently, the microstream technology (Oridion Capnography Inc.) sensor uses molecular correlation spectroscopy, which operates within a small spectral range (4.2-4.35 μm) and does not require filtering. The gas sample demand can be as low as 15 μL, allowing for a very low sampling flow rate (50 ml/min). Additionally, microstream technology uses innovative small diameter and low dead space sampling tubes, which accelerate the delivery of gas and increase the sensitivity for recognizing events such as respiratory pauses [15]. This has expanded the use of $P_{ET}CO_2$ monitoring in populations with low tidal volumes, such as newborns [16]. The micrometer-level filter in the sampling tube can filter out particles down to the 0.2μm level, and the use of Nafion drying tube can adsorb condensate in the sampling tube and prevent water vapor blockage, eliminating the need for a water trap. Zhang et al. found that two types of sampling tubes using microstream technology (Smart CapnoLine (Oridion Capnography Inc., A) and Filterline H Set (Oridion Capnography Inc., B)) were utilized to collect $P_{ET}CO_2$ via nasal or pharyngeal routes in non-intubated patients who underwent digital subtraction cerebral angiography (DSA). The $P_{ET}CO_2$ and $PaCO_2$ were significantly correlated (0.832 vs. 0.836, $P<0.001$), which provides valuable clinical references [17].

$P_{ET}CO_2$ monitoring in specific populations

Obesity is considered as a risk factor for postoperative respiratory depression, and obese patients with respiratory system complications and obstructive sleep apnea (OSA) may benefit from $P_{ET}CO_2$ monitoring [18, 19]. However, there are some challenges in measuring $P_{ET}CO_2$ in OSA patients, as mouth breathing and low tidal volume can result in greater dilution of the sample by ambient air. The cap-ONE (Nihon Kohden, Tokyo, Japan) sensor was designed to

monitor respiratory pauses and measure $P_{ET}CO_2$ in OSA patients, as it can better accommodate mouth breathing [20]. Latham applied $P_{ET}CO_2$ monitoring to postoperative high-risk OSA patients in the PACU as a part of hospital continuous quality improvement program. Latham et al. reported that $P_{ET}CO_2$ monitoring allowed for timely detection of postoperative respiratory complications in patients and provided a better understanding of their conditions, enabling them to provide better care for the patients [21].

Gupta reviewed 13 studies and reported that advanced age, COPD, and heart disease are important risk factors for opioid-induced respiratory depression (OIRD) [22]. Older patients are more sensitive to the central inhibitory effects of opioid drugs, and they also have higher rates of comorbidities, leading to decreased plasma clearance of medications by the liver and kidneys [23]. Therefore, monitoring respiratory function in elderly patients after surgery is vital for their respiratory function.

Taylor et al. conducted a retrospective case-control analysis of 62 adult patients who experienced respiratory events (defined as respiratory rate <10 breaths/min and/or SpO_2 <90%) after surgery and found that patients aged 65 years and above had an increased risk of respiratory events (OR: 2.34; 95% CI: 1.14 - 4.82) [24]. Overdyk et al. evaluated respiratory function in 205 adult patients receiving PCA analgesia after surgery. The results showed that the rates of respiratory depression (respiratory rate <10 breaths/min) lasting for more than 2 or 3 minutes were 77.8% and 66.7%, respectively, in patients aged 65 years and above, which were higher than the mean occurrence rates (58.4% and 41.0%, respectively) [25].

$P_{ET}CO_2$ monitoring is critical in children because respiratory depression is prone to occur due to their larger tongue. In 1997, Hart et al. used relatively advanced $P_{ET}CO_2$ equipment to monitor children and found that $P_{ET}CO_2$ monitoring provided earlier indications of respiratory depression than pulse oximetry during procedural sedation with preserved spontaneous breathing [26]. Langhan et al. conducted a study on children aged 1-20 years in the PACU and found that the intervention group had higher rate of hypoventilation per minute (5% (95% CI: 2% - 8%) vs. 1% (95% CI: -1% - 3%); P=0.040], and higher apnea rate (11% (95% CI: 8% - 14%) vs. 1.5% (95% CI: -2% - 5%); P<0.001), as well as a faster rate of respiratory depression (5% (95% CI: 2% - 8%) vs. 1% (95% CI: 0% - 4%); P=0.050] compared to the control group, indicating that $P_{ET}CO_2$ monitoring in the PACU could better protect the postoperative respiratory function of children [27]. Yarchi et al. included 57 patients aged 4-62 years in a study on painless endoscopy and used $P_{ET}CO_2$ monitoring with $SpO_2 \leq 90\%$ or changes in heart rate or respiratory rate greater than 20% from baseline as an event. They found that $P_{ET}CO_2$ monitoring increased the probability of event occurrence in patients with lower average $P_{ET}CO_2$ values, higher $P_{ET}CO_2$ variability, and younger age [28]. Singh tested the correlation between $P_{ET}CO_2$ measured using microcapillary technology and $PaCO_2$ in newborns in the neonatal intensive care unit. The r value between $P_{ET}CO_2$ and $PaCO_2$ was 0.73 in 204 blood samples from very low birth weight (VLBW) infants (birth weight<1,500 g) and 0.82 in 82 blood samples from non-VLBW infants [29].

The identification of respiratory events and accurate estimation of $PaCO_2$ in patients with OSA, elderly individuals, and children through non-invasive means are the ongoing issues. The development of new measurement methods and sensors may provide us with more options to address this challenge.

$P_{ET}CO_2$ monitoring in non-intubated patients

$P_{ET}CO_2$ monitoring in patients under sedation outside operating room

With the advancements in endoscopy, interventional therapy, and radiological examination techniques, the number of procedures requiring sedation outside the operating room has significantly increased. The anesthesia plan for such procedures often requires moderate sedation, involving general anesthesia with preservation of spontaneous breathing [30]. During moderate sedation, patients are able to respond purposefully to verbal commands and respond to light tapping or verbal stimulation, usually without any intervention to maintain airway patency; their cardiovascular function is almost unaffected. However, in examination rooms for painless endoscopy, cholangioscopy, and DSA, the ambient light level is generally low, and internal medicine doctors and anesthesiologists often cannot detect respiratory impairment in patients in a timely manner, leading to respiratory depression [31]. In 2015, the Association of Anaesthetists of Great Britain and Ireland recommended $P_{ET}CO_2$ monitoring for all patients undergoing procedural sedation, especially for those requiring oxygen [32]. The American Society of Anesthesiologists also revised its basic anesthesia monitoring standards to include

$P_{ET}CO_2$ monitoring during moderate and deep sedation [33].

In recent years, multiple clinical studies have demonstrated that monitoring $P_{ET}CO_2$ can effectively detect respiratory events and reduce the incidence of hypoxemia during sedation in various non-operating room settings. Qadeer et al. reported that in 247 patients undergoing endoscopy, 69% of the patients experienced hypoxemia without $P_{ET}CO_2$ monitoring, and this proportion decreased to 46% after $P_{ET}CO_2$ monitoring (P<0.001) [34]. Similarly, Beitz et al. conducted a randomized trial and found that $P_{ET}CO_2$ monitoring during routine colonoscopy reduced the incidence of hypoxemia by 50% [35]. Ishiwata's study exhibited that the incidence of respiratory events during tracheal surgery was as high as 48.8%, and $P_{ET}CO_2$ monitoring could detect respiratory events earlier (30 seconds earlier than pulse oximetry), with a shorter duration of hypoxemia (20.4 vs. 41.7 seconds, P=0.029), a lower incidence of severe hypoxemia (SpO_2<85%) (16 (17%) vs. 29 (32%), P=0.019), and a higher mean lowest SpO_2 value (90.5 vs. 87.6, P=0.002) [36, 37]. Study of Schlag et al. confirmed that $P_{ET}CO_2$ monitoring during sedation for percutaneous transhepatic cholangiography drainage revealed significantly more respiratory events than clinical observation alone (113 vs. 7; P=0.012) [38]. Jiang et al. demonstrated that $P_{ET}CO_2$ monitoring in the painless abortion room was able to reveal a higher rate of respiratory events or abnormal ventilation (55.1%, 95% CI: 39.4% - 62.3% vs. 3.0%, 95% CI: 1.1% - 4.2%, P<0.001), leading to a lower incidence of hypoxemia (37.8%, 95% CI: 33.8% - 45.2% vs. 54.2%, 95% CI: 47.8% - 58.2%, P<0.001) [39]. It is indicated that $P_{ET}CO_2$ monitoring can also be used to identify early changes in ventilation parameters in the painless abortion room.

From an evidence-based medicine perspective, Waugh et al. conducted a meta-analysis on procedural sedation and analgesia (PSA) and demonstrated that $P_{ET}CO_2$ monitoring during PSA increased the detection rate of respiratory events by 17.6 times compared to no $P_{ET}CO_2$ monitoring (95% CI: 2.50 - 122.10; P<0.004) [40]. Similarly, Askar et al. carried out a meta-analysis on dental procedural sedation and found that $P_{ET}CO_2$ monitoring during sedation reduced the incidence of hypoxemia (RR 0.76, 95%CI: 0.70 - 0.83, P<0.001) and decreased oxygen saturation (RR 0.79, 95%CI: 0.71 - 0.87, P<0.001) [41]. These studies support the benefits of $P_{ET}CO_2$ monitoring during sedation in non-operating room settings.

In summary, the use of $P_{ET}CO_2$ monitoring during sedation and anesthesia procedures performed outside the operating room can improve the detection efficiency of respiratory pauses, enabling clinical physicians to provide timely intervention, and can reduce the incidence of hypoxemia in patients. Thus, $P_{ET}CO_2$ monitoring provides an effective safety guarantee for sedation and anesthesia procedures performed outside the operating room.

$P_{ET}CO_2$ monitoring in PACU

The PACU is a vital location for the monitoring of patients who have undergone general anesthesia and intubation. During the recovery period, the patient's vital signs and respiratory function need to be closely monitored [42]. $P_{ET}CO_2$ monitoring is an effective tool for evaluating the patient's respiratory and circulatory conditions [43]. The fourth national audit project of the National Audit Project of the Royal College of Anesthetists and the Difficult Airway Society indicates that around 30% of anesthesia-related airway complications occur during the recovery period [44]. Kawanishi et al. reported that airway adverse events exhibited an incidence of 16% in the PACU and about one-fourth of these events occurred at the end of anesthesia or in the recovery room [45]. Chung et al. conducted a study to monitor the respiratory function with microstream technology in 250 adult patients during the recovery period after general anesthesia and found that approximately 55% of patients experienced at least one episode of hypoxemia [46]. In addition, Potvin et al. discovered that $P_{ET}CO_2$ monitoring before tracheal extubation or removal of a laryngeal mask airway significantly reduced the proportion of patients with $P_{ET}CO_2$>45 mmHg in the minute before extubation (83.3% and 54.1%, respectively, P = 0.029) [43].

Although there is limited research in this area at present, future studies can explore whether monitoring vital signs such as respiratory rate, depth, and CO_2 concentration with $P_{ET}CO_2$ during the recovery period can improve the detection rate of adverse events such as airway obstruction, pulmonary embolism, respiratory distress, respiratory failure, and pneumothorax, with the aim of improving the safety of clinical anesthesia.

$P_{ET}CO_2$ monitoring in patients under non-invasive ventilation (NIV)

Patients with COPD, acute respiratory distress

syndrome, severe asthma, respiratory failure, congestive heart failure, OSA/hypopnea syndrome, and other respiratory conditions often require NIV [47]. NIV can correct alveolar hypoventilation, improve sleep quality and survival rate, and capnography can be used to monitor the respiratory and circulatory functions of these patients [48, 49]. Sakuraya et al. found that mainstream and sidestream $P_{ET}CO_2$ monitoring during NIV could effectively predict $PaCO_2$ levels in adults (mainstream: r=0.92, P<0.001 vs. sidestream: r=0.79, P<0.001) [50]. Duggal et al. conducted a systematic review on the safety and efficacy of NIV for blunt chest trauma patients without respiratory failure and concluded that early use of NIV could prevent intubation events [51]. Aarrestad et al. monitored $PtCO_2$ in 67 patients with chronic respiratory failure receiving long-term NIV, and reported a significant correlation between $PaCO_2$ and $PtcCO_2$ (r=0.9, P<0.0001) [52].

Currently, there is limited research on capnography for NIV. Hence, further studies are needed to support its benefits for non-invasive ventilation.

$P_{ET}CO_2$ monitoring in cardiopulmonary resuscitation

In 1978, Dr. Kalenda proposed to use CO_2 monitoring for the evaluation of pulmonary blood flow during cardiac resuscitation, which would help assess systemic circulation [53]. The 2015 Resuscitation Council UK guidelines identified the role of capnography in cardiopulmonary resuscitation (CPR), including endotracheal tube placement, monitoring ventilation rate during CPR to avoid hyperventilation, assessing the quality of chest compressions during CPR, and monitoring the return of spontaneous circulation after CPR [54]. In a retrospective analysis of 14,504,809 internal medicine and 6,771,882 surgical patients, Izrailtyan et al. identified 96,554 cases of cardiac arrest, with surgical patients experiencing twice as many events as internal medicine patients (6.17 vs. 3.77 events per 1000 cases) [55]. Independent predictors of cardiac arrest following opioid treatment included hispanic ethnicity, obesity, mild liver disease, and COPD. Baldi's study showed that changes in $P_{ET}CO_2$ before and within 10 minutes after intubation during cardiac arrest were independent predictors of CPR outcomes (OR 1.83, 95% CI: 1.02 - 3.30; P=0.040 and OR 3.9, 95% CI: 1.97 - 7.74; P<0.001) [56]. Murphy's study found that increasing chest compression depth by 10mm was associated with a 4.0% increase in $P_{ET}CO_2$ (P<0.001), increasing compression rate by 10 per minute was associated with a 1.7% increase in $P_{ET}CO_2$ (P=0.020), and increasing chest compression recoil speed by 10mm per second was associated with a 2.8% increase in $P_{ET}CO_2$ (P=0.030) [57]. Additionally, Gutiérrez et al. demonstrated that the average percentage change in $P_{ET}CO_2$ during chest compressions could be used to differentiate spontaneous circulation recovery (sensitivity: 95.4%, 95% CI: 90.10 - 98.10; specificity: 94.9%, 95% CI: 91.40 - 97.10) [58].

Although $P_{ET}CO_2$ monitoring can aid in monitoring spontaneous breathing and circulation recovery during cardiopulmonary resuscitation, there is currently limited evidence to suggest that the use of $P_{ET}CO_2$ monitoring during CPR can improve patient outcomes [59].

$P_{ET}CO_2$ monitoring and patient-controlled analgesia (PCA)

The implementation of the enhanced recovery after surgery concept has led to the widespread use of PCA for postoperative pain management in the ward. However, the use of opioid analgesics can lead to OIRD, which is a significant risk factor [22]. The Anesthesia Patient Safety Foundation recommends monitoring SpO_2 and respiratory rate, especially after extubation and when using opioid analgesics for pain management [60]. Lee et al. conducted a claims analysis on postoperative OIRD and reported that among 92 claims (κ=0.690), the majority of respiratory depression events (88%) occurred within 24 hours after surgery, and 97% were considered preventable with better monitoring [61]. Therefore, $P_{ET}CO_2$ monitoring is necessary when patients are using PCA pumps. In a survey of 178 patients using PCA pumps conducted by Overdyk et al., $P_{ET}CO_2$ monitoring detected a sustained decrease in pulse oxygen saturation (SpO_2<90%) in 12% of patients and a slow respiratory rate (RR<10 breaths/min) in 41% of patients, highlighting the need for $P_{ET}CO_2$ monitoring in the population using PCA pumps [25].

Despite the frequent occurrence of OIRD in clinical practice, most clinicians in hospitals rely on intermittent assessments to monitor PCA patients. However, there is currently limited research on real-time monitoring and timely intervention to reduce the occurrence of respiratory depression. $P_{ET}CO_2$ monitoring can provide real-time monitoring of a patient's respiratory status and promptly detect respiratory events, allowing for timely intervention.

Conclusion

In conclusion, $P_{ET}CO_2$ monitoring could be used not only in patients undergoing general anesthesia with endotracheal incubation, but also in many other medical settings such as endoscopy rooms, catheterization labs, ICU, PACU and emergency departments. Multiple studies have confirmed that $P_{ET}CO_2$ monitoring can also benefit non-intubated patients. As CO_2 detection technology and sampling circuits continue to improve, $P_{ET}CO_2$ monitoring is expected to better reflect respiratory and circulatory functions of patients, thereby expanding its use in non-intubated patients. Presently, $P_{ET}CO_2$ monitoring is primarily employed in non-intubated patients for PSA, while more research is required to investigate its application in post-extubation after general anesthesia, cardiopulmonary resuscitation, as well as the diagnosis and management of respiratory and circulatory system disorders.

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The interaction of *Candida albicans* with C-type lectin receptors

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Highlights

- Candidiasis is a substantial cause of perioperative mortality in immunocompromised and immunodeficient patients.
- β-glucan and α-mannan are two major pathogen-associated molecular patterns in the *Candida albicans* cell walls recognized by C-type lectin receptors (CLRs).
- CLRs, such as Dectin-1 and Dectin-2, as β-glucan and α-mannan receptors, are essentially involved in recogni tion of *Candida albicans*.
- CLRs are promising drug targets for treating chronic candidiasis.

Abstract

Candida albicans (*C. albicans*) is a ubiquitous commensal in the mammalian flora and the most prevalent fungal pathogen of humans. As an opportunistic fungus, *C. albicans* can cause mucosal and invasive infections. Invasive candidiasis infected by *C. albicans* is a leading cause of perioperative death in immunocompromised and immunodeficient patients. The morphological change from the yeast to the mycelium plays a key role in the pathogenesis of *C. albicans*. C-type lectin receptors (CLRs), including Dectin-1, Dectin-2, Dectin-3, Mincle, and dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin, are among the pattern recognition receptors expressed by innate immune cells that can recognize *C. albicans*. The emergence of drug-resistant *C. albicans* put pressure on the healthcare system, whereby CLRs have also attracted extensive attention from physicians. Thus, in this article, we discuss the interaction between CLRs and *C. albicans* and the treatment prospects of CLRs on anti-*C. albicans*.

Keywords: *Candida albicans*, virulence, C-type lectin receptors, anti-fungal immunity

Introduction

Candida species (*Candida* spp.) are common commensals in the skin and gut microbiota, colonizing the skin and mucosal surfaces of healthy individuals. *Candida albicans* (*C. albicans*) is the most common *Candida* spp. in clinic and one of the major causes of hospital-acquired infections. *C. albicans* is responsible for more than 400,000 invasive candidiasis cases annually with a high mortality rate of 75% [1, 2]. In healthy humans, *C. albicans* is usually harmless. However, they can be hyperproliferative, leading to invasive *Candida* infections in individuals, due to pH changes, nutrition, illness, and immune system disorders from the use of antibiotics and immunosuppressive agents [3]. Intensive care unit (ICU) patients usually have chronic underlying diseases with low immunity and disordered pathophysiological conditions [4]. In the last two decades, there is an increase in fungal isolates from ICU subjects due to improvements in diagnostics, overuse of antibiotics, and better organ support systems prolonging ICU stay [5]. In a report from eastern India, *Candida* spp. were detected in nearly 15% of isolates [6]. Perioperative medicine is a subject of multidisciplinary perioperative

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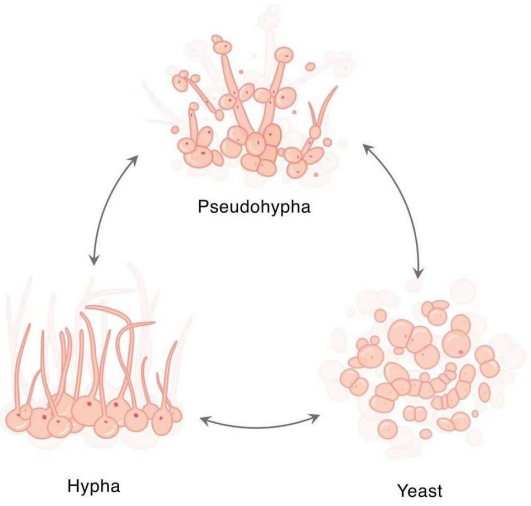

Figure 1. Phenotypic switching in *C. albicans*. *C. albicans* can switch among yeast, hypha, and pseudohypha cell types, depending on the environmental and nutritional factors. *C. albicans, Candida albicans.*

management, which is centered on surgical patients, based on value medicine, and aimed to promote the high quality of postoperative recovery of patients [7]. Surgical treatments play important roles in curing diseases. With the update of ideas and the progress of technology, clinicians gradually realize that the focus of disease treatment is not only the operation itself but also the preoperative and postoperative treatment. After some surgeries like cancer surgery, patients may require ICU admission for postoperative therapy [8]. However, ICU settings are conducive to *C. albicans* infection [9]. It has become increasingly challenging for clinicians to manage the *C. albicans* in ICUs, which was recently found in 52% of the observed cases in ICU [10, 11]. *C. albicans* is the most frequent isolate in yeast-positive cultures in patients with sepsis, and the mortality rate can reach 80% in patients with candidemia if no treatment is received within the first 24 h of septic shock [12].

In recent years, the annual incidence of invasive candidiasis has increased due to the widespread use of broad-spectrum antibiotics, glucocorticoids, and immunosuppressive agents. *C. albicans* infection is particularly severe in immunocompromised patients, such as those with acquired immunodeficiency syndrome, those receiving chemotherapy and immunosuppressive agents, and those implanted with medical devices. Virulence factors for *C. albicans* allow it to adhere to and penetrate host tissues, resulting in local diseases such as oral candidiasis, onychomycosis, and vaginitis. *C. albicans* have a strong morphological plasticity and can grow in yeast, pseudohyphae, or hyphae, and this polymorphism is strongly associated with its pathogenicity [13]. Additionally, biofilm formation is also one of the important virulence factors for this microorganism.

Pathogen-associated molecular patterns (PAMPs) exist on the surface of various pathogenic microorganisms. They exhibit unique characteristics specific to certain microorganisms, possess constant structural features, and demonstrate evolutionary conservation. Mainly expressed on the surface, cytosol, and serum of innate immune cells (macrophages, dendritic cells, etc.), pattern recognition receptors (PRRs) directly recognize pathogen surfaces such as the fungal cell wall components mannose, chitosan and β-glucans. Common PRRs include toll-like receptors (TLRs), nucleoside receptors (NLRs), retinoic acid-inducible gene I-like receptors, and C-type lectin receptors (CLRs) [14]. In recent years, CLRs play a pivotal role in host antifungals especially *anti-C. albicans* infection, which has attracted increasing attention. The interactions between CLRs and *C. albicans,* as well as their role in the induction of protective immunity, is elaborated in this study. The main CLRs involved in the recognition of *C. albicans* include Dectin-1 (*CLEC7A*), Dectin-2 (CLEC6A), Mincle (CLEC4E), DC-SIGN (CD209), and MCL / Dectin-3 (CLEC4D).

Virulence of *C. albicans*

Fungal cell walls are highly dynamic complex structures that play a role in maintaining cell shape and protecting cells. The robustness of the cell wall is the key to the maintenance of fungal morphology. Fungal cell walls are composed of rich composition of an inner layer of β-glucans and underlying chitin and an outer layer of mannosylated proteins. β-glucan is the major PAMP in the fungal cell walls and is cleared after recognition by the innate immune system [15]. Under normal conditions, *C. albicans* can mask the inner wall of cells by coating it with an outer layer of mannosylated protein β-glucans, which reduces the recognition of *C. albicans* by innate immune cells, enhancing their viability [16-18]. It has also been reported that the pathway for the synthesis of phosphatidylserine plays an important role in the masking of β-glucans [19]. *C. albicans* infection of macrophages triggers macrophage death, which is largely attributed to RIPK3/mixed linear kinase domain-like protein (MLKL)-mediated necroptosis. The TSC1/mTOR pathway is involved in regulating Dectin-1/2 and TLR-2/4 pathways, respectively, by binding fungal

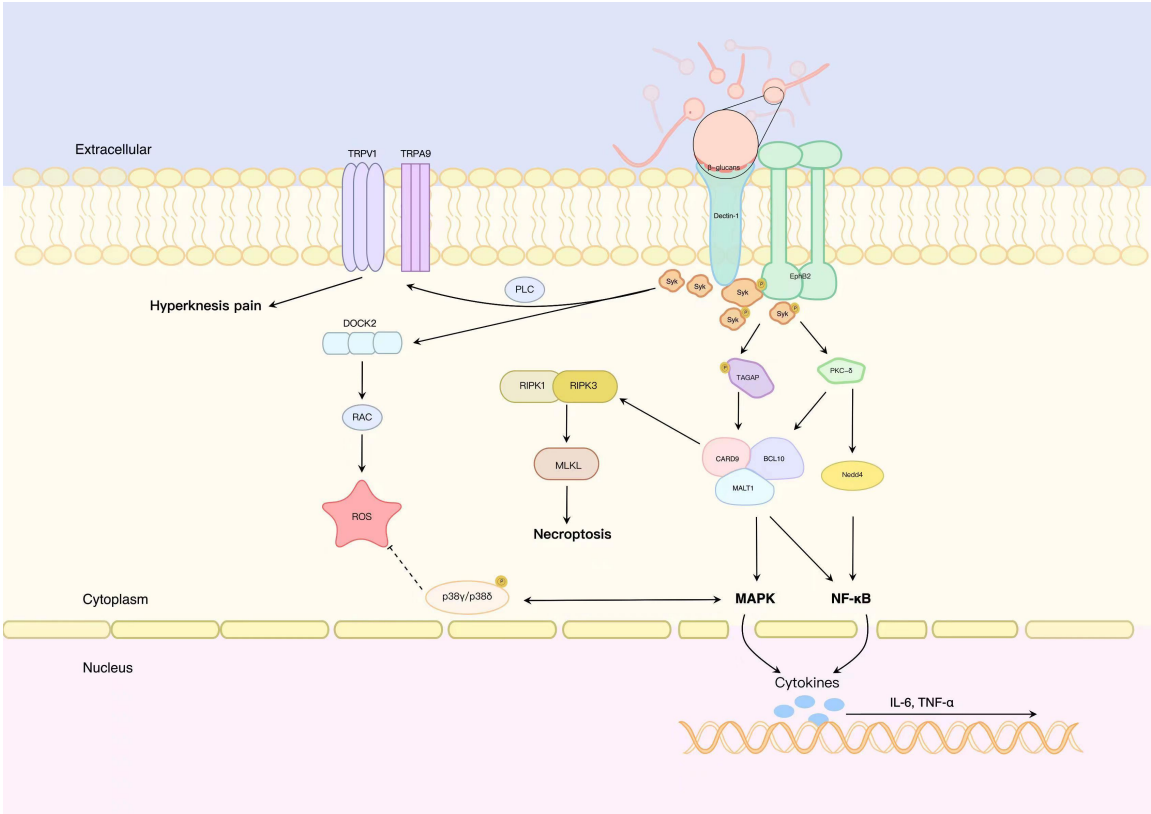

Figure 2. Dectin-1 against *C. albicans*. The recognition of ligands by Dectin-1 triggers SYK recruitment and downstream intracellular signaling. EphB2 is required for SYK phosphorylation and activation following Dectin-1 ligand stimulation. TAGAP is tyrosine phosphorylated by the EphB2 gene, which links dectin-1-induced EphB2 activity to downstream CARD9-mediated signaling pathways. PKC δ is activated upon Dectin-1-SYK signaling, which mediates phosphorylation of CARD9, and favors CARD9-BCL10-MALT1 complex formation and activation of NF- κB. The ubiquitin ligase Nedd4 is located in PKC-δ downstream, which is critical for signaling through Dectin-1 and the activation of NF-κB. Necroptosis is a newly discovered type of programmed cell death. It activates the actuator MLKL through the specific signal cascade of RIPK1 and RIPK3 complex. p38γ/p38δ deficiency protects against *C. albicans* infection by increasing the production of reactive oxygen species. DOCK2 is a nucleotide exchange factor for RAC. Fungus-induced ROS production is partially dependent on the DOCK2-RAC GTPase pathway. In addition, β-glucan can stimulate Dectin-1-dependent nociceptors, which causes unpleasant sensations. *C. albicans*, *Candida albicans*; TAGAP, T cell activation Rho GTPase activating protein; EphB2, Eph receptor B2; CARD9, caspase recruitment domain-containing protein 9; PKC, Protein kinase C; SYK, spleen tyrosine kinase; NF-κB, nuclear factor-κB; MLKL, mixed linear kinase domain-like protein; RIPK, receptor interaction protein kinase; DOCK2, dedicator of cytokinesis 2; ROS, reactive oxygen species.

component β-glucan or α-mannan. The pathway also plays a key role in controlling macrophage necroptosis [20].

C. albicans is a polymorphic fungus that can grow in yeast or hyphal forms, and its ability to interconvert between these forms is considered an important virulence trait (**Figure 1**) [21]. When the flora is dysregulated or the mucosal barrier function is altered, *C. albicans* switches from a yeast state to a mycelial state, releases secretory proteins, invades and colonizes host cells, thus destroying host cells. Yeast wall protein 1 is an abundant mannoprotein of the yeast cell wall. When anchored in the cell wall, yeast wall protein 1 has an anti-adhesive and masking effect, leading to β-glucan unexposed, reducing the adhesivity of *C. albicans*, and protecting *C. albicans* from recognition by the immune system [22]. *UME6* is a transcriptional regulator of *C. albicans* hyphae and is essential for systemic Th17 immunity triggered by intestinal *C. albicans*. Studies have demonstrated a greater ability of hyphal *C. albicans* to invade the host than in the yeast state. Once hyphae are formed, their associated virulence factors are abundantly expressed, thus increasing the pathogenicity of *C. albicans* [23].

C. albicans exotoxin candidalysin is the first peptide toxin secreted by hyphae of *C. albicans* found in human pathogenic fungi [24]. Candidalysin is encoded by the *C. albicans* gene *ECE1*, which is one of the most expressed genes during the formation of mycelial. The expression of *ECE1* can increase to 10,000 times within a few minutes after the induction of mycelial growth [25]. When *C. albicans* are engulfed by macrophages, the expression of the *ECE1* gene encoding *C. albicans* is significantly enhanced. Therefore, mature *C. albicans* may be produced by *C. albicans* cells engulfed

by macrophages and play a toxin-dependent effect [26]. Candidalysin has dual functions in the interaction with the host. On the one hand, candidalysin can promote the damage to the host cell membrane, which is related to escape from phagocytes. On the other hand, it can activate NLRP3 inflammatory corpuscles and trigger a pro-inflammatory reaction that protects the host, which is beneficial to the elimination of fungus [26, 27]. In addition, Candidalysin can destroy primary hepatocytes in a dose-dependent manner in vitro [28]. It can promote alcohol-induced liver disease and is positively correlated with the severity of liver disease and mortality of patients with alcoholic hepatitis.

CLRs and *C. albicans*

Dectin-1

Dectin-1 is a type II transmembrane receptor with a single extracellular C-type lectin-like domain encoded by the *CLEC7A* gene [29-31]. It is mainly expressed by myeloid cells (e.g., neutrophils, monocytes, and dendritic cells) and is the major CLR that recognizes β-glucans in fungal cell walls (**Figure 2**) [32-34]. The recognition of its ligands by Dectin-1 triggers complex downstream signaling pathways with interconnected relationships [31]. Spleen tyrosine kinase (SYK) is a cytoplasmic nonreceptor protein tyrosine kinase that plays an important role in oxidative response and bactericidal activity. Dectin-1 is essential for SYK recruitment and triggers intracellular signaling [35, 36].

It is generally believed that DOCK2, a member of the CDM protein family, is an upstream molecule of RAC and functions as a guanine nucleotide exchange factor for RAC. Recently, Ma et al. found that in DOCK2-KO THP-1 cells, reactive oxygen species (ROS) production was severely impaired, but after treatment with RAC GTPase inhibitors, ROS production was not completely blocked [37]. This indicates that fungal-induced ROS production is partially dependent on the DOCK2-RAC GTPase pathway, and there is a RAC GTPase-independent and Dock2-dependent mechanism for ROS production. Protein kinase C-δ (PKC-δ) is activated upon Dectin-1-SYK signaling, mediates phosphorylation of CARD9, and favors CARD9-BCL10-MALT1 complex formation and activation of NF- κB [36, 38].

The tyrosine kinase receptor Eph receptor B2 (EphB2), a kinase of SYK, was recently shown to be required for SYK phosphorylation and activation following Dectin-1 ligand stimulation [39]. It has also been shown that SYK can promote phosphorylation of EphB2, and co-expression of SYK significantly facilitates the interaction between Dectin-1 and EphB2. T cell activation Rho GTPase activating protein (TAGAP) is essential in Dectin-1-induced antifungal signaling and proinflammatory cytokine production by myeloid cells. Upon stimulation by Dectin-1 ligands, EphB2 was phosphorylated by SYK and further phosphorylates TAGAP, which links Dectin-1-induced EphB2 activity to downstream CARD9-mediated signaling pathways. During *C. albicans* infection, mice lacking TAGAP can develop defective immune responses, impaired Th17 cell differentiation, and a higher fungal burden [40]. The ubiquitin ligase Nedd4 is located in PKC-δ downstream and plays a crucial role in signaling through Dectin-1, as well as in the activation of NF-κB [41].

Dectin-1 is regulated by multiple factors. miR-155, as a multifunctional microRNA (miRNA), is a key regulator of innate immune responses against bacteria and viruses. The Dectin-1 pathway can be activated by NF-κB, p65, and Bcl-10, promote the expression of miR-155 in SYK-dependent manner, and reduce the excessive inflammation caused by *C. albicans* [42, 43]. Overexpression of granulocyte-macrophage colony-stimulating factor (GM-CSF) is a dependent feature of β-glucan-induced macrophage priming. GM-CSF can upregulate Dectin-1 expression. However, a study found that blockade of the GM-CSF pathway did not affect levels of β-glucan, suggesting that GM-CSF is not acting primarily on β-glucan [44]. Song et al. recently found the activation of mast cells and the overexpression of Dectin-1 in patients with *C. albicans* infection, which promoted the activation of downstream MAPK signal pathway [45]. The deletion of CD82 could regulate Dectin-1 signal transduction, resulting in the reduction of SYK phosphorylation and the production of ROS in response to *C. albicans* infection [46]. Lactobacillus down-regulated the transcription of *CLEC7A*, resulting in a decrease in the expression of Dectin-1. Lactobacillus changed the cytokine profile of macrophages stimulated by *C. albicans*, increasing the expression of IL-10 and IL-1β and decreasing the expression of IL-12. These results indicate that lactobacillus can damage the recognition of PAMP by macrophages and regulating inflammation [47]. The autoimmune regulatory gene (*AIRE*) can also regulate the SYK-dependent Dectin-1 pathway. *AIRE*-knockdown macrophage-like THP-1 cells showed down-regulation of Dectin-1 and Dectin-2 receptors, and reduction in activity of hyphal recognition, phagocytosis of C. albi-

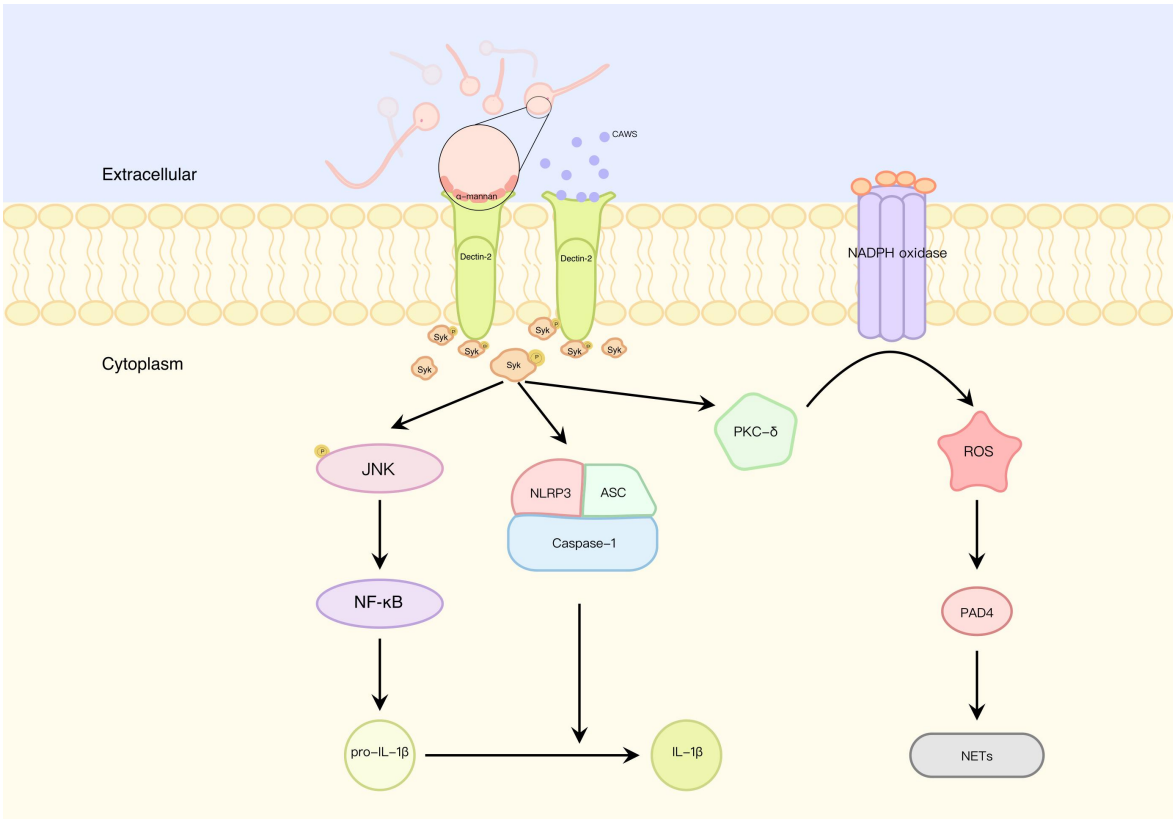

Figure 3. Dectin-2 against *C. albicans*. Dectin-2 can recognize α-mannan in the fungal cell wall. After α-mannan is recognized by Dectin-2, it can also send signals through CARD9, causing the activation of NF-κB. Dectin-2 can activate the downstream SYK-Ca^{2+}-PKC δ PAD4 signal pathway, mediate the production of NADPH oxidase independent NETs, and contribute to the production of ROS. CAWS can induce NLRP3 and pro-IL-1β expression via Dectin-2/SYK/JNK/NF-κB pathways and activate Dectin-2 as well as cleavesIL-1β precursor via caspase-1/SYK/JNK mediated production of ROS. *C. albicans*, Candida *albicans*; PAD4, protein arginine deiminase 4; CARD9, caspase recruitment domain-containing protein 9; NF-κB, nuclear factor-κB; SYK, spleen tyrosine kinase; NADPH, nicotinamide adenine dinucleotide phosphate; NETs, neutrophil extracellular traps; IL, interleukin; ROS, reactive oxygen species.

cans, and formation of lysosomes. Besides, the expression of IL-1β, IL-6, and TNF-α were also reduced [48].

The insolubility of the cell wall of *C. albicans* β-glucan can increase the generation of IL-6 and TNF-α by Dectin-1-SYK-NF-κB and p38 MAPK pathways [49]. Dectin-1 recognizes β-glucan by activating PKC-δ and regulates glucose transporter 1 (GLUT1) phosphorylation, localization, and early glucose transport in neutrophils. The host response to disseminated candidiasis involves renal immunity, modulation of GLUT1 expression, and localization. This increases neutrophil glycolytic activity and upregulates glucose uptake [50]. Necroptosis is a newly discovered type of programmed cell death. It activates the actuator MLKL through the specific signal cascade of receptor interaction protein 1 (RIPK1) and RIPK3 complex. Fungi trigger the necrotic apoptosis of myeloid cells, which helps the host defense against pathogen infection. The activation of *C. albicans* and its sensor Dectin-1 induces necroptosis of myeloid cells through the RIPK1-RIPK3-MLKL pathway. CARD9 is a key adapter of Dectin-1 signal transduction and is identified as a link between RIPK1 and RIPK3 complex-mediated necroptosis pathway. RIPK1 and RIPK3 also enhance the MLKL-independent inflammatory response induced by Dectin-1. Both MLKL-dependent and MLKL-independent pathways are necessary for host defense against *C. albicans* infection [51].

In addition, β-glucan can stimulate Dectin-1-dependent nociceptors, as well as pathways of inflammatory pain. The major pathway acts through a Dectin-1-mediated ATP-P2X3/P2X2/3 axis via the intercellular relationship between keratinocytes and primary sensory neurons, which depends on the ATP transporter vesicular nucleotide transporter (VNUT). Another pathway works through a Dectin-1-mediated PLC-TRPV1/TRPA1 axis in primary sensory neurons. Interestingly, in the cell wall of *C. albicans*, β-glucan can enhance histamine-dependent itching, and the VNUT inhibitor clodronate can be used to treat itch induced by β-glucan-induced unpleas-

ant sensations (**Figure 2**) [52]. β-glucan was masked at low oxygen level, which hinders the PAMP sensing of Dectin-1 on the surface of polymorphonuclear leukocytes. This in turn contributes to the immune escape and improves the survival rate of fungus [53]. Homologous phosphatases Sts protein negatively regulates phagocyte activation by regulating selective elements of the Dectin-1-SYK tyrosine kinase signaling axis, and genetic inactivation of Sts significantly improves the survival of mice infected with *C. albicans*, which may facilitate the development of novel therapeutic approaches to enhance protection against invasive candidiasis [54].

C. albicans, through the β-glucan receptor Dectin-1, stimulates nav1.8-positive nociceptors, inducing calcitonin gene-related peptide (CGRP). CGRP can directly inhibit P65 through transcriptional repressor JDP2, thereby inhibiting β-glucan-induced inflammation and osteoclast multinucleation, indicating a role for the Dectin-1-mediated sensory secretion pathway in the resolution of fungal bone inflammation [55]. Taurochlorolamine (TauCl), formed by the reaction between taurine and hypochlorite in leukocytes, is especially abundant in activated neutrophils with an oxidative burst. As neutrophils undergo apoptosis, TauCl is released into the extracellular matrix at the site of inflammation, thereby affecting coexisting macrophages in the inflammatory microenvironment. Exogenous TauCl can significantly increase the phagocytic efficiency of macrophages by upregulating Dectin-1. This may be mediated by TauCl induction of heme oxygenase-1 expression and subsequent production of carbon monoxide. TauCl has an important role in host defense against fungal infections and has a therapeutic potential in the management of inflammatory diseases [56].

Recently, a new TAK1-TPL2-MKK1-ERK1/2 pathway was found in macrophages. It is considered to be activated by Dectin-1 and positively regulated by p38γ/ p38δ in bone marrow cells. In mice, p38γ/p38δ deficiency has a protective effect against *C. albicans* infection. This protection is achieved through increased production of ROS, which enhances the antifungal capacity of macrophages. Additionally, p38γ/ p38δ deficiency helps in reducing excessive inflammation, which can lead to severe damage to the host. In murine models, pharmacological inhibition of p38 MAPK was shown to reduce the fungal burden, suggesting that p38 MAPK may be a therapeutic target for the treatment of human *C. albicans* infections [57]. Furthermore, β-glucan triggers the production of neutrophil extracellular trap nets through Dectin-1 and the engagement of CD11b and CD18 receptors, which is a fascinating antifungal mechanism for neutrophils [58].

Dectin-2

Dectin-2 (CLEC6A) is a CLR that mainly exists in dendritic cells, macrophages, and neutrophils. Dectin-2 has been proven to recognize α-Mannan in the fungal cell walls (**Figure 3**) [59, 60]. After α-mannan is recognized by Dectin-2, it can also send signals through CARD9, causing the activation of NF-κB, and inducing the production of inflammatory cytokines [61]. Dectin-2 can activate the downstream SYK-Ca^{2+}-PKC-δ protein arginine deiminase 4 (PAD4) signal pathway, mediate the production of NADPH oxidase independent neutrophil extracellular traps (NETs), and contribute to the inhibition of fungal dissemination [62]. Dectin-2 has been shown to mediate phagocytosis, cytokine, and ROS production. In *C. albicans* infection, it promotes IL-12p40, IL-1β, and IL-23 production by dendritic cells (DCs) to induce the generation of protective Th1 and Th17 responses [63]. Also, Dectin-2-deficient mice were shown to have a poor capacity to secrete Th1 and Th17 cytokines to generate ROS [64].

Recently, it has been shown that the recognition of α-mannans by Dectin-2 is a key to the pathogenesis of Kawasaki disease (KD)-like vasculitis induced by cell wall of polysaccharide of *C. albicans* in mice [65]. In a study of a *C. albicans* water-soluble fraction (CAWS)-induced murine KD model, it was found that the NLRP3 inflammasome was required for the development of CAWS-induced vasculitis and that Dectin-2 signaling in macrophages in the aortic root of the heart induced early CCL2 production, which in turn induced vascular inflammation [66]. CAWS triggers Dectin-2/SYK/JNK/NF-κB pathways, leading to the induction of NLRP3 and pro-IL-1β expression. It also activates Dectin-2 as well as cleaves IL-1β precursor via caspase-1/SYK/JNK mediated production of ROS [67, 68]. These findings provide new insights into the pathogenesis of KD vasculitis, and suggest that NLRP3 inflammasome may be a potential therapeutic target for KD.

Dectin-3

Dectin-3 (CLEC4D), which can be expressed by multiple myeloid cells, is a myeloid cell-specific CLR family member that can recognize bacterial and fungal components and induce

intracellular signaling pathways to regulate immune responses[69]. Dectin-3 recognizes the α-mannan on the surface of *C. albicans* and induces NF-κB activation [70]. Recently, it was found that Dectin-3 knockout (Dectin-$3^{-/-}$) mice exhibited increased tumorigenesis and *C. albicans* burden during chemical induction, indicating that Dectin-3 may be the key CLR to identify and prevent *C. albicans* [71]. In addition, the interaction between Dectin-3 and symbiotic fungi is indispensable for the homeostasis regulation of the intestinal immune system. Mice lacking Dectin-3 are more likely to suffer from colitis induced by dextran sulfate [72].

Mincle

Mincle (CLEC4E) is a CLR that is expressed in macrophages. Mincle binds to α-mannan that interferes with Dectin-1-mediated antifungal responses in human dendritic cells [73, 74]. Mincle receptor is an Fc receptor-γ coupled receptor that can transmit signals through SYK pathway [75]. It has been demonstrated that mincle regulates antifungal immune function by binding to ITAM connector molecule Fc receptor-γ, recognizing damaged cells and inducing inflammation [76]. Upon recognition of the ligand, mincle activates SYK and other downstream signaling cascades to induce inflammatory cytokines [77, 78]. In the absence of mincle, the TNF-α produced by macrophages is reduced, and mice lacking mincle exhibits a significantly increased susceptibility to systemic candidiasis. This indicates that the mincle receptor plays an important role in the immune process of organisms against *C. albicans* infection. Mincle has been shown to mediate the production of TNF-α by BMDMs in response to *C. albicans* [73]. Both mincle and Dectin-2 play a role in regulating cytokine production in response to multiple Candida spp. In BMDCs, mincle mediates IL-12p40 production and inhibits IL-1β production, whereas Dectin-2 promotes the production of IL-12p40 and IL-10, in response to multiple Candida spp [79].

Mincle receptors from different cells also seem to have varying effects. The expression of mincle on neutrophils seems to be beneficial to early cell response, leading to the elimination of organisms. However, its expression on monocytes may contribute to the polarization of cell reactions, avoiding clearance and promoting the generation of TNF-α, IL-1β [80]. Furthermore, mincle is required for *C. albicans* clearance in the kidney [73].

DC-SIGN

DC-SIGN (CD209) is another member of the CLR family that mainly found on the surface of immature DCs in peripheral tissues, mature DCs in lymphoid tissues, and some macrophage subsets [81]. DC signaling reduces TGF-β1 through the activation of Raf-1 and p38 [82]. DC-SIGN directly binds to glycan structures exposed on the surface of pathogens [79]. DC-SIGN directly binds to glycan structures exposed on the surface of *C. albicans*, activates the Raf-1-acetylation-dependent signaling pathway to increased IL10 transcription to enhance anti-inflammatory cytokine responses [83, 84].

CLRs in the treatment of *C. albicans*

In a recent study on GPI7 mutants of *C. albicans*, Dectin-1 was observed to signal through the recognition of GPI7 mutants on the cell surface β-1,3-glucan, leading to atypical NF-κB nuclear translocation. This regulates the production of IL-18 as well as major Candida antibodies. A2-aminonicotinamide derivative, 11G, which is revealed by β-glucan, activates Dectin-1-dependent protective immune responses and enhances fungal immunogenicity, is a very promising antifungal drug [85]. Morphological conversion between *C. albicans* yeast and hyphae is essential for its interaction with the defense system of the host, and the Flo8 gene may regulate this conversion process. Furthermore, Flo8 induces Dectin-2/CARD9 to mediate IL-10 production by DCs and macrophages, blocks thymic atrophy by suppressing *C. albicans*-induced apoptosis of thymic T cells, and promotes sustained export of naive T cells from the thymus to the spleen [86]. Dectin-2 is a drug target for controlling IL-10 production in vivo and treating chronic candidiasis.

Amphotericin liposomes coated with Dectin-2, specifically the mannan-binding domain of Dectin-2, exhibited enhanced binding to *C. albicans* than untargeted control liposomes, significantly reducing the effective dose. Further, amphotericin B-loaded Dectin-2-coated liposomes demonstrated 50 to 150 times stronger binding to *C. albicans*, compared to untargeted liposomes [87]. DectiSomes are a novel antifungal drug targeting technology [88]. Two types of DectiSomes, DEC1-AmB-LL and DEC2-AmB-LL, were developed by coating AmB-LL with the carbohydrate recognition domains of Dectin-1 and Dectin-2, respectively [89]. These targeted formulations demonstrated superior efficacy compared to non-targeted drugs in terms of fungal cell binding and killing, both in vitro and in vivo. Additionally, they effectively reduced the

burden of fungi in the kidney [90]. But for cryptococcus neoformans, Dectisomes may reduce antifungal activity. Moreover, with only moderate effects in penetrating the blood-brain barrier as well as significant cost, further efforts are required to make Dectisomes a clinical reality.

Ligand recognition by DC-SIGN is provided by a carbohydrate recognition domain (CRD) linked to membrane transport and signaling sequences, and different combinations of eight neck repeats (NR1 to NR8) expressed in different protein isoforms may alter the orientation of the CRD and the ability to bind to different polysaccharides. Two recombinant isomers were prepared and connected with lipid carriers to produce DCS12-AmB-LLs and DCS78-AmB-LLs. The liposome AmB was targeted to fungal cells with DC-SIGN. In the mouse model of invasive candidiasis and pulmonary aspergillosis, low-dose DCS12-AmB-LLs significantly reduced the fungal burden on the kidney and lung, which sheds light on future research in anti-*Candida* therapy [91].

In recent years, traditional Chinese medicine has been used to treat Candida infections. Sodium houttuyfonate is a promising anti-Candida traditional Chinese herbal medicine, which can induce β-glucan exposure, through the cooperation of Dectin-1 and TLR2/4, promotes intestinal macrophages to get rid of colonized *C. albicans*, reduces fungal load, and alleviates colitis associated with *C. albicans* [92]. Kangbainian lotion (KBN) is a Chinese plant preparation, which has achieved good clinical efficacy in the treatment of vulvovaginal candidiasis. It inhibits biofilm and hyphal formation, reduces adhesion, and inhibits ergosterol synthesis and the expression of ergosterol synthesis-related gene *ERG11*. KBN can also reduce the protein expression of inflammatory factors TNF-α, IL-1β, and IL-6 in vaginal tissue and inhibit the expression of proteins related to the Dectin-1 signal pathway [93]. Butyl alcohol extract of Baitouweng Decoction down-regulates key proteins in TLRs/MyD88 and Dectin-1/SYK signaling pathways, including ASC, caspase-1, Dectin-1, SYK, MyD88, TLR2, TLR4, and NF-κB, and exerts therapeutic effect in mice with vulvovaginal candidiasis [94, 95]. Paeonol can improve liver inflammatory injury by alleviating intestinal fungal flora imbalance and inhibiting fungal flora mediated Dectin-1/IL-1β signal pathway [96]. Cinnamaldehyde can reduce the content of TNF-α, IL-1β, IL-6, and IL-8 in serum and colon tissues, increase the content of IL-10, inhibit the infiltration of macrophages, and down-regulate the protein expression of Dectin-1, TLR2, TLR4 and NF-κB in colon tissues, showing a therapeutic effect on mice with ulcerative colitis [97].

Discussion

C. albicans are usually a benign member of human intestinal microflora, but in some cases, such as in the host with low immune function, the ecological imbalance of intestinal fungi can lead to invasive infection and inflammatory bowel disease [98, 99]. Intestinal epithelial cells (IECs) may recognize the activation of the Wnt pathway by *C. albicans* through Dectin-1, leading to the progression of colorectal cancer [96]. However, IEC recognition of *C. albicans* does not lead to any detectable secretion of pro-inflammatory cytokines [100, 101].

This review summarizes the major CLRs against *C. albicans* besides CD23 (CLEC4J), which is also a kind of CLR and a well-known B-cell surface marker. CD23 can sense the components of *C. albicans* in antifungal immunity and recognize the components of *C. albicans* or Aspergillus fumigatus in the cell wall α-mannan and β-glucan, but it cannot recognize the glutaraldehyde xylimanna in Cryptococcus. By interacting with the FCR-γ and forming a complex, CD23 can induce NF-κB activation [102]. However, it remains unclear how CD23 functions as a fungal PRR and whether the antifungal effect of CD23 is specific to *C. albicans*. Infection of macrophages with *C. albicans* can cause cell death, which is mainly due to RIPK3/MLKL-mediated necrotic apoptosis [20]. The size of *C. albicans* affects the phagocytosis of DCs, which prolongs the duration of Dectin-1 signal transduction, increases the expression of IL-33, and promotes the TH9 response [32]. Several microbial recognition receptors, including TLR2, MyD88, Dectin-1, Dectin-2, and the signaling molecule CARD9, are dispensable for host defense against *C. albicans* invasion in the epidermis. Instead, the production of IL-17A and IL-17F by innate lymphoid cells plays critical roles. Further studies are needed to understand how *C. albicans* is recognized in the superficial layers of the epidermis [103]. Besides, the coordinated action of CLRs plays a key role in effectively controlling *C. albicans* and preserving organ function during infection [104]. Dectin-2 and Dectin-3 form heterodimers to combine α-mannan more effectively, which leads to an effective inflammatory response against *C. albicans* infection. Dectin-1 signal activates RHOA pathway, leads to actin contraction, and promotes DC recruitment. Dectin-1 and DC-SIGN synergistically enhance the clear-

ance of *C. albicans* [70, 105].

Due to the long-term use of limited antibacterial drugs, the drug resistance of fungi is continuously increasing. However, the development of novel antibacterial drugs lags far behind the emergence of fungal resistance. Further studies of the mechanism of action between CLRs and *C. albicans* can provide new insights and strategies for the research of broad-spectrum antibacterial drugs, antitumor drugs, immunosuppressive agents, as well as the prevention and treatment of fungal infections caused by interventional surgery, organ transplantation, acquired immunodeficiency syndrome and so on.

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MicroRNAs: Regulators of the host antifungal immune response

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Highlights

- Patients are at a high risk of fungal infection during perioperative period.
- MicroRNAs are involved in inflammatory responses, pyroptosis and autophagy in antifungal immunity.
- MicroRNAs modulate the activation of Th cells during fungal infection, thereby regulating the adaptive immune response.
- Differentially expressed miRNAs could be used as fungal infection biomarkers.

Abstract

Fungi pose a severe threat to human health worldwide, especially to patients with weakened immune systems. Perioperative patients are at a high risk of fungal infection and death because of the immunosuppression caused by the surgery, as well as the use of surgical instruments. Perioperative patients in ICU are at greater risk of fungal infection. Fungal infections are often difficult to identify, and the treatment is particularly challenging. A well-functioning host immune and an appropriate level of inflammation is essential for controlling fungal infections. MicroRNAs (miRNAs) play critical roles in regulating host immune function, primarily through participating in the post-transcriptional regulation of target genes. After fungal infection, miRNAs are differentially expressed in various tissues, cells, and extracellular vesicles, promoting or inhibiting antifungal effects through different mechanisms to modulate the host immune response. In addition, differentially expressed miRNAs could serve as potential biological markers for the diagnosis and treatment of fungal infections. In this review, we discuss the role and significance of miRNAs in fungal infections.

Keywords: MicroRNA, fungal infection, antifungal immunity, inflammatory response, potential biomarkers

Introduction

There are 2.2 to 3.8 million species of fungi worldwide [1]. However, only a tiny fraction are typically associated with humans, acting as opportunistic pathogens [2]. These fungi generally inhabit in healthy individuals' mucosal and epidermal surfaces. The fungi are commensal organisms that do not cause disease under normal conditions. However, they have the potential to cause mucocutaneous fungal infections and invasive fungal infections (IFIs) in immunocompromised individuals.

IFIs are becoming increasingly common in critically ill patients, especially during perioperative period [3]. The length of hospital stay was longer among patients undergoing surgery, and prolonged hospital stay is a risk factor of hospital infection [4]. The use of central venous catheter and shunt and other medical equipment in patients with immunosuppression in the process of the operation will increase the risk of fungal infection [5, 6]. IFI can be fatal in patients receiving organ or stem cell transplantation [7]. For patients with abdominal surgery, intestinal fungi could enter blood, causing invasive fungal infections. Perioperative critically ill patients admitted to intensive care unit (ICU) are at a high risk of fungal infections. About 20% of infections in ICU are caused by fungi [8], and fungal infection is an important cause

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of death in ICU patients. IFIs have become increasingly prevalent, accompanied by high mortality [9-11]. The most common IFIs are invasive *Candida albicans* (*C. albicans*) and invasive aspergillosis. *C. albicans* is the third frequent cause of infections for ICU patients, contributing to more than 40% of the crude mortality [12-14]. Early diagnosis and immediate treatment are critical for a favorable IFI prognosis. However, clinical diagnosis of IFIs remains challenging. Fungal culture is the gold standard for the diagnosis of IFIs, but the long culture time, typically around 48 hours, can delay treatment [15].

Presently, the most common detection method for IFI is (1,3) β-D-glucan assay, which identifies the fungal-specific cell wall component (1,3) β-D-glucan in serum. The (1,3) β-D-glucan assay is a serological test for early dection with high predictive value [16]. However, (1,3) β-D-glucan are widely present in fungal cell walls, and the (1,3) β-D-glucan assay cannot distinguish fungal species. Additionally, (1,3) β-D-glucan assay sometimes shows false positive due to several factors, such as wound gauze and blood products [17, 18]. In recent years, molecular biological detection of fungal pathogen has made significant progress, such as T2 magnetic resonance assay and next generation sequencing. Molecular biology methods can detect fungi infections in a short time, but are not mature enough to replace routine microbiological, serological and histopathological examinations [19-21].

Treatment for IFIs is challenging because only three distinct antifungal drug classes are available—azoles, polyenes, and echinocandins. These drugs treat fungal infections through different mechanisms. Polyenes (Amphotericin B) directly bind to ergosterol, a crucial component of the fungal cell membrane [22]. Azoles (fluconazole, voriconazole, and posaconazole) inhibit ergosterol biosynthesis [23]. Echinocandins directly inhibit β-1,3-glucan synthesis, resulting in a loss of cell integrity [24]. All these drugs are toxic to the host, e.g., nephrotoxicity and hemotoxicity from polyenes, hepatotoxicity from azoles, and headaches and hepatotoxicity from echinocandins. Also, similar to the antimicrobial resistance of bacteria, the long-term use of broad-spectrum antifungal agents has also resulted in the development of resistance in numerous fungal strains, making it difficult to cure [25]. Therefore, healthy host immune system is vital for defending against fungal infections.

The host immune response and modulation of the immune response play critical roles in fungal infections. MicroRNAs (miRNAs) have been reported to be involved in regulating immune system [26, 27]. The dysregulation of miRNA expression can lead to immunological dysfunction. In addition, aberrant expression of miRNAs has been confirmed to be implicated in various types of diseases. As a result, miRNA expression profiles can serve as biomarkers for the diagnosis, prognosis, and treatment response of certain diseases [28-30]. Furthermore, miRNAs have recently been found to play crucial roles in antifungal immunity. This review summarizes recent research progresses on the role of miRNAs in antifungal immunity. We believe that understanding the mechanisms of miRNAs-mediated antifungal immunomodulation would be helpful for developing more effective methods to combat fungal infections in the perioperative period.

The role of miRNAs in antifungal immunity

miRNAs and their role in immunity

miRNAs are short non-coding RNA molecules that range in length from 18 to 23 nucleotides. They are capable of regulating gene expression post-transcriptionally by reducing or preventing the translation of target messenger RNAs [31]. Primary miRNA transcripts are transcribed to form precursor miRNA molecules. As precursor miRNAs are exported to the cytoplasm, they are further processed into miRNA-5p and miRNA-3p by the Ribonuclease III domain of Dicer. To date, miRNAs have been identified to regulate most of all protein-encoding genes and play critical roles in varying biological processes and diseases. miRNAs target multiple mRNAs, and each messenger RNAs may be regulated by several miRNAs [32-35].

miRNAs are involved in regulating both innate and adaptive immunity. miR-155-dependent downregulation of MyD88 suppresses the inflammatory response [36]. Downregulation of miR-885-5p promotes nuclear factor-κB (NF-κB) pathway activation and immune recruitment in cutaneous lupus erythematosus [37]. Members of the miR-146 family act as key molecular brakes to coordinately control germinal center reactions to generate protective humoral responses without eliciting unwanted autoimmunity [38]. Immune defense plays an important role in fungal infections, and miRNAs regulate antifungal immunity by regulating immune response (**Table 1**).

Table 1. Differentially expressed microRNAs following fungal exposure

miRNA	Regulation	Fungal species	Exposure model	Function in antifungal immunity	Reference
miR-132-5p	↑	*C. albicans* *A. fumigatus*	DC (human)	miR-132-5p may enhance adaptive immunity by increasing T cell activation through the regulation of FKBP1B.	[64]
miR-140-5p	↑	*C. albicans*	RAW264.7	miR-140-5p may target TGF-β1 and promote inflammatory response through the MAPK signaling pathway.	[44]
miR-146a	↑	*C. neoformans*	THP-1	miR-146a negatively regulates NF-κB activation by targeting IRAK1 and TRAF6 and inhibits *C. neoformans*-induced release of inflammatory cytokines in monocytes.	[57]
	↑	*C. albicans*	THP-1	miR-146a inhibits the activation of p-IκBα and the translocation of NF-κB p65.	[55]
	↑	*A. fumigatus*	THP-1	miR-146a negatively regulates TNF-α and IL-6 secretion.	[56]
miR-124	↓	*C. albicans*	mice	miR-124 targets MCP-1 to reduce the excessive inflammatory response.	[60]
miR344b13p	↓	*A. fumigatus*	NR8383	miR-344b-1-3p inhibits macrophage autophagy by targeting TLR2.	[54]
miR-155	↑	*C. albicans*	DC (human)	miR-155 inhibits proinflammatory cytokine secretion by targeting NF-κ B p65 and BCL-10.	[22]
	↑	*C. albicans*	MH-S	miR-155 can target SOCS1 to enhance the inflammatory response.	[49]
miR-142-3P	↓	*A. fumigatus*	$CD4^+$ T	miR-142-3p inhibited $CD4^+$ Th1 activation and targets RICTOR to reduce IFN-γ expression.	[69]
miR-384-5p	↑	*C. albicans*	RAW264.7 and J774A.1	miR-384-5p can target PGC-1β and enhance the activation of NF-κB, MAPK, and AKT inflammatory signaling pathways.	[78]

Note: miRNA, microRNA; *C. albicans*, *Candida albicans*; A. fumigatus, Aspergillus fumigatus; DC, dendric cell; FKBP1B, FK506-binding protein 1B; TGF-β1, transforming growth factor-β1; MAPK, mitogen-activated protein kinase; NF-κB, nuclear factor-κB; TNF-α, tumor necrosis factor-α; IL, interleukin; IRAK1, interleukin receptor-associated kinase 1; TRAF6, tumor necrosis factor receptor-associated factor 6; MCP-1, monocyte chemoattractant protein-1; TLR, toll-like receptor; BCL-10, B-cell leukemia/lymphoma-10; MH-S, macrophages; SOCS1, suppressor of cytokine signaling 1; CD4, cluster determinant 4; RICTOR, rapamycin-insensitive companion of mTOR; IFN, interferon; PGC-1β, peroxisome proliferator-activated receptor gamma co-activator 1β.

Inflammatory responses

Fungi, when sensed by individual and synergistic pattern recognition receptors, initiate intricate signaling cascades in innate immune cells. These cascades mediate the production of pro-inflammatory cytokines and chemokines, promote the recruitment and phagocytosis of immune cells, enhance the generation of reactive oxygen species, and improve the killing capacity of the phagocytes. Additionally, these processes influence the activation of Th cell responses [39]. An appropriate level of inflammation is essential for controlling fungal infections, but excessive inflammatory response can damage normal tissues.

miR-155

miR-155, up-regulated in both lymphoid and myeloid cells, is associated with inflammation [40, 41]. miR-155 is one of the first miRNAs discovered to participate in antifungal immunity. Heat-killed *C.albicans* could up-regulate miR-155 in bone marrow-derived macrophages. NF-κB, an important regulator of pro-inflammatory genes, is indepensible for miR-155 transcription. The C-Type lectin receptor Dectin-1, a major pattern recognition receptor in antifungal immunity, is essential for recognizing unique component of fungi cell wall-β-glucan and controlling fungal infections. NF-κB may be the primary downstream molecule of Dectin-1 that regulates pri-miR-155 transcription in macrophages [42]. Spleen tyrosine kinase (SYK) is the upstream molecule of NF-κB. Daniel et al.

showed that Dectin-1 orchestrated miR155 upregulation in a SYK-dependent manner. By activating toll-like receptor (TLR) 2 or 4, *C. albicans* reduces the accumulation of mature miR-155, though the mechanism is unclear [43]. Large amounts of chitin produced by fungi can induce the expression of TLR2 and TLR4 as well as miR-155. Chitin treatment can inhibit the expression of suppressor of cytokine signaling 1 (SOCS1) and SH2 domain-containing inositol polyphosphate 5 phosphatase 1 (SHIP1), which are known targets of miR-155 [44]. Moreover, knock-down of miR-155 can suppress inflammatory factors and cell apoptosis through upregulation of SOCS1 [45]. According to these findings, miR-155 enhances the antifungal effect by promoting proinflammatory chemokines.

The anti-inflammatory effects of miR-155 have also been reported to be a protective factor [31]. Studies on fungal infections discovered its anti-inflammatory actions. The Dectin-1-SYK/Raf-1-mitogen-activated protein kinase (MAPK) signaling pathway is necessary for miR-155 induction by *C.albicans*. The miR-155 molecule also inhibited the expression of pro-inflammatory cytokines induced by *C. albicans* by targeting NF-κB, p65 and B-cell leukemia/lymphoma-10 [46]. In addition, *C. albicans* germ tube formation was markedly decreased when miR-155 was knocked down. On the contrary, the growth of germ tubes was greatly accelerated by transfection with miR-155 mimics [45]. By suppressing different targets, miR-155 plays opposing roles in antifungal immunity. miR-155 may promote the inflammatory response to enhance antifungal immunity through targeting SOCS1. By targeting NF-κB, p65 and B-cell leukemia/lymphoma-10, miR-155 exerts anti-inflammatory actions.

miR-140-5p

In response to heat-inactivated *C.albicans* stimulation, miR-140-5p is markedly elevated in RAW264.7 cells. miR-140-5p is involved in some biochemical processes such as inflammatory response, cytokine production, and cell apoptosis [47, 48]. Transforming growth factor-β1 may be a potential therapeutic target for treating *C. albicans* infection via miR-140-5p, which promotes inflammatory responses. Moreover, the MAPK signaling pathway might play a role in the regulation of TGF-β1 by miR-140-5p. Through RPS6KA1, vascular endothelial growth factor-A, and PRKAA1, miR-140-5p might participate in the mTOR signaling pathway, and through B-cell lymphoma-2, it might participate in the JAK-STAT signaling pathway [49]. The miR-140-5p can enhance the antifungal effects by activating inflammatory pathways.

miR-146a

As a member of the miR-146 family (miR-146a and miR-146b), miR-146a plays an important role in immune and inflammatory responses by negatively regulating the NF-κB signaling pathway in macrophages [50, 51]. The expression level miR-146a is increased in THP-1 cells treated with β-glucan. The interaction between Dectin-1 and β-glucan results in a long-lasting increase in miR-146a expression, which is dependent on Dectin-1-SYK-NF-κB and p38 MAPK pathways. In contrast, the levels of pro-inflammatory cytokines such as interleukin (IL)-6 and tumor necrosis factor-α (TNF-α) exhibit a rapid and transient increase. Overexpression of miR-146a can significantly suppress the production of IL-6 and TNF-α. miR-146a mimics inhibit the β-glucan-induced activity of p-IκBα and translocation of NF-κB p65. miR-146a also inhibits NF-κB promoter-binding activity [52]. Similar phenomena are observed when THP-1 macrophage-like cells are infected with *Aspergillus fumigatus* (*A. fumigatus*). The interaction between THP-1 macrophage-like cells and *A. fumigatus* results in a long-lasting increase in miR-146a expression, which is dependent on the p38 MAPK and NF-κB signaling. In *A. fumigatus*-challenged THP-1 macrophage-like cells, miR-146a overexpression can decrease TNF-α and IL-6 production. Conversely, miR-146a downregulation significantly enhances TNF-α and IL-6 levels. A study demonstrated that the crosstalk between miR-146a and the inflammation regulating p38 MAPK and NF-κB pathways might act as a fine-tuning mechanism in the modulation of the inflammatory response in macrophages infected with *A. fumigatus* [53]. The role of miR-146 in negatively regulating the NF-κB signaling pathway was also found in *Cryptococcus neoformans* (*C. neoformans*) infection. *C. neoformans* can induce elevated miR-146a expression by interacting with TLR receptors and negatively regulate NF-κB activation by targeting IL-1 receptor-associated kinase 1 (IRAK1) and TNF receptor-associated factor 6 (TRAF6), leading to the inhibition of *C. neoformans*-induced NF-κB activation and subsequent release of inflammatory cytokines from monocytes [54]. Immune cells play an anti-inflammatory role by promoting the expression of miR-146a after recognizing the different components of fungal cells. miR-146a negatively regulates antifungal immunity by inhibiting inflammatory pathways.

miR-124

miR-124 has been shown to play an important role in regulating the inflammatory response of the immune system [55]. By inhibiting pro-inflammatory cytokines, miR-124 mediates anti-inflammatory effects [56]. Fungal infections are the most common cause of sepsis, and acute kidney injury (AKI) is a frequent consequence. The activation of the pro-inflammatory response contributes to candidiasis-induced AKI. miR-124 mimics can improve the survival outcome in candidiasis-induced septic mice. Moreover, a significant downregulation was found in the serum levels of TNF-α, IL-1β, and IL-6 in septic mice treated with miR-124 mimics. Monocyte chemoattractant protein-1 (MCP-1) has been revealed to contribute to the pathogenesis of sepsis. After treatment with the broad-spectrum triazole antifungal agent itraconazole, the miR-124 expression significantly increased, and MCP-1 level decreased in the kidneys of septic mice. Additionally, over-expression of miR-124 reduced the MCP-1 expression and attenuated candidiasis-induced AKI in septic mice. Transfection with miR-124 mimics was equivalent to the effect of itraconazole in reducing excessive inflammatory response and renal lesions in septic mice [57]. Circular RNA homeodomain-interacting protein kinase 3 (circHIPK3), which is derived from the second exon of the HIPK3 gene, plays a vital role in the modulation of cell cycle, inflammatory response, and oxidative damage [58]. CircHIPK3 was reported to aggravate septic acute kidney injury (SAKI) inflammatory responses via miR124-3p/KLF6. Mechanically, circHIPK3 upregulates KLF6 expression by competitively binding to miR-124-3p, thereby promoting the binding of KLF6 and NLRP3, activating NLRP3/caspase-1-mediated pyroptosis, and eventually aggravating SAKI inflammatory responses. Downregulation of miR-124-3p attenuates the protective effect of circHIPK3 silencing on SAKI [59]. In summary, miR-124-3p can inhibit excessive inflammatory response to attenuate the fungi induced organ injury.

Th cell activation

It is vital for both innate and adaptive immune cells to collaborate in detecting and eliminating fungi. $CD4^+$ T helper cells are the most important cells of the adaptive immune response. Several effector cells can arise from naive $CD4^+$ T helper cells, including Th1, Th2, and Th17. The major $CD4^+$ T cells involved in the antifungal immune response are Th1 and Th17 [60]. Th1 cells promote phagocyte maturation and killing by secreting interferon (IFN)-γ, GM-CSF, and TNF. Since Th1 cells and Th2 cells inhibit the functions of each other, maintaining Th1/Th2 balance is vital to antifungal immunity.

miR-132

miR-132 is considered a relevant regulator of the immune response directly against *A. fumigatus* as it is differentially expressed in monocytes and dendritic cells upon stimulation with *A. fumigatus*, but not with lipopolysaccharide. Furthermore, miR-132 expression is associated with the activation of TLR2 or Dectin-1 but not TLR4 [61]. As a result of *C. albicans* infection, miR-132 expression in dentric cells is also up-regulated. On both the RNA and protein levels, miR-132-5p is validated to interact with immunologically relevant target gene FK506-binding protein 1B (FKBP1B). Moreover, a study observed an up-regulated trend of the target genes after silencing miR-132, although not statistically significant. Therefore, it is suggested that miR-132 fine-tuned the FKBP1B gene during fungal infection [62]. In a case-control study, miRNA-132 expression was significantly higher in the plasma of patients with allergic bronchopulmonary aspergillosis (ABPA) compared to patients with allergic asthma and severe asthma with fungal sensitisation and controls. miRNA-132 expression was positively correlated with serum IL-5 levels in ABPA patients [63]. The proliferation of T cells in mice was associated with FKBP1B [64]; when Th2 cells were activated, they released IL-5, which caused eosinophil activation, B cell differentiation, and mast cell degranulation [65]. Overall, a fungi-induced increase in miR-132 expression may enhance adaptive immunity by increasing T cell activation through the regulation of FKBP1B.

miR-142-3p

In patients with systemic lupus erythematosus, the activation of T cells is negatively regulated by miR-142-3p [66]. Similarly, it was observed that miR-142-3p inhibited $CD4^+$ Th1 activation after *A. fumigatus* infection [67]. $CD4^+$ T cells are the primary source of IFN-γ. By increasing the level of phosphorylated AKT *in vivo*, RICTOR can promote Th1 cell activation [68]. RICTOR was identified as a target of miR-142-3p in endothelial cells [69]. miR-142-3p expression is downregulated in *A. fumigatus*-activated $CD4^+$ T cells, and the downregulation of miR-142-3p leads to an increase in IFN-γ expression by promoting RICTOR expression. Thus, miR-142-3p negatively regulates antifungal immunity.

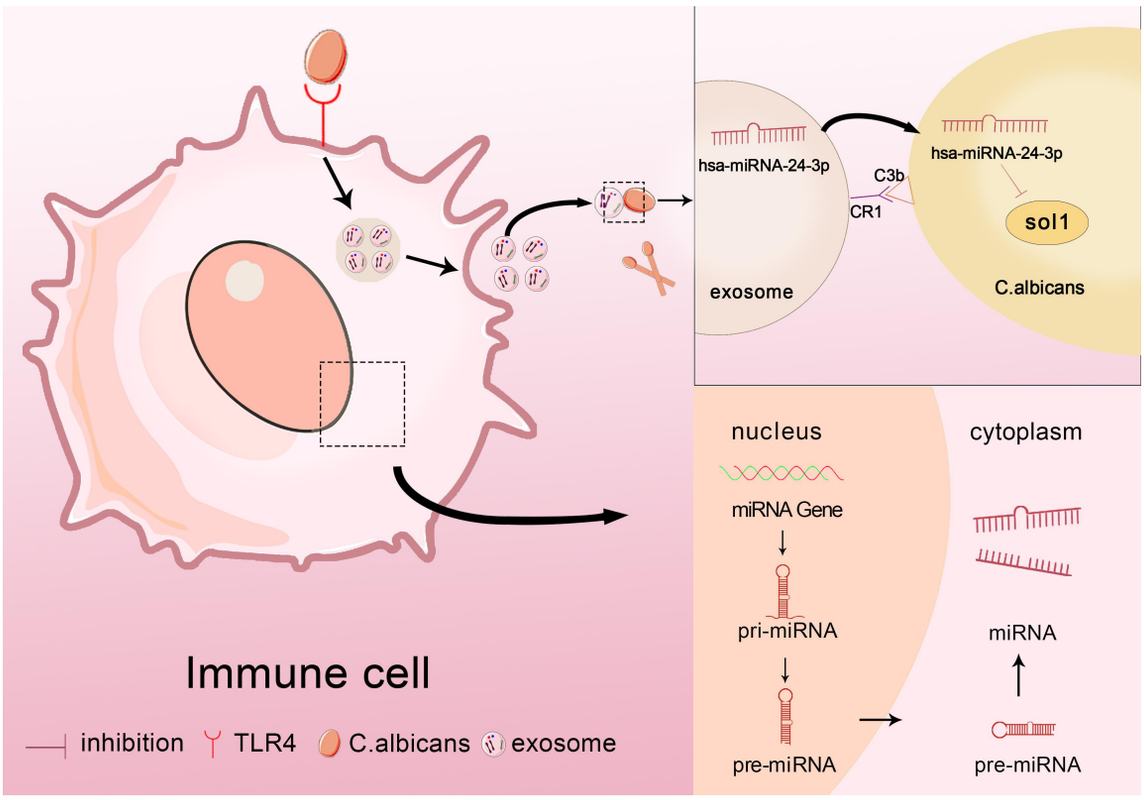

Figure 1. Interaction of *C. albicans* with miRNA-24-3p in host immune cell exosomes. Primary miRNAs are processed to form precursor miRNAs with hairpin structures in the nucleus. Precursor miRNAs are transferred to the cytoplasm and later cleaved into miRNAs of approximately 22 nucleotides in length. After *C. albicans* infection, soluble β-glucan and mannan in the cell wall of *C. albicans* bind to immune cell CR3 and TLR4 receptors, respectively, inducing the production and release of hsa-miR24-3p containing exosomes. The exosomes bind to *C. albicans* C3b via CR1, after which *C. albicans* can uptake hsa-miR-24-3p in the exosomes and inhibit the translation of sol1 mRNA, thus promoting the proliferation of *C. albicans*. *C. albicans, Candida albicans*; miRNAs, microRNAs; CR, complement receptor; TLR4, toll-like receptor; mRNA, messenger RNA.

But in a clinical study among hemato-oncology patients with profound neutropenia, free circulating miR-142-3p was significantly upregulated because of invasive aspergillosis. The reason for this difference may be related to the type of diseases [70].

Autophagy

Autophagy is an intracellular degradation mechanism that plays a crucial role in maintaining macrophage homeostasis, function, and metabolism and preventing immune senescence [71]. It is known to regulate inflammatory responses by mediating the production and secretion of cytokines, such as TNF-α and type I IFN [72]. Autophagy serves a dual role. On the one hand, it removes senescent organelles, converts them into substances such as amino acids for reuse, destroys intracellular pathogens, and promotes cell survival [73-75]. On the other hand, it induces cell death under specific caspase-independent conditions [76]. In specific tissue macrophages, autophagy enhanced NF-κB activity by sequestering A20 to boost antifungal immunity [77]. Consequently, the regulation of autophagy is a key for antifungal immunity [78].

miR-344b-1-3p

Recent studies have shown that miR-344b-1-3p negatively regulates antifungal immunity in controlling autophagy after *A. fumigatus* infection. miR-344b-1-3p can target TLR2 and negatively regulate the TLR2 signaling pathway, which is essential for activating macrophage autophagy [79, 80]. Infection of rat alveolar macrophages by *A. fumigatus* resulted in decreased miR-344b-1-3p expression. As a direct target of miR-344b-1-3p, TLR2 expression increased, thereby enhancing the activation of autophagy in macrophages. Although miR-344b-1-3p is only detected in rats at present, it is suggested that in the future, miR-344b-1-3p may be a potential therapeutic approach for aspergillosis [81].

Cross-species interaction of miRNAs

Exosomes are important signaling mediators for communication between immune cells that

Table 2. Diagnostic performance of microRNAs for invasive fungal diseases

Detection model	miRNAs	Sensitivity	Specificity	AUC	Type of disease	Reference
tetramiR	miR142-3p miR142-5p miR26b-5p miR21-5p	0.96	0.95	0.97	hemato-oncology patients with profound neutropenia	[65]
miR142-3p	miR142-3p	0.90	0.88	0.92	hemato-oncology patients with profound neutropenia	[65]
miR142-5p	miR142-5p	0.89	0.86	0.97	hemato-oncology patients with profound neutropenia	[65]
miR-26b-5p	miR-26b-5p	0.93	0.89	0.97	hemato-oncology patients with profound neutropenia	[65]
miR21-5p	miR21-5p	0.86	0.81	0.92	hemato-oncology patients with profound neutropenia	[65]
6-noncoding-RNA detection panel (4 miRNAs and 2 lncRNAs: NR_027669.1; NR_036506.1)	miR-215a mir -let- 7c miR-154 miR-193a	0.944	0.910	0.927	transplanted patients	[80]

Note: miRNA, microRNA; AUC, area under the curve.

can shuttle miRNAs to recipient cells. After infection, human immune cells release exosomes to coordinate the immune response. Exosomes are vesicles that contain various cellular components, including proteins, nucleic acids, and significant miRNAs [82, 83]. A recent study has demonstrated that miR-24-3p in exosomes released by human monocytes participates in cross-species evasion via *C. albicans* [84]. Hsa-miR-24-3p is the most common miRNA in exosomes released by human monocytes in response to the pathogenic fungus *C. albicans*. In the early stages of *C. albicans* infection, soluble β-glucan and mannans in *C. albicans* induce the production and release of hsa-miR-24-3p transport vesicles by binding to host blood monocyte complement receptor 3 and TLR4 receptors. These RNA-transport vesicles attach to the fungal surface via complement receptor 1 on the vesicle surface, after which *C. albicans* can uptake has-miR-24-3p. The host-derived hsa-miR-24-3p interacts with *C. albicans* sol1 mRNA to inhibit sol1 mRNA translation, which in turn accelerates the growth of *C. albicans* (**Figure 1**). Other miRNAs induced by *C. albicans* may also promote the survival of *C. albicans* in the host through unknown mechanisms, suggesting that miRNA inhibitors may be used to treat candidiasis.

miRNAs as potential biomarkers for fungal infection

Invasive fungal infections have high morbidity and mortality in perioperative period. In recent years, the incidence of fungal sepsis has been increasing. An accurate early diagnosis is beneficial to reducing the mortality and improving patient outcomes, but all the commonly used clinical methods for early diagnosis of fungal infections present some limitations. miRNAs with differential expression in cells, blood, and tissues have been potentially helpful for the ancillary diagnosis of fungal diseases (**Table 2**). Previous study detected differentially expressed miRNAs in peripheral blood samples from patients diagnosed with *Aspergillus* infection and found that miR-142-3p, miR-142-5p, miR-26b-5p, and miR-21-5p were significantly upregulated. After confirming a significant association between these four miRNAs and invasive aspergillosis, this group of miRNAs was subsequently labeled as a novel group of biomarkers supporting the diagnosis of invasive aspergillosis (the tetramiR group), after which the diagnostic power and accuracy of this group were evaluated. The receiver operating characteristic analysis demonstrated an area under the curve (AUC) of 0.97. Although the limited number of patients may introduce bias to determine the optimal diagnostic cutoff for this approach, there is potential value in using tetramiRs for diagnosing aspergillosis [70]. After fungal infections, miR-215 and miR-let-7c levels were up-regulated in the plasma of transplanted patients, while miR-154, miR-193a levels were down-regulated in their peripheral blood mononuclear cells (PBMCs). These four miRNAs were modeled with two lncRNAs which high expressed in PBMCs after fungal infections. The detection panel showed excellent diagnostic efficacy, with an AUC of 0.927 [85]. Another study compared the

levels of circulating miRNA between patients with paracoccidioidomycosis (PCM) and healthy controls and found that 8 miRNAs (miR-132-3p, miR-604, miR-186-5p, miR-29b-3p, miR-125b-5p, miR-376c-3p, miR-30b-5p, and miR-423-3p) were differentially expressed in the serum samples from PCM patients. The miR-132-3p expression was more than 10-fold higher in patients with PCM infection than in healthy individuals. The researchers concluded that given the relative difficulty in diagnosing PCM, these differentially expressed circulating miRNAs could be novel diagnostic biomarkers for PCM [86]. As noted earlier, miR-132 plays a role in ABPA detection and distinguishing ABPA from allergic asthma and severe asthma with fungal sensitisation. miR-132, a specifically elevated miRNA after fungal infection, can also be used as a potential diagnostic biomarker to distinguish bacterial and fungal infections.

Conclusion

This review summarizes differentially expressed miRNAs after fungal exposure and their roles on host immune responses. The expression of miRNAs varies in different cells after fungal infections, and both species and morphology of the fungi affect miRNA expression. These differentially expressed miRNAs regulate the host immune response after fungal exposure through different mechanisms. miR-155 exerts pro-inflammatory and anti-inflammatory effects by targeting different signaling pathways. miR-146 inhibits the expression of inflammatory cytokines and has an anti-inflammatory effect on antifungal immunity. miR-384-5p targets peroxisome proliferator-activated receptor gamma co-activator 1β (PGC-1β), enhancing the activation of NF-κB, MAPK, and AKT inflammatory signaling pathways, thereby exacerbating *C. albicans*-induced acute lung injury [87]. Moreover, some miRNAs prevent organ damage by suppressing excessive inflammatory responses after fungal exposure. Differentially expressed miRNAs are also involved in regulating other immune response processes. miR-344b-1-3p can regulate cellular autophagy after *A. fumigatus* exposure. *C. albicans* can induce the release of exosomes from the host and use miR-24 in exosomes to achieve accelerated growth. In addition, differentially expressed miRNAs, such as miR-132, can contribute to early diagnosis of fungal infections.

The detection technology of miRNAs has been improved. Although many articles have demonstrated miRNA expression profiles after fungal exposure, there is currently a limited number of in-depth studies on the mechanisms by which miRNAs are involved in the immune response. Understanding the regulation mechanism of miRNA in antifungal immunity can help us to deepen the understanding of fungal infections and host immunity, as well as offer potential novel therapeutic targets for fungal infections.

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