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Difficult airway management in patients with laryngeal tumor: Case series and systematic review

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Highlights

- SEEK^{flex} (Safe Easy Endotracheal Kit-flexible) is a modified introducer, which provides a simple and rapid way for intubating patients with laryngeal tumors.
- With its non-invasive and gentle approach, SEEK^{flex} minimizes patient discomfort, enhancing the overall patient experience.
- Flexible fiberoptic bronchoscope remains the most frequently used tool for managing difficult airways.

Abstract

Airway management in patients with laryngeal tumor presents significant challenges and risks. SEEK^{flex} (Safe Easy Endotracheal Kit-flexible) is a modified introducer developed by our team for the intubation in severe COVID-19 patients. Here, we present 4 cases where SEEK^{flex} facilitated tracheal intubation in patients with laryngeal tumors underwent surgeries and achieved a definitive airway. A systematic review of MEDLINE, EMBASE, CINAHL, and Web of Science databases was also performed using the keywords such as “laryngeal tumor”, “airway management” and “anesthesia” to identify the reports on airway management techniques for patients with laryngeal tumors. 14 papers involving 17 patients were retrieved. All the cases reported positive patient outcomes, though there were instances of intubation failure after general anesthesia. Despite increased availability of basic airway management techniques and various types of intubation tools, challenges persist, especially in patients with pre-existing severe airway obstruction. SEEK^{flex} provides a simple and rapid solution for intubating patients with laryngeal tumors, which ensures a clear airway for patient safety.

Keywords: SEEK^{flex}, laryngeal tumor, airway management, anesthesia

Introduction

Laryngeal tumors include cancers, papillomas, sarcomas, chondromas, hemangiomas and other lesions, and the patients with laryngeal tumors who undergo surgery (such as a tracheotomy, laser resection, tumor excision or biopsy) may experience difficulty airway [1]. In addition, cysts may be encountered in the glottic area, which may complicate tracheal intubation. In

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the patients with laryngeal tumors, ventilation or intubation difficulties should be anticipated. The risk of acute airway emergencies, often referred to as "Can't Intubate, Can't Oxygenate" scenarios, is particularly high during the postoperative period [2]. According to a survey, unanticipated difficult airways could account for up to 25% of anesthesia-related fatalities [3, 4]. Therefore, anesthesiologist should conduct a thorough preoperative assessment and plan for complete airway obstruction upon the induction of general anesthesia [5, 6].

Prior to surgery, anesthesiologists need to design a tailored airway management plan based on the patient's condition and their proficiency with airway tools [7]. There is a wide variety of tools used for tracheal intubation for the patients with laryngeal tumors, with flexible fiberoptic bronchoscope guided intubation as the most widely used technique (**Table 1**). However, flexible fiberoptic bronchoscopy has many drawbacks, such as patient intolerance, poor visualization due to airway secretions or blood, haemodynamic instability, high demands on the anesthesiologist 's operating skills and long learning cycles, which limit its widespread application in clinical practice [8-10].

Our group has developed a new intubation tool - Safe Easy Endotracheal Kit-flexible (SEEK^{flex}) - a modified introducer initially for the intubation of critically ill patients with COVID-19 [11]. SEEK^{flex} is a new type of disposable tracheal introducer, and its features and advantages and comparison with other tools have been summarized [12, 13]. We have successfully demonstrated the efficacy of SEEK^{flex} in managing difficult airway during awake tracheal intubation and bronchoscopic balloon dilation [12, 13]. The purpose of this report is to present 4 cases where SEEK^{flex} was utilized for patients with severe vocal and proximal tracheal obstruction due to laryngeal tumors in the awake state. Moreover, this report provides a systematic review of the tracheal intubation approaches for managing difficult airways attributed to laryngeal tumors.

Case presentation

Case 1

A 29-year-old male, weighing 70 kg, with no history of smoking or alcohol consumption, underwent an extended local excision for laryngeal cancer 10 months ago. He was scheduled for radical laryngeal cancer resection and neck debridement. Preoperative evaluations revealed no abnormalities or metastases in the surrounding lymph nodes. The patient was classified as Malampatti class II, exhibited no apnoea or major depressive symptoms, and had normal neck flexibility. Routine non-invasive blood pressure, ECG and SPO_2 monitoring was performed. Dexamethasone (5 mg), midazolam (1 mg), sufentanil (20 μg), dezocine (5 mg), propofol (80 mg), cis-atracurium (15 mg) were administered for general anaesthesia, followed by preoxygenation and routine intubation using video laryngoscopy (Zhejiang UE Medical Corp) and endotracheal tube with stylet. The glottis was not seen on video laryngoscop and conventional intubation failed, followed by a drop in SPO_2 from 100% to 89% and an increase in heart rate from 65 to 120 beats/min. At the same time, the anesthesiologist immediately performed face mask ventilation and called other physicians, which was effective. After SPO_2 returned to 100%, intubation was successfully performed using video laryngoscopy combined with intubation using SEEK^{flex} [12]. Following this, SPO_2 and heart rate were stabilized after oxygen delivery via a 5.0 mm diameter tracheal tube. Anaesthesia was continued with inhaled sevoflurane and infusions of propofol and remifentanil. The patient regained consciousness at the end of the procedure with no adverse effects or sequelae, and the postoperative follow-up was normal. Refer to **Supplementary video 1**.

Case 2

A 68-year-old male, weighing 65 kg, with a 40-year history of smoking and a 4-year history of hoarseness, was scheduled for a vocal cord tumour resection. The preoperative physical examination was unremarkable. The patient was classified as Malampatti class III and exhibited no apnoea or major depressive symptoms. Routine non-invasive blood pressure, ECG and SPO_2 monitoring were carried out. Dexamethasone (5 mg), midazolam (1 mg), sufentanil (15 μg), dezocine (3 mg), propofol (65 mg), and cis-atracurium (12 mg) were administered as general anesthesia, followed with preoxygenation and intubation by video laryngoscopy (Zhejiang UE Medical Corp) combined with intubation using SEEK^{flex} [12]. Although the glottis was not visible with the video laryngoscope, SEEK^{flex} facilitated access to the airway. A 6.0 mm diameter tracheal tube was successfully inserted into the airway along the SEEK^{flex}. SPO_2 was maintained above 96% throughout the surgical procedure. Anaesthesia was continued at the end of induction with inhalation of sevoflurane and infusion of propofol and remifentanil. The patient regained consciousness at the end of the procedure without any adverse effects or sequelae, and postoperative follow-up was normal. Refer

Table 1. Case reports of airway management in patients with laryngeal tumours

First author	Year	Age	Condition before surgery	Laryngeal tumor type	Airway management	Result
Wehner [16]	1982	M/55	Dyspnea	Laryngeal tumor	Awake blind nasal intubation	Successful but possibility of obstruction
North [17]	1986	F/65	Respiratory failure	Laryngeal tumor	Trans-nasal fiberscopy monitoring-guiding oro-tracheal fiber	Successful
Humle [23]	1999	F/51	Pronounced acromegalic features	Multiple papillomata	Cook Airway Exchange Catheter	Successful but having difficulty
Matsumoto [14]	2001	M/69	Dyspnea	Huge laryngeal cyst	Trans-nasal fiberscopy monitoring-guiding oro-tracheal fiber	Successful but having difficulty
Kale [24]	2014	M/64	Worsening shortness of breath	Obstructing laryngeal chondrosarcoma	Supraglottic jet ventilation	Successful
Tange [15]	2014	F/21-day-old	Dyspnea	Jawbone medullary hemangioma	A spiral tube using a guide wire and bronchofiber	Successful
Nakahira [25]	2014	F/20	Hoarseness	Laryngeal granulomas	Airway Scope® and video laryngoscope	Successful
Uzawa [19]	2016	F/93	Altered mental status	Subglottic tumor	Tracheal tube and tube introducer were difficult to insert	General anesthesia was failed
Zhang [18]	2018	M/54	Primary partial laryngectomy	Laryngeal cancer	Macintosh laryngoscopy	Fail, urgent tracheostomy, finally
Zhang [18]	2018	M/57	Inspirational apnea	Total laryngectomy	Fibroscope-guided conscious intubation	Successful
Zhang [18]	2018	M/63	Neck immobility	Recurrent laryngeal cancer	Fibroscope-guided nasal intubation	Failed, finally tracheostomy
Constable [20]	2018	M/52	Acute breathing difficulty	Advanced glottic cancer	'Over bougie' technique	Successful
Tsay [26]	2019	F/46	Hoarseness	Vocal Cord Granuloma	Oro-tracheal intubation (Shikani video-assisted intubating stylet technique)	Successful
Hewage [27]	2020	M/48	Progressive hoarseness, dyspnoea and dysphagia	Pedunculated vocal cord nodule	Awake fibreoptic intubation	Successful
Warnakulasuriya [21]	2020	M/52	Dyspnoea, stridor and loss of voice	Large obstructing trans-glottic tumour	Awake tracheal intubation with a videolaryngoscope	
Tsay [26]	2021	M/63	Hoarseness	Hypopharyngeal Cancer	Oro-tracheal intubation (Shikani video-assisted intubating stylet technique)	Successful
Bailey [22]	2021	M/43	Worsening shortness of breath	Transglottic squamous cell carcinoma	The TriTube® and Evone® ventilator	Successful

to **Supplementary video 2**.

Case 3

A 59-year-old male, weighing 70 kg and with a smoking history for over 30 years, was diagnosed with laryngeal cancer with vocal stenosis. He was scheduled to undergo radical laryngectomy for laryngeal cancer. Preoperative evaluation showed no abnormalities and no metastases in the surrounding lymph nodes. The patient was classified with Malampatti class II, exhibited no apnoea or major depressive symptoms. Routine non-invasive blood pressure, ECG and SPO_2 monitoring were carried out. Dexamethasone (5 mg), midazolam

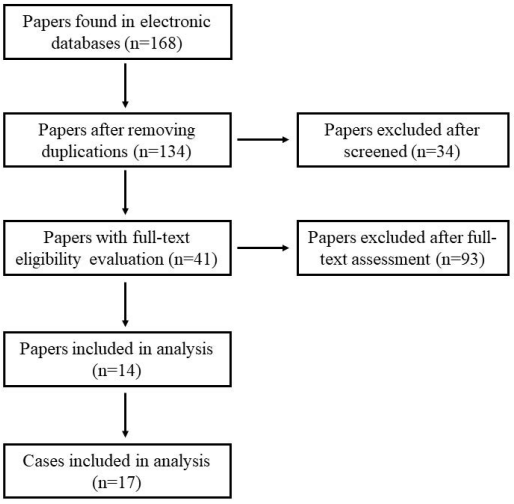

Figure 1. Bibliographic search of literature.

(1 mg), sufentanil (20 μg), dezocine (5 mg), propofol (80 mg), cis-atracurium (15 mg) were administered for general anaesthesia, followed with preoxygenation and intubation using video laryngoscopy (Zhejiang UE Medical Corp) and intubation using SEEK^{flex} [12]. The glottis was visible under the video laryngoscope and the SEEK^{flex} reached the airway. A 6.0 mm diameter tracheal tube was successfully inserted along the SEEK^{flex} into the airway. SPO_2 was maintained above 98% throughout the surgery. Anaesthesia was continued after induction with inhalation of sevoflurane and infusion of propofol and remifentanil. The patient regained consciousness at the end of the procedure, with no adverse effects or sequelae and, and postoperative follow-up showed no abnormality. Refer to **Supplementary video 3**.

Case 4

A 66-year-old woman, weighing 40 kg, with dysphagia for one year, was scheduled for radical tonsillectomy following the discovery of a tonsillar tumour by electronic laryngoscopy. The preoperative physical examination showed no significant findings. The patient was classified as Malampatti class II with apnoea symptoms. Routine non-invasive blood pressure, ECG and SPO_2 monitoring were performed. General anesthesia was administered with dexamethasone (5 mg), midazolam (1 mg), sufentanil (10 μg), dezocine (3 mg), propofol (40 mg), cis-atracurium (8 mg), followed by preoxygenation and intubation via video laryngoscope (Zhejiang UE Medical Corp) in combination with the intubation using SEEK^{flex} [12]. The glottis was visible under the video laryngoscope, and the SEEK^{flex} reached the airway. A 6.0 mm diameter tracheal tube was successfully inserted into the airway along the SEEK^{flex}. SPO_2 was maintained above 96% throughout the surgery. Anaesthesia was continued at the end of induction with inhalation of sevoflurane and infusion of propofol and remifentanil. The patient regained consciousness at the end of the procedure without experiencing adverse effects or sequelae, and the postoperative follow-up was normal. Refer to **Supplementary video 4**.

Results

Literature search

In our search, we identified 168 articles. After removal of duplications, 134 records were reviewed based on inclusion criteria (**Figure 1**). After removing 93 duplications, 41 abstracts were determined suitable for full-text evaluation.

Study characteristics

14 papers including 17 cases published between 1982 and 2022 discussing the airway management of laryngeal tumors were included in the review. Two of the included papers were in Japanese, but their abstracts revealed sufficient clinical information to be included in the review [14, 15]. The most frequent reasons for exclusion were failing the predetermined inclusion criteria, and inability to obtain detailed patient information. A total of 17 patients were included in this review. Results are summarized in **Table 1**.

The patients with difficult airway had different kinds of laryngeal tumors, including: laryngeal tumor (5 patients), glottic tumor (4 patients), multiple papillomata (1 patient), huge laryngeal cyst (1 patient), laryngeal chondrosarcoma (1 patient), jawbone medullary hemangioma (1 patient), laryngeal granulomas (1 patient), vocal cord granuloma (1 patient), pedunculated vocal cord nodule (1 patient), and hypopharyngeal cancer (1 patient) [16-27]. The techniques used for intubating these patients fell into three categories: flexible fiberoptic bronchoscope (5 patients), laryngoscope (11 patients), and jet ventilation (1 patient) [14-27]. Among the patients who were incubated with laryngoscope, various introducers were applied, including exchange catheter and over bougie [20, 23]. Most of the published cases reported that the patients were successfully intubated, except three patients had failed intubation and two had difficult intubation [14, 18, 19, 23]. In 2018, Zhang et al. reported two cases where patients experienced ventilation difficulties with decreased oxygen saturation after the induction of general anesthesia, who were eventually resuscitated

with a tracheostomy [18]. In addition, Uzawa et al. reported one case where patient got into the "cannot ventilate, cannot intubate" situation after the induction of general anesthesia, and finally the patient regained consciousness after airway maintenance efforts [19]. The use of flexible fiberoptic bronchoscope and video laryngoscopy in these failed intubation cases implies that these intubation tools have certain shortcomings and underscores the need for improved methods. Possible reasons for failure include inadequate handling skills, obscured visual fields, and inability to visualize the glottis.

Discussion

In otorhinolaryngology head and neck surgery, ensuring airway safety is the key to anaesthetic management, necessitating comprehensive preoperative airway assessment [28-30]. Laryngeal tumors can lead to vocal stenosis, difficult vocal exposure and scar contracture of previous incisions, often resulting in a challenging airway [31-34]. Therefore, it's imperative to devise a safe airway management plan in anticipation of these difficulties. There are many tools available for difficult airway management, including video laryngoscopes, flexible fiberoptic bronchoscopes, lighted or optical stylets, supraglottic airway devices, and assisted introducers [28, 29]. However, in clinical practice, all these tools have their own certain disadvantages and limitations.

The role of the fiberoptic bronchoscope in the management of difficult and failed intubations has been widely recognized [35]. However, several drawbacks of fiberoptic bronchoscopy hinder its wide application, including high operational proficiency skill requirements, poor visibility due to secretions or blood, time-consuming multiple-attempt procedures, poor patient tolerance, and hemodynamic instability caused by repeated disturbance of the vocal cords and nearby tissues. Such excessive stimulation may lead to significant psychiatric distress and additional cardiovascular issues for patients [8-10]. The use of supraglottic airway devices in airway management for patients with laryngeal tumors is somewhat limited, as tumors may prevent the supraglottic airway device from providing oxygen to the patient [36]. Another intubation tool, the video laryngoscope, usually paired with a stylet for tracheal intubation, makes it difficult to insert a tracheal tube after several attempts, particularly when the epiglottis is visible but not the vocal canal, or when the vocal canal is too narrow [28]. Subsequently, introducers emerged as an aid, such as the Frova intubation introducer, offering a high first-attempt success rate of intubation due to the stiffer material of the catheter [37, 38].

SEEK^{flex}, a novel disposable probe intubation kit developed from our initial intubation kit for COVID-19 patients, is an easy intubation and extubation device that can aid the intubation of any tracheal tube [11]. SEEK^{flex} is structurally and functionally similar to the Airway Exchange Catheter and the Frova Intubating Introducer, but has its own advantages. Its flexible design not only accommodates a broader range of functions but also offers a more cost-effective solution compared to the aforementioned devices; additionally, SEEK^{flex}'s user-friendly nature allows for operation by a single individual and facilitates ease of learning, marking it as a valuable tool for medical practice [12, 13, 39, 40]. Furthermore, based on the features and functions of SEEK^{flex}, we have designed a novel "Twelve-Step" strategy for awake tracheal intubation with video laryngoscope and SEEK^{flex}, which was effectively applied in patients with cervical spinal tumor [12]. This strategy integrates various approaches to manages difficult airway in tracheal, enhancing the success rate of intubation in patients with foreseeable airway complications and is recommended for challenging airway scenarios [29, 41-43].

We report 4 patients with laryngeal tumors who were successfully intubated using video laryngoscope and SEEK^{flex} in this review. This method not only ensured successful intubation but also resulted in more stable haemodynamics and less injury during induction of anaesthesia, due to the softer and slimmer profile of SEEK^{flex} compared to that of fiberoptic bronchoscopes, offering better patient tolerance [10, 12]. According to literature review, 3 patients of the 17 screened cases had failed intubation with fiberoptic bronchoscopes and video laryngoscopy, leading to a transient oxygenation failure. Guidelines by the American Society of Anesthesiologists, the Difficult Airway Society of Great Britain and Ireland, and the Canadian Airway Focus Group emphasize the importance of sustaining adequate tissue oxygenation [7, 44-49]. The Canadian Airway Focus Group difficult airway guidelines state underscore the critical importance of maintaining adequate tissue oxygenation, advising that airway management strategies should prioritize ensuring sufficient oxygenation and ventilation over tracheal intubation alone [46]. Notably, SEEK^{flex} not only facilitates rapid and secure endotracheal intubation but its outer catheter, equipped with multiple small vents, can serve temporarily as a mini-tracheal tube to sustain oxygenation [12, 13].

Awake tracheotomy is a frequently utilized technique for patients with laryngeal tumors [18]. This technique is associated with increased harm and discomfort for the patient, in addition to being more hemodynamically provocative. During elective surgery for laryngeal tumor, jet ventilation is sometimes used to maintain oxygenation [24]. However, in the case of near-complete airway blockage, jet ventilation poses an unacceptable risk of volutrauma, barotrauma, pneumothorax, hyperventilation, and stomach insufflation [50].

SEEK^{flex} offers a less invasive approach, minimizing patient discomfort through its gentle handling. Recent reports suggest that video laryngoscopy combined with introducer-guide enhances the success rate of first-attempt intubation due to the rigidity of the catheter material [29, 51, 52]. Compared to Frova intubating introducer and Airway Exchange Catheter, SEEK^{flex} mitigates some of their limitations, such as operational complexity, long learning curve and high cost [12, 13].

SEEK^{flex} also has its limitations. Structurally, lacks an integrated light source or a miniature camera, necessitating its use alongside a video laryngoscope for tracheal intubation. From a practical standpoint, if the patient's mouth opening is too small to accommodate video laryngoscope, SEEK^{flex} cannot be used for tracheal intubation either. In terms of safety and feasibility, there is a lack of randomized controlled trials comparing SEEK^{flex} with other intubation tools, leaving room for further research to establish its comparative effectiveness.

Conclusions

In this review, we have examined traditional tracheal intubation techniques for patients with laryngeal tumors and present a novel tool designed to facilitate intubation in difficult airway scenarios associated with laryngeal tumors. The tool is easy to use and has a high success rate of intubation, low airway irritation, and a low incidence of adverse effects. However, this study has its limitations, and as a new device, it still requires comprehensive testing to substantiate its effectiveness. Future efforts will focus on refining the trial design, building upon previous research, conducting additional studies, and evaluating its potential for clinical use.

Supplementary Material: Four videos of tracheal intubation in four cases.

Availability of data and material: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author contributions: Conception and design of the study: Zui Zou, Wenyun Xu, Chenglong Zhu. Conduct of the study and data collection: Chenglong Zhu, Wenyun Xu, Miao Zhou. Writing and review of the manuscript: Chenglong Zhu, Yongchu Chu. Study supervision: Zui Zou, Wenyun Xu.

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Progress of ultrasound-guided nerve block in foot and ankle arthroscopy

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Highlights

- Foot and ankle arthroscopic techniques are vital for diagnosing and treating foot and ankle disorders.
- Ultrasound-guided nerve blocks in the foot and ankle provide precise nerve selection.

Abstract

Foot and ankle arthroscopy frequently results in severe perioperative swelling and pain. The ultrasound-guided nerve block technique stands out for its ability to offer reliable and potent pain relief. This technique not only promotes early functional exercise, but also realizes enhanced recovery after surgery, which has demonstrated significant advantages in the realm of foot and ankle arthroscopy. In recent years, blocking techniques targeting different nerve planes have been reported to expand the options available for clinical use. This article primarily describes the current application of foot and ankle arthroscopy, detailing various local nerve blocks under innervation and ultrasound guidance. By doing so, this review intends to provide insights for the selection of clinical anesthesia in foot and ankle arthroscopy.

Keywords: Nerve block, ultrasound guidance, foot and ankle arthroscopy, high ankle block, sciatic nerve block

Introduction

The foot and ankle region is characterized by intricate interactions among muscles, tendons, and bones [1]. Initially, the foot and ankle arthroscopic techniques were applied to the ankle joint and then gradually expanded to small joints such as the first metatarsophalangeal joint and talar joint, as well as tendon (tendoscopy) [2]. Technological developments, alongside enhancements in arthroscopic equipment, and surgical methods, have significantly advanced the field of foot and ankle arthroscopy, which has evolved as a vital tool for both diagnosing and treating foot and ankle diseases.

Along with the increasing demand for surgery and rapid recovery, the focus on controlling postoperative pain, reducing the reliance on sedatives and opioids, and avoiding the side effects associated with spinal or general anesthesia has intensified [3, 4]. In recent years, ultrasound-guided nerve block has emerged as a noteworthy advancement in foot and ankle arthroscopy, which benefits of providing visual guidance and delivering precise analgesic effect.

Review of research progress

Innervation of the foot and ankle

The sensory and motor innervation of the foot and ankle is provided by branches derived from the sciatic nerve (SN) and femoral nerve (FN), which mainly include the tibial nerve (TN), deep

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Table 1. Optional nerve blocks for different arthroscopies

Foot and ankle arthroscopy	SNB	FNB	ACB	GPB	High ankle block	Classical ankle block	Modified deep peroneal nerve block
Ankle arthroscopy	√	√	√	√	√		
Tendoscopy	√	√	√	√	√		
Subtalar arthroscopy	√	√	√	√	√	√	
Foot mini-arthroscopy	√	√	√	√	√	√	√

Note: SNB, sciatic nerve block; FNB, femoral nerve block; ACB, adductor canal block; GPB, gastrocnemius plane block.

peroneal nerve (DPN), superficial peroneal nerve (SPN), sural nerve and saphenous nerve (SaN) [5].

The SN, recognized as the most substantial nerve in human body, emerges from the sacral plexus, and traverses the pelvis region through the inferior foramen of the pyriformis muscle, descending into the gluteal region. Proceeding beneath the gluteus maximus, the nerve intricately passes sequentially through the obturator internus, flanking the upper and lower segments of trapezius. It then aligns with the posterior boundary of the vastus muscle, eventually extending towards the lower limb, specifically to the semitendinosus, semimembranosus, and biceps femoris muscle. Before reaching the popliteal fossa, the SN divides into TN and common peroneal nerve (CPN), which innervates all the muscles of the calf and foot as well as skin sensation in the calf and foot except for the area innervated by the SaN [6]. The TN, as a direct extension of the SN, progresses along the posterior part of the calf, nestles between the layers of superficial-deep muscles, and bifurcates into the medial and lateral plantar nerves just posterior to the medial ankle. The muscular branch is distributed to the posterior calf muscle groups. The cutaneous branch encompasses the medial sural cutaneous nerve, which extends sensation to the posterior lateral calf and plantar aspect of the foot [7]. The CPN descends along the upper outer edge of the popliteal fossa, passes through the inner edge of the biceps femoris to the posterior side of the fibular head, bypasses the neck of the fibula, and then goes forward through the beginning of the peroneus longus muscle, and divides into two terminal branches, SPN and DPN. The sural nerve, formed by the conjunction of a cutaneous medial branch from the TN and a lateral cutaneous branch from the CPN, innervates the lateral border of the plantar aspect of the foot and the outer part of the heel. This includes sensory control over the lateral aspect of the foot, the lateral ankle, the posterior lateral skin of the distal third of the calf, and the sensation of the fifth toe [8].

The FN originates from the lumbar plexus, descending along the lateral border of the psoas major muscle and the iliacus muscle. It travels beneath the deep surface of the inguinal ligament to reach the femoral triangle, with a muscular branch that distributes to the anterior group of the thigh muscles, including the pubococcygeus muscle, the suture muscles, and the quadriceps muscle. The cutaneous branch distributes to the skin of the anterior femur. Its terminal branch evolves into the SaN, a pure sensory nerve that traverses through the retractor canal. Accompanying the descending genicular artery, it surfaces from beneath the medial aspect of the knee joint. Here, the SaN navigates past the adductor magnus tendon and through the vastus medialis muscle, continuing subcutaneously. It then travels along with the saphenous vein from the knee to the ankle, providing sensory innervation to the medial part of the calf and the medial part of the foot [9].

Foot and ankle arthroscopy

Foot and ankle arthroscopy enables direct visualization of the ankle, subtalar joints, and adjacent structures through small incisions, which allows targeted lesion management while minimizing postoperative pain, complications, and facilitating quicker recovery. Anesthesia and analgesia for different arthroscopic procedures involve various nerve blocks based on the innervation and ultrasound guidance (**Table 1**).

Ankle arthroscopy

The ankle joint comprises the distal ends of the tibia and fibula as well as the talus. The anterior and posterior walls of joint capsule are thin and lax, complemented by ligamentous enlargements on both sides to bolster stability. Indications for ankle arthroscopy include bone and soft tissue impingement syndromes, arthrofibrosis, arthritis, osteochondral injuries, post-traumatic ossification and free bone, chronic synovitis, ankle instability, tarsal coalition, tarsal sinus pain, and hindfoot fracture [10]. In a comprehensive review involving 150 studies, Arshad et al. highlighted ankle arthros-

copy as a safe treatment with low overall complication rates and most of which are mild [11]. The standard techniques for ankle arthroscopy encompass anteromedial, anterolateral, and posterolateral approaches, with the anteromedial approach positioned posteromedially behind the tibialis anterior tendon, the anterolateral approach positioned posterolaterally to the third gastrocnemius muscle, and the posterolateral approach positioned between the Achilles tendon and the peroneal tendon [12].

Tendoscopy

Tendoscopy can be used to diagnose and treat disorders of the Achilles tendon, tibialis posterior tendon, bunion flexor tendon, and peroneal longissimus tendon, with indications for symptomatic tenosynovitis and tendon tears [13]. Stornebrink et al. evaluated surgical tendoscopy with a 2-mm diameter scope on cadaveric model of the posterior tibialis, peroneus brevis, and Achilles' tendons, and underscored tendoscopy's capability to provide a safe and efficient surgical view that was significantly less invasive compared to traditional methods [14]. For the Achilles tendoscopy procedure, patients were placed in the prone position, with surgical approaches including the posterior medial and the posterior lateral routes. The peroneal tendoscopy approach is located proximal and distal to the central region of the tendinopathy. Caution was advised during the establishment of the approach and the tendon resection process due to the risk of peroneal nerve injury [15].

Subtalar arthroscopy

The subtalar joint consists of the posterior articular surface of the talus and the calcaneus. The joint capsule is thin and lax, and surrounded by the anterior, posterior, medial, and lateral talocalcaneal ligaments. The development of subtalar arthroscopy was initially hindered by the constrained space within the joint, confining its primary usage to diagnostic purposes. However, its use has been progressively extended to therapeutic interventions. Lauf et al. after evaluating and treating 22 patients with tarsal sinus syndrome, reported that subtalar arthroscopy yielded favorable outcomes in the long-term follow-up and facilitated the motion restoration and recovery rate [16]. Furthermore, studies conducted by Rungprai et al. and Oshba et al. evaluated the outcomes of either arthroscopic or open joint fusion surgery, and found that patients who underwent arthroscopic procedures experienced shorter recovery time [17, 18].

The standard approaches for talar arthroscopy are anterolateral, central, and posterior approaches. The anterolateral approach is located approximately 1 cm anterior to the tip of the lateral ankle and 2 cm below the tarsal sinus. The central approach is located at the tip of the lateral ankle and anterior to the peroneal tendon. The posterior lateral approach can be found 1 cm below the tip of the lateral ankle and posterior to the peroneal tendon. It is important to note that establishing access through these approaches carries the risk of causing damage to the peroneal nerve branches, SPN, and peroneal tendon [19].

Foot mini-arthroscopy

Arthroscopy for the small joints of the foot has advanced with improvements in surgical equipment and innovative techniques broadening the scope of its applications while also minimizing complications. This form of arthroscopy encompasses procedures on the first metatarsophalangeal joint, the lesser metatarsophalangeal joint, tarsometatarsal joint, calcaneal dice joint, and intermetatarsal joint, with the arthroscopy of first metatarsophalangeal joint being the most widely applied [20, 21]. There are three approaches to first metatarsophalangeal arthroscopy: medial, dorsomedial, and dorsolateral. The medial dorsal and lateral dorsal approaches are localized to the medial and lateral sides of the extensor digitorum longus tendon, respectively, while the medial approach is positioned anteriorly and inferiorly to the terminal branch of the SPN [22].

Nerve blocking modalities

Sciatic nerve block (SNB)

Frequently used accesses comprise the parasacral approach, subgluteal space approach, anterior approach, and popliteal approach [23].

The hallmark para sacral SNB was first described by Mansour et al. in 1993, and involves blocking the SN distal to the sacrum's lateral edge and caudal to the sacroiliac joint [24]. This technique not only effectively block the branches of the SN, which include the TN and CPN, but also encompasses the posterior cutaneous nerve of the thigh as well as both sensory and motor functions of the buttocks. However, it is worth noting that it may produce postoperative incontinence if the parasacral approach SNB is bilateral [25]. The subgluteal space is a well-defined anatomical space between the anterior surface of the gluteus maximus and the posteri-

or surface of the quadratus femoris. Subgluteal SNB has a superficial depth of puncture entry, allowing ultrasound to more distinctly reveal the alignment and structural features of the SN. An anterior approach to the SNB targets the nerve at the proximal thigh, with research suggesting that the optimal position for ultrasound-guided anterior SNB involves externally rotating the hip joint by 45° and flexing the knee joint by 15° or 45° [26]. The advantage of the anterior approach is that it can be performed in the lying position to minimize discomfort associated with positional changes. However, the puncture point is very close to the femoral nerve, femoral vein, and femoral artery, and attention must be paid to avoid potential damage to these related structures.

Popliteal sciatic nerve block (PSNB) is performed for SN in the popliteal region, including TN and CPN. When carrying out PSNB, it is crucial to ascertain whether the SN has branched at the puncture site to avoid incomplete block [27]. Cutaneous innervation of the medial calf is provided by the SaN, which must be blocked separately to ensure complete anesthesia below the knee. SNB combined with SaN block can provide anesthesia for the entire foot and ankle surgery. However, popliteal blocks may result in calf muscle paralysis, foot drop, and more pronounced dyskinesia than distal ankle blocks, as well as weakness of knee motion, increasing the risk of ankle sprains and inpatient falls [28].

Femoral nerve block (FNB)

The FN consists of a lumbar 2-4 anterior branch of the posterior femur within the femoral triangle. It bifurcates into anterior and posterior divisions, each further branching into muscular and dermatomal segments. FNB is usually performed after the completion of SNB. The FN is generally located in a triangular, hyperechoic area located lateral to the femoral artery, on the surface of the iliopsoas muscle, which is usually hyperechoic and roughly triangular or ovoid. When performed, FNB results in the loss of quadriceps motor function (hip flexion, knee extension), inability to straighten the calf, loss of knee tendon reflexes, dullness or loss of sensation in the anterior femoral region, and may be associated with an increased risk of postoperative falls [29]. For procedures involving the foot or medial ankle, blockade of the SaN, an extension branch of the femoral nerve is essential. Besides, it has been noted that its effect can reach the distal tibial periosteum, the medial and ventral regions of the medial ankle capsule, and, in some cases, the medial region of the talar joint capsule [30].

Adductor canal block (ACB)

The anatomy of the adductor canal has been described in detail by JÆGer et al. [31]. The adductor canal, also known as Hunter's canal or the infraspinatus canal, is located in the anterior medial third of the thigh, nestled deep within the adductor muscle layer. The canal is surrounded by the vastus medialis, vastus intermedius, vastus longus, and vastus lateralis muscles. It is a tendinous channel of about 15-17 cm in length with a roughly triangular cross-section, the anterior wall of which is the tendinous plate of the vastus lateralis muscle straining between the vastus lateralis muscle and the vastus medialis muscle, covered by the suture muscle, the lateral wall of the vastus medialis muscle, as well as the posterior wall of the vastus longus and vastus lateralis muscles. The retractor canal contains the femoral artery, femoral vein, branches of the femoral nerve and the posterior branch of the obturator nerve (especially the SaN and the nerve innervating the medial femoral muscle), as well as lymphatic vessels and loose connective tissue.

In a study comparing the anesthetic analgesic effects of ACB versus FNB combined with SNB in posterior foot and ankle surgery, Joe et al. discovered that ACB significantly preserved quadriceps strength from 30 minutes up to 2 hours postoperatively and was not inferior to FNB in terms of pain scores, need for analgesia, and duration, making it an effective alternative to FNB for patients undergoing posterior foot and ankle surgery [32]. A majority of studies of ACB have focused on arthroscopic knee surgery or total knee arthroplasty [33, 34]. Nonetheless, given its lower muscular impact compared to conventional FNB, ACB is anticipated to gain broader acceptance and application in clinical practice.

Gastrocnemius plane block (GPB)

Due to the high incidence of nerve complications, including the potential nerve injury following the PSNB, coupled with anatomical observations showing that branches of the popliteal sciatic nerve either penetrate or are adjacent to the gastrocnemius muscle, it is theorized that administering local anesthetics at on the surface of the gastrocnemius muscle can achieve a similar effect as a PSNB [35-37]. Li et al. initiated the approach by conducting ultrasound-guided planar staining on the peroneal muscles of two amputated limbs destined for incineration, and the results of the staining

highlighted the common PN, the medial and lateral peroneal cutaneous nerves, as well as the TN below the peroneal muscle, successfully meeting anesthesia prerequisites [38]. Subsequently, a study involving 60 patients undergoing foot and ankle surgery demonstrated that GPB could provide good postoperative analgesia, reduce the use of opioids, and improve patient satisfaction.

Ultrasound-guided GPB is a novel approach for precise blockade of the tibial nerve, common peroneal nerve, and medial and lateral peroneal cutaneous nerves. Ma et al. suggested that postoperative analgesia for foot and ankle surgery should be provided by PSNB in combination with ACB [39]. Consequently, integrating GPB with a SaN block can offer safe and effective postoperative analgesia to patients.

Classical ankle block

An ankle nerve block involves five nerves: tibial, deep peroneal, superficial peroneal, peroneal, and saphenous [40]. The tibial nerve is found posterior to the tibial artery with block executed by positioning the probe in cross-section on the medial aspect of the calf. Ultrasound-guided techniques allow for selective blocking of the pudendal nerve while conserving the heel branch, thereby facilitating early post-operative walking. The DPN, lying superficially near the dorsalis pedis artery in the ankle, is blocked anteriorly at the anterior ankle joint in front of the tibia [28]. Located between the peroneus brevis muscle and the intermuscular septum of the distal lateral calf, the SPN emerges through the calf fascia to become the distal superficial nerve, which can be blocked either subfascially or immediately after puncturing the fascia. Furthermore, the PN, which innervates sensation in the lateral aspect of the foot, is in the same superficial fascial sheath as the lesser saphenous vein at the level of the ankle joint, and perivascular local anesthetics can be injected on either side of the lesser saphenous vein to produce an adequate block [40]. In the distal 1/3 of the calf, there is a fascial sheath encasing SaN alongside the saphenous vein. Extending from the posterior tibia to its medial side, the saphenous vein is locatable proximally and anteriorly to the ankle, permitting a focused block on the SaN [41].

Korwin-Kochanowska et al. conducted a comprehensive review including 55 randomized controlled trials and 1 systematic review for the optimal pain management regimen after bunion revision and concluded that ankle blocks were currently the preferred analgesic technique [42]. Similarly, Ravanbod et al. in a systematic review comparing the analgesic effects of local nerve blocks for bunion surgery, noted that ankle blocks were as effective as popliteal blocks in controlling postoperative pain [40, 43]. Given the impact of popliteal blocks on lower extremity motion, ankle blocks emerged as a superior choice. It should be emphasized that ankle blocks are predominantly applied in anterior midfoot surgery, with a cautionary note regarding their potential inadequacy for hindfoot procedures. If the surgery extends beyond the midfoot or requires a thigh tourniquet, studies have shown that a “double block” of the femoral and sciatic nerves can be used, which can also provide better surgical anesthesia and good postoperative pain control [9].

High ankle block

The high ankle block emerges as an advanced technique for surgeries situated around the ankle joint. For surgery around the ankle joint, SNB is widely used, but it affects calf motor function, delays postoperative functional exercise and ambulation, and poeses a higher risk of nerve injury [1, 35]. Addressing these concerns, Hofmann-Kiefer et al. proposed the concept of “high ankle block” for the first time and initially proved that blocking the SPN, SaN, and peroneal nerve through subcutaneous infiltration at a distance of 15-20 cm proximal to the ankle joint, combined with ultrasound-guided blocks of the DPN and the TN, could achieve the required nerve coverage [44]. Marko et al. shared findings at the 2023 Annual Meeting of the American Society of Regional Anesthesiology and Pain Medicine from a preliminary trial involving 17 patients undergoing foot and ankle surgery, which demonstrated noteworthy benefits in postoperative pain relief and motor recovery [45].

The high ankle block provides adequate anesthesia and pain management for ankle surgery and is less time-consuming than the distal SNB. Executed beneath the site of the “distal” SNB, this technique superiorly maintains the motor function of the lower leg, and helps to preserve ankle motion, allowing for early rehabilitation and fast patient recovery [45]. The block is particularly well suited for mild-to-moderate surgical patients who do not require delicate catheter-based long-term regional anesthesia, and the block is easy to administer and guarantees effective pain relief within the first 24 hours after surgery.

Modified DPN block

Nerves innervating below the plane of the ankle include the tibial, superficial peroneal, saphenous, peroneal, and DPNs. These nerves, often running alongside blood vessels and encased in the sheaths, navigate through confined spaces, rendering them susceptible to compression and injury [46]. Particularly, the DPN and the anterior tibial artery share a tight compartment at the front of the ankle joint, where they are prone to compression and trauma, potentially leading to anterior tarsal tunnel syndrome. Fu et al. altered the traditional DPN block site and instead used ultrasound guide to locate the dorsal pedicle artery in the proximal end of the second phalanx and metatarsal gap, and then performed a nerve block after determining that the DPN was located around the dorsal pedicle artery [47]. It was found that there was no significant difference between this block and the traditional anterior tibial block. The modified new block point could avoid narrowing the internal drug injection space and reduce the risk of compression, and the modified peroneal nerve block combined with the ankle nerve block could meet the anesthesia needs of foot surgery in the ankle plane.

Conclusion

Ultrasound-guided nerve blocks have become an important adjunctive analgesic technique for foot and ankle arthroscopy, significantly relieving patients' postoperative pain, facilitating their early functional exercise, and accelerating recovery. The foremost clinical justification for employing ultrasound guidance lies in its prowess to pinpoint the precise nerve location. By providing real-time and dynamic visualization of the needle and observation of the spread of the local anesthetic, this technique offers immediate feedback to the clinician, and therefore reduces the risk of unintentional intravascular injections and incorrect needle placement [48, 49]. The use of regional anesthesia has been promoted for its positive impact on patient comfort and safety, and advances in ultrasound technology have enabled anesthesiologists to perform more selective and precise nerve blocks.

In recent years, the concept of enhanced recovery after surgery has been widely proposed in clinical settings, emphasizing the need to minimize the preoperative wait time, incorporate perioperative multimodal analgesic programs, and carry out timely functional exercises, thus reducing the risk of complications and improving the patient recovery and satisfaction [50]. Within the framework of enhanced recovery after surgery, the precision of ultrasound-guided nerve blocks in choosing specific nerves becomes increasingly significant. Particularly for the foot and ankle procedures, understanding the relationship between the surgical site and its corresponding innervation area allows for potential substitution of higher-position blocks with sensory branch blocks. This tailored approach aims to minimize patient discomfort and expedite postoperative rehabilitation.

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Research advances in understanding the role and mechanism of pyroptosis in myocardial ischemia-reperfusion injury

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Highlights

Currently, ischemic heart disease ranks as the most prevalent form of primary heart disease. The risk of myocardial ischemia-reperfusion injury, along with its associated mortality, is notably rising among perioperative patients. Recognizing the underlying mechanisms of myocardial ischemia-reperfusion injury and identifying suitable treatments are crucial. Inhibitors targeting the key molecules involved in pyroptosis hold promise as potential therapeutic options for managing myocardial ischemia-reperfusion injury.

Abstract

Myocardial ischemia-reperfusion injury (MIRI) emerges when the restoration of blood flow fails to recover myocardial function following transient ischemia, marking a significant pathological challenge that adversely affects revascularization outcomes and patient mortality. This condition often occurs post-cardiac procedures, including cardiopulmonary bypass, angioplasty, primary percutaneous coronary intervention, and thrombolytic therapy. Over the last decade, researches have been pivotal in deciphering the pathophysiological underpinnings of MIRI, aiming to identify viable targets and therapeutics for mitigation. Among these, pyroptosis, a form of inflammatory, programmed cell death, has been recognized for its integral role in MIRI, interacting with various other mechanisms such as oxidative stress, calcium dysregulation, autophagy, ferroptosis, and apoptosis. This review delves into the mechanisms by which pyroptosis influences MIRI, discusses its impact on both cardiomyocytes and non-cardiomyocytes in MIRI, and highlights recent advancements in the development of inhibitors targeting key molecules involved in pyroptosis such as Nod-like receptor protein 3 inhibitors, Caspase-1 inhibitors, and traditional Chinese medicines.

Keywords: Myocardial ischemia-reperfusion injury, pyroptosis, Nod-like receptor protein 3

Introduction

Acute myocardial infarction (AMI) is characterized by acute myocardial necrosis resulting from various pathogenic factors, including coronary stenosis, coronary plaque rupture, and atherosclerosis. Due to its rapid progression, AMI can lead to a high incidence of severe complications and morbidity if not addressed promptly, making it a leading cause of death among patients with coronary artery disease globally [1-3]. Coronary artery disease ranks as the third leading cause of death worldwide, contributing to approximately 17.8 million fatalities each year [4]. Early coronary artery revascularization is crucial in treating AMI and

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minimizing infarct size. The main treatment strategies include percutaneous coronary intervention (PCI) and coronary artery bypass Grafting for managing ST-segment elevation AMI [5-7].

Nonetheless, a pathological condition known as myocardial ischemia-reperfusion Injury (MIRI) can occur, where, paradoxically, myocardial function fails to improve or even worsens after reperfusion, further aggravating the injury [8, 9]. MIRI often manifests immediately to within two hours post-PCI in myocardial infarction patients, with a marked decrease in postoperative diastolic function compared to pre-operative levels [10]. Factors such as the short duration between AMI onset and infarct-related artery revascularization, infarction in the inferior wall, reduced forward blood flow in the infarct-related artery (less than TIMI grade 1), multivessel lesions, and renal insufficiency heighten the risk of MIRI following primary PCI.

Conversely, pre-infarction angina might serve as a cardioprotective factor, mitigating the severity of MIRI [11]. MIRI is characterized by high morbidity and mortality and can lead to numerous complications, including myocardial stunning, the no-reflow phenomenon, and reperfusion arrhythmias [12-14]. MIRI significantly influences the efficacy of revascularization and the mortality among these patients. The currently acknowledged pathogenic mechanisms of MIRI encompass several theories and processes, including the leukocyte theory, calcium overload, elevated reactive oxygen species (ROS), endoplasmic reticulum stress, autophagy, and apoptosis [15]. However, the complete understanding of MIRI's mechanisms remains elusive, attributed to the myriad of contributing factors and the complexity of its underlying mechanisms.

Pyroptosis, a proinflammatory type of programmed cell death, has gained substantial interest in recent times. This process is triggered by inflammasomes and members of the cysteinyl aspartate-specific proteinase (caspase) family. It is marked by the rupture of the cell membrane and the consequent release of inflammatory factors, which intensify the inflammatory cascade. Pyroptosis accelerates many cardiovascular diseases, such as atherosclerosis, heart failure, myocardial infarction, and other disease processes [16, 17]. Therefore, elucidating the mechanism of pyroptosis may help alleviate MIRI by targeting this pathway.

Overview of pyroptosis

History of pyroptosis

Friedlander AM first documented that treating mouse macrophages with anthrax lethal toxin resulted in cell death accompanied by the release of cellular contents [18]. Following this discovery, Zychlinsky et al. observed that Shigella flexneri induced death in mouse macrophages through a mechanism akin to apoptosis [19]. Both studies highlighted a novel mechanism of cell death, distinct from traditional apoptosis, characterized by the secretion of cellular contents.

In 2001, D'Souza et al. introduced the term "pyroptosis", deriving from Greek roots to describe this phenomenon. Pyroptosis involves the rupture of the cell membrane and the release of inflammatory factors, intensifying the surrounding inflammatory response. This process visually resembles burning, hence the name "pyroptosis" [20]. As researches evolved, pyroptosis came to be defined as a form of proinflammatory cell death mediated by cysteine-aspartate-specific proteinase-1 (caspase-1), marking a significant advancement in our understanding of cell death mechanisms [21].

Following initial discoveries, subsequent researches identified that gasdermin protein D (GSDMD) serves as the ultimate substrate for caspase-1 and caspase-11/4/5, establishing pyroptosis as a form of programmed cell death predominantly triggered by the activation of GSDMD by the caspase family [22]. GSDMD acts as an executor, breaching the cell membrane to facilitate the release of inflammatory factors [16, 23]. In 2018, the Nomenclature Committee for Cell Death formally recognized pyroptosis as a type of regulatory programmed cell death. This process is characterized by the involvement of gasdermin protein family members, which perforate the cell membrane, leading to cell swelling and eventual rupture. This event is typically accompanied by caspase family activation and the consequent leakage of inflammatory factors, further elucidating the intricate mechanisms underlying pyroptosis [24].

Key molecules involved in apoptosis

Pyroptosis is orchestrated through the formation of inflammasomes, which trigger the cleavage and perforation of GSDMD and result in the proinflammatory cell death characterized by the release of interleukin-1β (IL-1β) and interleukin-18 (IL-18). The principal

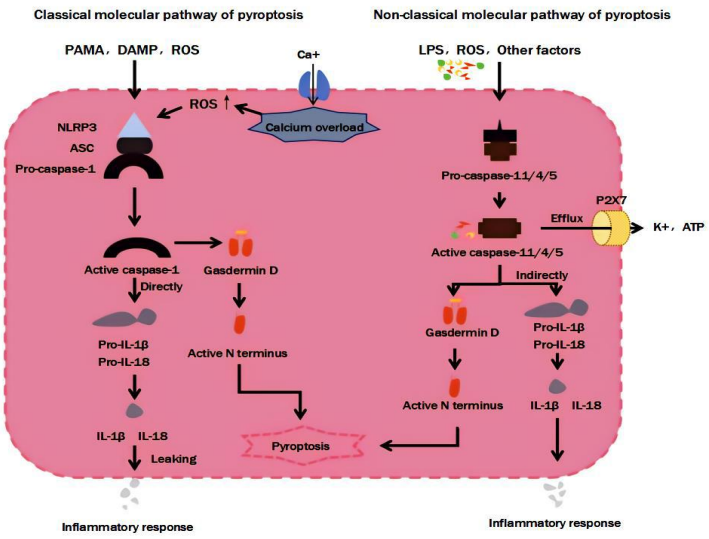

Figure 1. The process of pyroptosis. PAMP, pathogen-associated molecular pattern; DAMP, damage-associated molecular pattern; ROS, reactive oxygen species; LPS, lipopolysaccharide; ASC, apoptosis-associated speck-like protein; IL, interleukin; ATP, adenosine triphosphate.

proteins and molecules implicated in pyroptosis encompass the Nod-like receptor protein 3 (NLRP3) inflammasome, caspase-1, and GSDMD [25, 26].

Inflammasomes are multi-molecular complexes that are activated by various physical and chemical stimulus, such as pathogen-associated molecular patterns, ROS, and damage-associated molecular patterns [27, 28]. Activation occurs when such stimulus engages pattern recognition receptor on the cell surface, initiating a cascade of cell signaling events. This process leads to the activation of the inflammasome, which then orchestrates the assembly and activation of downstream signaling pathways, culminating in the release of inflammatory cytokines [29]. Inflammasomes encompass a variety of components, including CARD-domain containing 4, absent in melanoma 2, the Nod-like receptor (NLR) family pyrin domain containing NLRP1, NLRP3, and pyrin, among which NLRP3 is the most common.

The NLRP3 inflammasome is composed of three key elements: (1) the NLRP3 sensor molecule, (2) an apoptosis-associated speck-like protein (ASC) that includes a caspase-recruitment domain, and (3) the precursor form of cysteine aspartate-specific proteinase-1 (pro-caspase-1) [30]. NLRP3 facilitates the conversion of pro-caspase-1 into its active form, caspase-1, which plays a pivotal role in generating IL-18 and IL-1β and in cleaving the GSDMD protein [31, 32]. GSDMD, a member of the gasdermin protein family, is expressed across various cells and tissues in the cytoplasm. In its inactive state, GSDMD's N-terminus is bound to its C-terminal domain. Upon cleavage by caspase-1, the N-terminal fragment of GSDMD (GSDMD-N) separates and attaches to phosphoinositides on the cell membrane, subsequently perforating the membrane [33].

Classical molecular pathway of pyroptosis

The classical pathway of pyroptosis is orche-strated by Caspase-1 (See **Figure 1**). Upon exposure of pattern recognition receptors to pathogen-associated or damage-associated molecular patterns, NLRP3 becomes activated, facilitating the transformation of pro-caspase-1 into its active form, caspase-1. As previously discussed, GSDMD is subsequently cleaved by activated caspase-1 into two fragments: GSDMD-N and GSDMD-C. GSDMD-N forms pores ranging from 10–15 nm within the cell membrane's lipid layer, enhancing cell permeability. This increase in permeability leads to the leakage of intracellular inflammatory substances, amplifying the inflammatory response. Concurrently, the influx of extracellular fluid into the cells results in cell swelling, rupture and eventual lysis [34, 35]. Moreover, caspase-1 also cleaves pro-IL-1β and pro-IL-18, activating them into IL-1β and IL-18, respectively. These cytokines then escape through the pores formed by GSDMD-N, further propagating the inflammatory response in the surrounding tissue [36-38].

Non-classical molecular pathway of pyroptosis

The non-classical pathway of pyroptosis represents a divergence from the traditional caspase-1-mediated mechanism, relying instead on the activation of caspase-11/4/5 (See **Figure 1**). This pathway is triggered by bacterial lipopolysaccharide (LPS), ROS, and a variety of physical, chemical, and biological stimulus acting on caspase-11/4/5 [39]. Similar to caspase-1, activated caspase-11/4/5 can cleave GSDMD and facilitate the release of IL-1 and IL-18, contributing to the process of pyroptosis [40]. Additionally, caspase-11/4/5 plays a role in modulating the efflux of potassium (K^+) and adenosine triphosphate via the P2X7 membrane channel, thereby

mediating pyroptosis in target cells [41]. It is important to note that while caspase-11/4/5 does not directly target pro-IL-1β and pro-IL-18 for activation, it can indirectly influence and promote the release of these cytokines, further amplifying the inflammatory response associated with pyroptosis [42].

Other pathways of pyroptosis

Proteins within the gasdermin family exhibit highly conserved structural features, including C- and N-terminal domains, with the N-terminal domain acting as the functional executor responsible for inducing pyroptosis in target cells [43]. Traditionally, caspase-3/8 were not considered to impact GSDMD or to induce pyroptosis. However, current studies have revealed that certain molecular agents, such as chemotherapeutic drugs, can "trick" caspase-3 into cleaving Gasdermin E (GSDME), allowing the GSDME-N to perforate the cell membrane and effectively trigger pyroptosis in the target cell [33, 34].

Additionally, caspase-8, when influenced by factors like tumor necrosis factor-alpha, can cleave Gasdermin C (GSDMC) into GSDMC-N, which then perforates the cell membrane and mediates pyroptosis [44]. Liu et al. have also demonstrated that chimeric antigen receptor T cells can activate caspase-3 within target cells, leading to pyroptosis through the caspase-3/GSDME pathway [45]. Furthermore, the activation of the Gasdermin B (GSDMB) pathway has been shown to induce pyroptosis [46]. These novel mechanisms significantly broaden the understanding of pyroptosis, highlighting its complexity and the diverse roles of caspases and gasdermin proteins in cell death.

Role of pyroptosis in MIRI

Pyroptosis occurs in both cardiomyocytes and non-cardiomyocytes, significantly contributing to the progression of MIRI. During MIRI, the pyroptosis of various cell types, such as cardiomyocytes, fibroblasts, vascular endothelial cells, and macrophages, is triggered by mechanisms such as increased ROS, calcium overload, and an inflammatory response. This process intensifies the development of MIRI through multiple regulatory mechanisms, including mitochondrial dysfunction, altered energy metabolism, and oxidative stress. Pyroptosis interacts with MIRI and affect each other.

Xu et al. demonstrated that, in comparison to normal rats, the MIRI model group exhibited a higher rate of myocardial cell pyroptosis, an enlarged area of myocardial infarction, and an intensified inflammatory response. However, the use of NLRP3 inhibitors or the genetic knockdown of NLRP3 was shown to mitigate myocardial pyroptosis, reduce infarct size, and lessen the inflammatory response [47]. Similarly, Sandanger et al. found that, during myocardial MIRI, the combined effects of ROS and potassium (K^+) efflux could activate the NLRP3 inflammasome in cardiac fibroblasts, leading to the secretion of IL-1β and the subsequent pyroptosis of these cells [48].

Furthermore, Zhang et al. reported that the surge of ROS during MIRI stimulates the NLRP3 inflammasome in myocardial microvascular endothelial cells, inducing pyroptosis and thereby aggravating inflammation and myocardial damage in the affected area [49]. Moreover, Dai et al. demonstrated that microRNA-2a, carried by exosomes derived from M2 macrophages (M2D-exos), can mitigate MIRI by targeting the TXNIP and TLR4/NF-κB/NLRP3 signaling pathways [50]. In a related vein, Wang et al. observed that hypoxia/reoxygenation treatment prompts macrophages to adopt the M1 phenotype, which in turn mediates cardiomyocyte pyroptosis through miR-1a carried by exosomes [51]. Further research by Wang et al. uncovered that an increase in hypoxia-inducible factor-1 alpha can diminish MIRI by lowering mitochondrial ROS production and minimizing mitochondrial damage [52]. Additionally, Tian et al. found that preconditioning with isoflurane, especially when combined with captopril treatment over three days (as opposed to just one hour), significantly reduces MIRI by lessening oxidative stress and inflammation [53].

These findings collectively underscore the critical role of pyroptosis in both myocardial and non-myocardial cells, such as fibroblasts, vascular endothelial cells, and macrophages, is inextricably linked to MIRI. Thus, targeting pyroptosis across various cellular components emerges as a pivotal approach in the prevention and treatment of MIRI.

Relationship between pyroptosis and other MIRI-related mechanisms

Pyroptosis and oxidative stress

During MIRI, a significant increase in ROS occurs, especially in the early phases of reperfusion. These excessive ROS levels can lead to lipid peroxidation in cell membranes or trigger inflammatory responses, causing

cellular damage [54, 55]. Moreover, the surge in ROS amplifies oxidative stress, promotes apoptosis, and intensifies the severity of MIRI [56, 57]. Beyond contributing to oxidative stress, ROS also play a pivotal role in pyroptosis during MIRI. Shen et al. discovered that ROS could directly activate the NLRP3 inflammasome, thereby inducing pyroptosis [58]. Furthermore, ROS facilitates the activation and production of IL-18, which in turn promotes tissue inflammation and aggravates MIRI [59]. Pyroptosis itself can enhance ROS production through various mechanisms, including the disruption and impairment of mitochondrial function. Consequently, the interplay between pyroptosis and oxidative stress significantly contributes to the onset and progression of MIRI.

Pyroptosis and calcium overload

Calcium overload, often triggered by sodium pump dysfunction and an increase in ROS, is both a common cause and consequence of MIRI. This condition can disrupt the oxidative phosphorylation cycle and mitochondrial membrane potential, a well-acknowledged pathogenic mechanism in MIRI [60]. Researches have established a close link between calcium overload and pyroptosis. For instance, Wang et al. discovered in a rat MIRI model that calcium overload could initiate cardiomyocyte pyroptosis via the NLRP3/caspase-1 pathway. The application of ginsenoside, targeting the retinoblastoma susceptibility gene (Rb1) to mitigate calcium overload, was found to decrease myocardial pyroptosis and cellular damage [61]. Similarly, Zhou et al. demonstrated that inhibiting calcium overload could lessen pyroptosis in glioblastoma cells [62]. While the precise mechanism through which calcium overload directly influences pyroptosis remains unclear, there is an undeniable link between the two in the context of MIRI. Future research should delve into the reciprocal regulatory mechanisms between calcium overload and pyroptosis.

Pyroptosis, apoptosis, and programmed necrosis

The pathogenesis of MIRI is multifaceted, with apoptosis, pyroptosis, and programmed necrosis playing significant roles in its development [63]. Numerous studies have highlighted how these distinct forms of cell death may interact and impact one another, suggesting the presence of "crosstalk" between pyroptosis, apoptosis, and programmed necrosis, wherein caspase-8 plays a pivotal role [64-67]. As a protease, caspase-8 primarily governs apoptosis but is also known to mediate programmed necrosis [68, 69]. This dual function raises questions about the multifaceted roles caspase-8 may play in cell death processes. Recent research has further elucidated caspase-8's critical role in the non-classical pathway of pyroptosis. Upregulation of caspase-8 can suppress the expression of GSDMD by inhibiting the formation of ASC and pyroptosis [70]. These findings underscore the complex interplay between pyroptosis, apoptosis, and programmed necrosis, indicating that their interactions may significantly contribute to the progression of MIRI. Future research should delve into the potential crossover, superposition, or feedback mechanisms among these modes of cell death, aiming to better understand their collective impact on the onset and evolution of MIRI.

Drugs for targeted inhibition of cell death and amelioration of MIRI

NLRP3 inhibitors

MCC950 is a small molecule known for its selective inhibition of the NLRP3 inflammasome, effectively preventing the activation conformation of NLRP3 and, consequently, inhibiting both NLRP3 activation and pyroptosis [71, 72]. In a porcine model of MIRI, various doses of MCC950 significantly reduced both the area of myocardial infarction and the inflammatory response [73].

Colchicine, traditionally used in the clinical management of gout, has recently been identified as an effective NLRP3 inhibitor, showing promise in the prevention and treatment of MIRI [74, 75]. Colchicine targets tubulin which is crucial for the localization and assembly of the NLRP3 inflammasome, by irreversibly binding to it, thereby inhibiting microtubule formation and NLRP3 activation [76-79]. Studies in an AMI rat model demonstrated that nanoparticles loaded with colchicine markedly decreased NLRP3 and pyroptosis-related protein expression, reducing infarct size [80].

Metformin, a primary medication for type 2 diabetes, has also shown efficacy beyond diabetes, particularly in ischemia-reperfusion injuries affecting cardiovascular, liver, and kidney tissues [81-83]. Research by Zhang et al. revealed that metformin mitigates the inflammatory response in MIRI by activating AMP-activated protein kinase (AMPK) and suppressing NLRP3 inflammasome activation,

thereby offering cardioprotective benefits [84]. Additionally, metformin postconditioning in isolated rat heart perfusion and neonatal rat MIRI models inhibited NLRP3 inflammasome activation and reduced the expression of inflammatory markers such as tumor necrosis factor-alpha, IL-6, and IL-1β, subsequently decreasing the area of myocardial infarction [81].

INF4E (ethyl 2-((2-chlorophenyl)hydroxyl) methyl) acrylate), another effective NLRP3 inflammasome inhibitor, has been shown to reduce the activity of caspase-1 and NLRP3-ATPase [85, 86]. Mastrocola et al. demonstrated that pretreatment with INF4E diminished myocardial infarct size, improved myocardial contractility, and downregulated the expression of the NLRP3 inflammasome and GSDMD via the reperfusion injury salvage kinase pathway, thereby alleviating MIRI [85].

These findings underscore the potential of targeting NLRP3 inhibition as a key strategy for preventing and treating MIRI. However, further research is necessary to develop more specific, safer, and efficacious NLRP3 inflammasome inhibitors, alongside large-scale clinical trials to verify their clinical safety and effectiveness.

GSDMD inhibitors

GSDMD serves as the executor and pivotal effector molecule in pyroptosis, playing a crucial role in the release of downstream inflammatory factors such as IL-18 and IL-1β [87]. Consequently, compounds that target GSDMD have been developed, demonstrating potential therapeutic value across various disease models. Necrosulfonamide (NSA) is one such GSDMD inhibitor that binds directly to the C191 site of GSDMD, preventing its oligomerization and inhibiting its expression [88]. He et al. demonstrated that NSA treatment could suppress GSDMD expression and pyroptosis, thereby ameliorating cardiac dysfunction following ischemia/reperfusion injury in rats [89].

Another GSDMD inhibitor, dimethyl fumarate (DMF), acts by succinylating the C191 site of GSDMD, which also prevents its oligomerization [90]. Shi et al. found that DMF could diminish NLRP3 inflammasome activation and GSDMD expression through the regulation of protein kinase A signaling, reducing pyroptosis and the inflammatory response and offering relief in mouse models of autoimmune hepatitis [91]. While DMF's anti-inflammatory properties have been documented in various conditions, including LPS-induced sepsis, familial Mediterranean fever, and autoimmune encephalitis, its effects on MIRI have yet to be explored [92].

Trimetazidine, a known inhibitor of free fatty acid oxidation, offers myocardial protection in patients with diabetes, angina, and those undergoing PCI [93, 94]. A recent study suggests that trimetazidine can also target GSDMD to modulate pyroptosis. It plays a significant role in regulating the expression of the TLR4/Myd88/NF-κB pathway and the NLRP3 inflammasome [95].

Given GSDMD's central role in controlling the release of inflammatory factors during pyroptosis, targeting this molecule presents a promising approach to inhibit pyroptosis.

Caspase-1 inhibitors

Intriguingly, a clinical trial demonstrated that colchicine significantly dampens the activity of caspase-1 in monocytes and diminishes the secretion of IL-1β by these cells, thereby delivering cardioprotective benefits [75]. VX-765, a highly selective inhibitor of caspase-1, has shown promise in a mouse model of MIRI [96, 97]. The concurrent use of VX-765 with antiplatelet medications markedly decreased myocardial infarct size and enhanced cardiac systolic function [98].

Further researches have revealed that VX-765 not only reduces the secretion of IL-1β but also inhibits the release of lactate dehydrogenase, thereby mitigating MIRI [98, 99]. Carmo et al. discovered that VX-765 also shields isolated rat hearts via the reperfusion injury salvage kinase pathway [100, 101]. Additionally, α-1 antitrypsin (A1AT), another caspase-1 inhibitor, has been observed to downregulate caspase-1 expression upon intraperitoneal injection in a mouse MIRI model, significantly shrinking the area of myocardial infarction and enhancing ventricular remodeling [102-104].

These findings underscore that with a deeper understanding of the pyroptosis mechanism and the ongoing development of novel small-molecule drugs, a new generation of compounds targeting pyroptosis-specific mechanisms and MIRI is on the horizon. The advent of small-molecule compounds adept at specifically inhibiting pyroptosis holds substantial promise for the prevention and treatment of MIRI, heralding a significant advancement in cardiovascular disease management.

TCM compounds and monomers

Due to its holistic approach, encompassing multiple components, pathways, and targets, traditional Chinese medicine offers distinctive advantages in treating cardiovascular and cerebrovascular diseases, especially myocardial ischemia-reperfusion injury. Emodin, known for its anti-inflammatory and antioxidant properties, also inhibits GSDMD-mediated pyroptosis via the TLR4/MyD88/NF-κB/NLRP3 inflammasome pathway, thereby reducing myocardial cell damage in MIRI [104, 105]. Researches have highlighted that naringin and β-asarone can diminish pyroptosis by suppressing the expression of ASC, caspase-1, NLRP3, and GSDMD, consequently reducing infarct size in rat models of MIRI [106, 107]. Similarly, the cinnamoyl ethyl acetate extract offers protection against MIRI damage in rats by inhibiting the activation of the NLRP3 inflammasome and pyroptosis [108]. Li et al. demonstrated that apigenin treatment lowers the expression of caspase-1, NLRP3, and GSDMD in cardiomyocytes subjected to hypoxia/reoxygenation (H/R), decreasing pyroptosis incidence and providing myocardial protection [109]. Sun et al. found that pre-treatment with gastrodin in cardiac microvascular endothelial cells can obstruct pyroptosis via the classical pathway, alleviate inflammation, and reduce myocardial cell damage [110].

These studies illustrate that Chinese medicines and their monomers possess significant potential in combating cell pyroptosis and MIRI due to their pharmacological actions. Nonetheless, future efforts should aim at a more thorough investigation and translational research on the modulation of pyroptosis and the protective effects of traditional Chinese medicine against MIRI, paving the way for their early clinical adoption.

Anesthetic

In recent years, the cardioprotective effects of anesthetics on cardiovascular and cerebrovascular diseases have garnered increasing attention from researchers globally. Both intravenous and inhalational anesthetics have been shown to offer myocardial protection [111, 112]. Sevoflurane, a widely used inhalational anesthetic in clinical settings, has been recognized for its cardioprotective properties in various studies [110].

Dharmalingam et al. reported that pre-treatment with volatile anesthetics, including isoflurane and sevoflurane, can suppress ROS, thereby preventing oxidative stress during coronary artery bypass grafting [113]. Additional researches indicate that sevoflurane can also block the P2X7 ion channel on mitochondrial membranes, decrease the expression of NLRP3, ASC, caspase-1, and GSDMD, and reduce myocardial enzyme release, thereby playing a role in mitigating MIRI [114-116]. Deng et al. further revealed that sevoflurane can modulate autophagy via the AMPK/ULK1 pathway and inhibit NLRP3-mediated pyroptosis in cardiomyocytes, thus improving myocardial ischemia/reperfusion injury [117].

Dexmedetomidine, a highly selective α-2 adrenergic receptor agonist commonly utilized for perioperative sedation, has been found to protect against ischemia-reperfusion injury by enhancing myocardial function [118-120]. Zhong et al. and Wang et al. discovered that dexmedetomidine could mitigate MIRI in a rat model by downregulating miR-29b, activating FoxO3a, and reducing pyroptosis [121, 122]. While there is significant evidence to suggest that both inhaled and intravenous anesthetics have profound effects on the prevention and treatment of MIRI, there remains a scarcity of studies and mechanistic insights into how anesthetics improve MIRI by regulating pyroptosis [114, 123]. Further investigations into the specific targets and mechanisms by which anesthesia influences MIRI are crucial for advancing our understanding and therapeutic approaches.

Summary and outlook

MIRI is a multifaceted pathophysiological phenomenon influenced by numerous genes, molecules, cells, and tissues across different signaling pathways. This review delves into the role and mechanisms of pyroptosis in MIRI, summarizing the impact of various drug categories, including NLRP3 inhibitors, GSDMD inhibitors, caspase-1 inhibitors, anesthetics, and traditional Chinese medicines, on both MIRI and pyroptosis. Key pathogenic mechanisms of MIRI, such as calcium overload, disturbances in energy metabolism, oxidative stress, and autophagy, have been thoroughly investigated, highlighting their importance in modulating the onset and progression of MIRI. The contribution of pyroptosis to MIRI, especially the interactions between pyroptosis, MIRI mechanisms, and associated signaling pathways, remains a critical area for further research.

Most existing research on pyroptosis and MIRI concentrates on mitigating pyroptosis and improving MIRI outcomes by targeting the NLRP3 inflammasome, caspase family proteins, and key GSDMD targets. While the use of pyroptosis inhibitors in animal models of MIRI has shown promising results in reducing myocardial infarct size and enhancing cardiac function, the majority of these studies are confined to preclinical settings. The clinical application of drugs that inhibit pyroptosis-related proteins for MIRI treatment is limited, which restricts our comprehensive understanding of these inhibitors' effects in human clinical trials. Consequently, there is a pressing need for more clinical trials to corroborate the findings from basic research.

Based on current studies and available evidence, NLRP3 inhibitors, caspase-1 inhibitors, and traditional Chinese medicines emerge as potential therapeutic avenues for MIRI treatment. However, given the intricate nature of pyroptosis and MIRI, a singular focus on targeting either pyroptosis or MIRI may not suffice for effective prevention and treatment strategies. Instead, a multi-targeted and multi-mechanism approach to combination therapy may offer a more effective treatment paradigm for MIRI.

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Research progress of sphingosine 1-phosphate receptor 3 in the cardiovascular system

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Highlights

- Sphingosine 1-phosphate receptor 3 (S1PR3) promotes the proliferation of vascular endothelial cells and enhances barrier function.
- S1PR3 is a promising target for clinical treatment of cardiac ischemia-reperfusion, cardiac fibrosis and atherosclerosis.
- Fingolimod and other modulators of S1PR3 have shown therapeutic efficacy in phase I and II clinical trials for cardiovascular diseases.
- S1PR3 play crucial roles in the perioperative evaluation and treatment of the cardiovascular system, as well as in sepsis.

Abstract

Sphingosine 1-phosphate receptor 3 (S1PR3) is one of the five receptors of sphingosine 1-phosphate, actively participating in physiological processes such as angiogenesis and endothelial cell differentiation. Widely expressed in various tissue cells such as muscle cells, immune cells, lymphocytes, endothelial cells, and fibroblasts, S1PR3 has garnered increasing attention in research, showcasing its involvement in various pathophysiological processes and its important role in the body's inflammatory and immune responses. In the cardiovascular system, S1PR3 is involved in many pathophysiological processes, including angiogenesis, maintaining vascular permeability, lymphocyte transport, and physiological function of the heart. Moreover, it also plays a regulatory role in the treatment of cardiovascular diseases, such as heart ischemia/reperfusion, atherosclerosis, and cardiac fibrosis. S1PR3 also plays a crucial role in evaluation and treatment during the cardiovascular system in perioperative period and has a powerful therapeutic effect in sepsis. Regulators related to S1PR3 exhibit therapeutic potential in clinical treatments of cardiovascular diseases. This article aims to explore the role and research progress of S1PR3 in the cardiovascular system.

Keywords: Sphingosine 1-phosphate, sphingosine 1-phosphate receptor 3, cardiovascular system

Introduction

Sphingosine 1-phosphate (S1P) serves a pivotal signaling lipid in cell membrane metabolism and synthesis, which is generated by phosphorylation of sphingosine kinase-1 (SPHK1) or sphingosine kinase-2 (SPHK2) in plasma [1]. S1P can also participate in regulating multiple physiological and pathological processes in the body, including cell proliferation and survival, maturation, aging, and death [2]. S1P can bind to five G protein coupled receptors and act as the main endogenous agonist of the sphingosine-1-phosphate receptor 3 (S1PR3). This interaction plays a significant role in physiological and pathological processes such as cell pro-

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liferation and migration, ischemia-reperfusion, inflammation, tumor invasion and migration, vascular tension, and tissue fibrosis.

Recent investigations have been delving into the potential of KRX-725, an antagonist targeting S1PR3. KRX-725 bears significant clinical relevance as a therapeutic agent against inflammation-related fibrotic responses, with potential applications extending to the treatment of myocardial ischemia, tissue transplantation or peripheral blood vessels [3, 4]. S1PR3 also plays a crucial role in evaluation and treatment during the cardiovascular system in perioperative period and has a powerful therapeutic effect in sepsis. Simultaneously, the emerging recognition of S1PR3 in the cardiovascular system not only indicates the research direction of S1PR3, but also underscores the clinical significance of S1PR3 in the prevention and treatment of cardiovascular diseases.

Structure and function of S1P and S1PR3

Structure and function of S1P

Sphingosine 1-phosphate (S1P) operates as a crucial sphingolipid involved in ceramide synthesis within the endoplasmic reticulum. Under the catalysis of serine palmitoyltransferase, it combines serine and palmitoyl-CoA to generate ceramides [5]. Additionally, ceramides can undergo hydrolysis via sphingomyelinases, swiftly deacylated by ceramidases to yield sphingosine [5]. Subsequently, sphingosine is phosphorylated by SPHK1 or SPHK2, ultimately forming S1P [6]. In cellular homeostasis maintenance, S1P may undergo phosphorylation mediated by phosphatases, yielding sphingosine [7]. Degradation pathways for S1P involve three enzymes: S1P phosphatase, S1P lyase and lipid phosphate phosphohydrolase. S1P lyase cleavage predominantly results in the irreversible generation of 1-phosphate ethanolamine and hexaenal in most cells [8].

Cells excrete S1P from the cytoplasm through paracrine or autocrine pathways. Hydrophobic S1P traverses the cell membrane by transport carrier, subsequently binding to chaperone proteins after extrication, and circulating within the bloodstream by associating with serum albumin and high-density lipoprotein (HDL) [6]. Despite its relatively low expression levels within cells or interstitial fluid, S1P is abundant in lymph and blood, establishing a notable gradient discrepancy [5]. This gradient plays a pivotal role in lymphocyte trafficking, facilitating efficient egress from lymphoid organs. Mature T cells, for instance, rely on precise S1P gradients for departure from the thymus; disruption of this gradient impedes their egress. Moreover, the S1P gradient influences the trafficking of natural killer cells, B cells, and dendritic cells [9].

The equilibrium of S1P concentration is jointly regulated by SPHK1 and SPHK2, ensuring its stability within cellular environments.

Structure and function of S1PR3

S1P binds to S1P receptors (S1PRs) to exert its diverse biological functions. S1PRs are G protein-coupled receptors with five isoforms of S1PR1-5, expressed in various tissues of the body [10]. The structure framework of S1PR3 shows the canonical seven-transmembrane bundles holding the unbent d18:1 S1P. Notably, it features an extracellular lid consisting of the N-terminal helix, extracellular loop 2, and extracellular loop 3. The N-terminal region forms a helical cap and contributes to ligand interaction, while disulfide bonds are established within extracellular loop 2 (Cys178-Cys185) and extracellular loop 3 (Cys269-Cys274) [11].

S1PRs are highly expressed across multiple tissue cell types, e.g., S1PR1, S1PR2, and S1PR3 in blood vessels; S1PR1 and S1PR3 in endothelial cells (ECs); and S1PR2 and S1PR3 in vascular smooth muscle cells (VSMCs) [12, 13]. Besides, S1PR3 mediates S1P signaling in myocardial fibroblasts [14]. Within endothelial cells, S1PR3 may contribute to nitric oxide (NO)-mediated vasodilation, while in vascular smooth muscle cells, it participates in Rho-mediated vasoconstriction [15, 16]. Activation of S1PR3 has been associated with effects on heart rate and the risk of atrioventricular blocks [17]. Furthermore, S1PR3 activation triggers the generation of reactive oxygen species (ROS) via nicotinamide adenine dinucleotide phosphate oxidase 2 (NOX2) under the influence of the class III phosphatidylinositol 3-kinase complex. This activation promotes phagosome maturation during sepsis, enhancing macrophage bacterial engulfment [18]. Upon LPS induced lung injury, S1PR3 detachment from endothelial cells disrupts endothelial barrier function. Mice lacking S1PR3 or treated with specific antagonists have demonstrated protection against LPS-induced fatal sepsis [19]. Studies have found that S1PR3 is an important molecule in the fibrosis process, where inhibiting S1PR3 can attenuate fibrosis by impeding epithelial-mesenchymal transition through the S1PR3/SMAD2/3 pathway [20]. S1PR3 can be coupled with Gq/11, Gi/o and G12/13 to regulate immune responses, mediating P-selectin-dependent leukocyte rolling through S1PR3

Table 1. Related pathways in this review

Pathway	Influence
S1P→S1PR3→PI3K/Akt [24]	Promoti the proliferation of EPCs
S1P→S1PR3/PDGFR-β/Akt [40]	Promoting migration and angiogenesis of endothelial progenitor cells
S1P→S1PR3/RhoA/ROCK [29]	Promoting endothelial cell permeability, enhancing barrier action
S1PR3-Ga12/13→RhoA, PKD [27]	Cardio-protection
S1PR2-S1PR3→Cx43-S368 [30]	Preventing cell-to-cell transmission of death signals
HDL-S1P→S1PR3-Gi protein→Rho/ROCK,PI3K/Akt,p38MAPK [34, 35]	Promoting EC migration and inhibiting atherosclerosis
HDL-S1P→S1PR3/STAT3/Survivin [36]	Inhibiting macrophage recruitment induced apoptosis
S1P/S1PR3/TGF-β/Smad3 [39]	Inhibiting cardiac fibrosis
S1PR3→Rho GTPases→ROS [39]	Ameliorating of cardiac fibrosis
S1P/S1PR3→SUR2/Kir6.1 [41]	Promoting the transportation of fibroblasts

Note: S1P, sphingosine 1-phosphate; S1PR, S1P receptor; PI3K, phosphatidylinositol-3 kinase; Akt, protein kinase B; EPC, endothelial progenitor cell; PDGFR-β, platelet-derived growth factor beta; ROCK, Rho and Rho kinase; PKD, protein kinase D; CX43-S368, connexin 43 at S368; HDL, high-density lipoprotein; MAPK, mitogen activated protein kinase; EC, endothelial cell; STAT3, Germline signal transducer and activator of transcription 3; TGF-β, Transforming growth factor beta; Smad-3, drosophila mothers against decapentaplegic protein 3; ROS, reactive oxygen species; SUR2, sulfonylurea receptor 2; Kir6.1, pore-forming subunit of K-ATP channel.

and Gq/11 coupling [21]. Additionally, reports suggest that S1P induces cyclooxygenase-2 expression and prostaglandin E2 production in human granulosa cells through the YAP signaling pathway mediated by S1PR1/S1PR3 [22].

S1PR3 and signaling pathway

S1PR3 exerts its influence on various physiological and pathological processes of the body through signaling pathways. S1PR3 functions by mediating the mitogen activated protein kinase (MAPK) and PI3K-Akt (phosphatidylinositol-3 kinase/serine threonine kinase) pathways, activating downstream Ras/extracellular signal-regulated kinase 1/2 and other downstream pathways. Research indicates that S1PR3-mediated PI3K-Akt pathway activation can ameliorate blood-brain barrier damage and stimulate endothelial progenitor cell (EPC) proliferation [23, 24]. Moreover, S1PR3 participates in the feedback loop, where the S1P-S1PR1/S1PR3-YAP (Yes-associated protein 1) pathway c has been implicated in lymphoma development and tumor invasion (**Figure 1**) [25]. ECs leverage the S1P-S1PR1/S1PR3 pathway to facilitate vascular relaxation [26]. In myocardial cells, S1PR3 can activate RhoA, Protein kinase D, and mitigate cellular damage [27]. S1PR3's activation also influences neural processes, contracting them rapidly through Rho and Rho kinase (ROCK) pathways, phosphorylating Collapse response regulatory protein 2, and modulating EC permeability [28, 29]. VSMCs contract blood vessels under the mediation of the S1P-S1PR2/S1PR3 pathway, which also regulates myocardial cell death and alleviates myocardial ischemia-reperfusion injury [26, 30]. Furthermore, S1PR3 can activate endothelial NO synthase in an NO - dependent pathway in ECs, leading to NO production and subsequent vascular relaxation [31]. HDL promotes angiogenesis by regulating S1P-S1PR3, protects against myocardial ischemia-reperfusion injury, migrates vascular ECs, inhibits atherosclerosis and macrophage-induced apoptosis [32-36]. The absence of S1PR3 can reduce the recruitment of monocytes/macrophages, increase the content of smooth muscle cells in the lesion site, and reduce the area of cardiac fibrosis [37-39]. Moreover, S1P can regulate endothelial progenitor cell migration and angiogenesis through the S1PR3/PDGFR-β (Platelet-derived growth factor beta)/Akt signaling pathway [40]. Additionally, it can modulate the S1PR3/TGF-β (Transforming growth factor

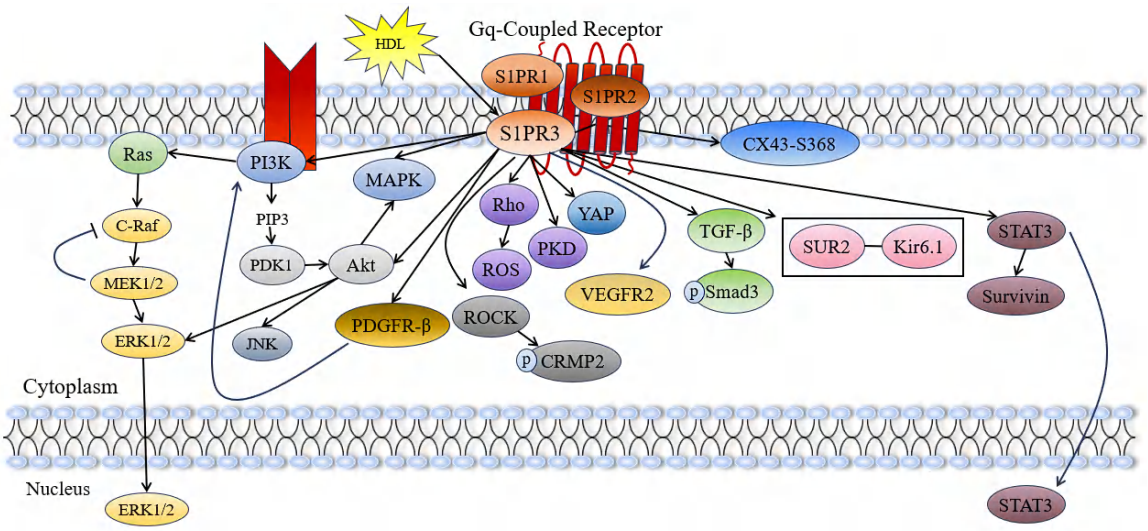

Figure 1. S1PR3 and signaling path. S1PR, sphingosine 1-phosphate receptor; Ras, rat sarcoma; C-Raf, C-Raf kinases; MEK1/2, mitogen-activated protein kinase kinases 1/2; ERK1/2, extracellular signal-regulated kinase1/2; PI3K, phosphatidylinositol-3 kinase; PDK1, 3-phosphoinositide-dependent protein kinase 1; JNK, c-Jun N-terminal kinase; HDL, high-density lipoprotein; MAPK, mitogen activated protein kinase; Akt, protein kinase B; PDGFR-β, Platelet-derived growth factor beta; ROS, Reactive oxygen species; ROCK, Rho and Rho kinase; YAP, Yes-associated protein 1; PKD, protein kinase D; CRMP2, collapse response regulatory protein 2; VEGFR2, vascular endothelial growth factor receptor-2; TGF-β, transforming growth factor beta; Smad-3, drosophila mothers against decapentaplegic protein 3; CX43-S368, connexin 43 at S368; SUR2k, sulfonylurea receptor 2; Kir6.1, pore-forming subunit of K-ATP channel; STAT3, germline signal transducer and activator of transcription 3.

beta)/Smad3 pathway, influencing cardiac fibrosis, and regulate the SUR2 (Sulfonylurea receptor 2)/Kir6.1 (Pore-forming subunit of K-ATP channel) pathway to promote fibroblast transport [39, 41]. S1PR3 activation also triggers Rho GTP enzyme activation, promotes ROS production, and contributes to myocardial fibrosis (**Table 1** and **Figure 1**) [39].

Effects of S1PR3 on the cardiovascular system

The cardiovascular system consists of two essential components: the heart and blood vessels, and the mortality rate of cardiovascular disease is extremely high. S1PR3 is expressed in a variety of cells of the cardiovascular system, such as ECs, VSMCs, cardiac fibroblasts, and cardiomyocytes [6].

Effect of S1PR3 on vascular ECs and barrier action

Under external stimuli, S1P can regulate vascular relaxation levels, EC permeability, and affect barrier effects through S1PR3.

Vascular maturation relies on the proliferation of vascular smooth muscle cells, pericytes and EC regeneration. S1P-regulated EDG signaling is instrumental in vascular EC neogenesis and VSMC recruitment. ECs promote vascular relaxation mediated by S1P-S1PR1/S1PR3 signaling, and VSMCs constrict blood vessels mediated by S1P-S1PR2/S1PR3 [26]. S1PR3 activation triggers the NO-dependent pathway, leading to nitric oxide synthase activation in ECs, NO production, and subsequent diffusion to VSMCs, inhibiting cell contraction and inducing vasorelaxation [31]. Furthermore, S1PR3 is closely related to the activity of EPCs. S1P activates S1PR3 and the downstream pathway PI3K/Akt to promote the proliferation of EPCs [24]. HDL upregulates the expression of vascular endothelial growth factor (VEGFR2) via S1PR3, fostering angiogenesis. The S1P-S1PR3-VEGFR2 signaling pathway holds significant implications for vascular remodeling in cardiovascular disease [32].

Moreover, research highlights the role of S1P in inducing migration and angiogenesis of EPCs through the S1PR3/PDGFR-β/Akt signaling pathway [40]. S1P activation of the S1PR3-RhoA-ROCK pathway enhances EC permeability and reinforces barrier action [29]. In acute lung injury, S1PR3 overexpression in plasma correlates with EC dysfunction, suggesting its potential as a novel acute lung injury marker [42]. Research has shown that FTY720 (fingolimod) may serve as a functional antagonist of S1PR3 to maintain a balance between angiogenesis and microvascular barrier function [43].

S1PR3 in cardiac ischemia-reperfusion

S1PR3 plays an important role in ischemia-reperfusion injury, exerting both direct protective action on the myocardium and a cardiosuppressive effect attributed to coronary vasoconstriction. The abundance of released S1P during ischemia-reperfusion may lead to competing influences on myocardial function via S1P3 receptor activation [44]. Elevated S1P levels, potentially induced by endogenous protective mechanisms, activate S1PR3 to mitigate myocardial defects and promote heart repair.

HDL-S1P binding to downstream S1PR3 receptors contributes to cardioprotection during ischemia-reperfusion, with S1PR3 activating the NO-dependent pathway [33]. Study has indicated that in mice lacking both S1PR2 and S1PR3 genes, the deletion of these receptors hinders Akt pathway activation, thereby inhibiting the damage-related extracellular signal-regulated kinase, c-Jun N-terminal kinase, p38MAPK pathways [45]. S1PR3, coupled to G12/13, activates downstream RhoA and Protein kinase D, further enhancing cardiac protection [27]. Additionally, during myocardial ischemia reperfusion, joint activation of S1PR2 and S1PR3 phosphorylates connexin 43 at S368, partially inhibiting cell-to-cell transmission of death signals and reducing cardiomyocyte damage (**Table 1** and **Figure 1**) [30].

Elevated S1P levels, triggered by endogenous protective mechanisms, activate S1PR3, alleviating myocardial defects and promoting heart repair. ECs promote vascular relaxation via S1P-S1PR1/S1PR3 signaling, while VSMCs mediate vasoconstriction under S1P-S1PR2/S1PR3 mediation [26]. FTY720 has been reported as a cardio-protective agent, alleviating either tachyarrhythmia or bradyarrhythmia induced by cardiac ischemia-reperfusion injuries [46].

In conclusion, S1PR3 has clinical research significance in ischemia-reperfusion injury. VPC01091, provides a similar protective effect to FTY720 on pulmonary ischemia-reperfusion injury, such as effectively protecting endothelial barrier function. The antagonistic activity of S1PR3 may not limit therapeutic potential, suggesting that VPC01091 may have therapeutic effects on cardiac ischemia-reperfusion by mediating S1PR3 [47].

S1PR3 in atherosclerosis

Disrupted lipid metabolism and inflammatory reactions contribute to elevated S1PR3 levels in atherosclerosis, further promoting inflammatory reaction and apoptosis to aggravate the damage of artery wall.

EC dysfunction stands as a key factor in atherosclerosis. S1P plays a crucial role in the maintenance of vascular integrity and the regulation of atherogenesis through the rearrangement of endothelial integrins [48]. S1PR3 regulates endothelial binding, uptake, and transport of HDL and low-density lipoproteins in an antagonistic manner. It influences the pathogenesis of atherosclerosis by inhibiting the trans endothelial transport of atherosclerotic low-density lipoproteins and promoting the trans endothelial transport of potentially anti atherosclerotic HDL [49]. It is currently believed that HDL-S1P in plasma initiates the coupling of S1PR3 with Gi protein to activate downstream pathways such as Rho/ROCK, PI3K/Akt and p38MAPK, which facilitate EC migration and inhibit atherosclerosis progression [34, 35].

Furthermore, HDL-S1P-mediated downstream S1PR3/STAT3 (Germline signal transducer and activator of transcription 3)/Survivin pathway can inhibit apoptosis induced by macrophage recruitment, thereby attenuating atherosclerosis (**Table 1** and **Figure 1**) [36]. S1P can be released from macrophages through ATP-binding cassette transporter A1, and regulate cholesterol efflux in a positive S1PR3 dependent feedback manner, thus hindering atherosclerosis [50]. In the bone marrow mosaicism model, S1PR3 deficiency reduces monocytes/macrophage recruitment but increases smooth muscle cell content at the lesion site [37, 38]. Existing studies have shown that 22(R)-hydroxycholesterol stimulates S1PR3, promoting the excretion of macrophage cholesterol into apolipoprotein A-I [51]. Hence, exhibits a dual role in atherosclerosis, both protective and modulating plaque composition.

Some anti-angiogenic effects of FTY720 involve blocking S1PRs implicated in recruitment of mural cells during angiogenesis. Combined inhibition of PDGFR and S1PR1/3 abolishes the network formation of VSMCs, making it a good candidate for anti-atherosclerosis treatment [52].

S1PR3 and cardiac fibrosis

Stimulation of S1PR3 in cardiac fibrosis escalates its expression and activity, promoting inflammatory response and cell apoptosis, thereby exacerbating the process of myocardial fibrosis. S1PR3 activates multiple pathways to promote this process.

S1P is highly expressed in fibroblasts and car-

diomyocytes, modulating them via paracrine mechanisms [43]. Cardiac fibroblasts endogenously express S1PR1, S1PR2, and S1PR3. Transgenic overexpression of SphK1 in mice leads to interstitial cardiac fibrosis mediated by S1PR3. Additionally, activation of S1PR3 coupled with Gq and G12/13 may also contribute to cardiac fibrosis [53]. The S1P/S1PR3/TGF-β/Smad3 pathway can orchestrates diverse downstream effects, including trans-activation of Smad3 phosphorylation, enhanced ROS production, reduced IL-1 and collagen fiber secretion, facilitated fibroblasts migration, and ultimately promotes cardiac fibrosis. Additionally, S1PR3 can activate Rho GTPase, promote ROS production and participate in the process of myocardial fibrosis, while S1PR3 deletion diminishes cardiac fibrosis [39]. Studies have revealed that S1P/S1PR3-mediated activation of the SUR2/Kir6.1 pathway in ventricular fibroblasts curbs IL-1 and collagen secretion, or enhances fibroblast migration, thereby mitigating fibrosis (**Table 1** and **Figure 1**) [41]. FTY-720 alleviates existing cardiac hypertrophy/fibrosis by negatively regulating NFAT (nuclear factor of activated T cells) activity in cardiomyocytes [54].

The advances in translational studies of S1PR3 for treating cardiovascular diseases

Reportedly, various regulators, including Fingolimod, VPC23019a, VPC01091, VPC44116, CYM5541, SPM242, exhibit affinity with S1PR3 [55]. While the regulatory effects of Fingolimod on S1PR3 have been explored in clinical phase I and II trials for cardiovascular disease, the impacts of other modulators remain to be fully elucidated.

FTY720 is a neural sphingosine 1-phosphate receptor modulator. It is the first S1PR modulator approved for the disease treatment [17]. Studies suggest that FTY720 may serve as a functional antagonist of S1PR3 to maintain a balance between angiogenesis and microvascular barrier function [43]. It mitigates tachycardia or bradycardia caused by myocardial ischemia-reperfusion injury by regulating S1PR3 [56]. Additionally, FTY720 exhibits anti-angiogenic effects by blocking S1PR involvement in mural cell recruitment during angiogenesis. The combined inhibition of PDGFR and S1PR1/3 completely eliminated the network forming ability of VSMCs, making it a good candidate for anti-atherosclerosis treatment [52]. FTY720 can also alleviate existing myocardial hypertrophy/fibrosis by negatively regulating the NFAT activity of myocardial cells [54].

Through chemical and biological assays, VPC01091 has been identified as an antagonist to S1PR3 [57]. VPC01091 provides a similar protective effect to FTY720 on pulmonary ischemia-reperfusion injury, such as effectively protecting endothelial barrier function. Importantly, the antagonistic activity of S1PR3 receptor may not limit therapeutic potential, suggesting that VPC01091 may have therapeutic promise for cardiac ischemia-reperfusion by mediating S1PR3 [47].

S1PR3 and perioperative period

Studies have shown that the measurement of circulating S1P can be used to predict the severity of inflammation caused by cardiac surgery, ICU hospitalization time, and general clinical outcomes [58]. Scholars have obtained S1PR3 related molecular features of 18 genes, in which many important immune pathways regulating the progression of sepsis have been enriched [59]. S1P lyase inhibition and S1PR3 stimulation can treat sepsis in mice [60]. Thrombin generated in the lymphatic compartment perturbs DCs to promote systemic inflammation and disseminated intravascular coagulation in severe sepsis. Signaling-selective aPC variants and selective modulators of the S1P receptor system attenuate sepsis lethality [61].

Conclusion

S1PR3, as a type of G protein coupled receptor in the body, exerts significant influence over a spectrum of pathological and physiological processes encompassing inflammation, cardiovascular function, oncogenesis, and neurological regulation. S1PR3 is expression varies across different tissues and cell types, being notably prevalent in EC, VSMC, glial cells, and lymphocytes. In the realm of cardiovascular diseases, including cardiac ischemia/reperfusion injury, atherosclerosis, and cardiac fibrosis, S1PR3 emerges as a key regulator, although further comprehensive research is warranted in this domain.

At present, modulators of S1PR3 like Fingolimod, VPC23019a, and VPC01091 are also widely used in clinical practice. S1PR3 also plays a crucial role during the perioperative period. The research on S1PR3 in cardiovascular disease continues to evolve. As a potential target for the treatment of cardiovascular diseases, S1PR3 holds the potential to significantly shape future treatment paradigms in this arena.

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study; Kecheng Zhai, Hui Su, and Renke Sun contributed to the literature and collection of materials; Yangmengna Gao and Ran Yuan contributed to material analysis and manuscript writing; Yangmengna Gao and Kecheng Zhai reviewed and refined the manuscript.

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