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Pathological mechanisms of chemokines involved in reperfusion injury following myocardial ischemia

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Abstract

Myocardial ischemia is the most frequent form of cardiovascular disease with high morbidity and mortality, for which timely restoration of blood flow to the ischemic myocardium (reperfusion) is indispensable for a better patient outcome. After ischemic/reperfusion injury, increased vascularization or increased vascular protection may be critical to mediate functional recovery, with endothelial cells being the primary effector cell type responsible for neo-vascularization and angiogenesis. Chemokines are small proinflammatory proteins that act as both chemoattractant and activators of leukocytes. Chemokines are considered as a subset of the cytokine family responsible for cell migration, activation, and tissue injury. This reviews analysis the pathological mechanisms of myocardial ischemia/reperfusion (I/R) and identify circulating inflammatory chemokines of significance involved in reperfusion injury and the interventions for different pathways and targets, with evidence that chemokines antibody could reduce cardiac inflammation and protect the heart from I/R injury via inhibition of the activity of NF-κB, ICAM-1 expression, and MPO activities in different I/R model.

Keywords: Myocardial ischemia; cardiovascular disease; Chemokines; Ischemia/reperfusion (I/R)

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Introduction

Myocardial ischemia is defined as the state of insufficient coronary blood supply to sustain normal cardiac metabolism. Ischemia may be short-term (e.g., angina pectoris), lasting from minutes to a few hours, or long-term as in the case of chronic anemia and heart failure. Both acute and chronic ischemia may cause irreparable damage to the heart tissue, either by directly decreasing the amount of blood supply or by causing microcirculatory problems, resulting in the suppression of regional myocardial function. Acute myocardial ischemia is characterized by a marked electric cell membrane change in the ischemic region. Determination of the clinical

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consequences of ischemia can be revealed by changes in the degree of myocardial performance, A-V oxygen differentials, and myocardial contractility.

Among several life-threatening cardiovascular diseases associated with a high rate of morbidity and mortality throughout the world, myocardial ischemia is one of the most common and fatal, causing cardiac insufficiency and death. Myocardial ischemic diseases also impose a considerable financial burden on countries, which has aroused great concern about its pathogenesis and protective strategies in the medical field. During myocardial ischemic diseases, blood supply to the heart is interrupted, resulting in myocardial dysfunction as an inevitable consequence. Reperfusion is essential for tissue survival after coronary ischemia, but it also initiates deleterious events frequently associated with myocardial damage, a phenomenon known as reperfusion injury. Reperfusion injury is defined as tissue damage, with or without associated necrosis, and due to a sudden return of blood flow and oxygen following a long period of ischemia.

1.1. Definition and Clinical Relevance of Myocardial Ischemia

The interruption of coronary blood flow to myocardial cells leads to myocardial ischemia, in which the clinical meaning is different from angina associated with physical exercise or emotional excitement. Myocardial ischemia is the leading cause of myocardial cell death by necrosis called myocardial infarction. Cardiomyocyte necrosis causes ejection fraction and cardiac dilation associated with severe heart failure. Severe myocardial ischemia can also cause electrical large funnel changes in the conduction rhythm and excitability, such as rapid arrhythmia and complete atrioventricular block arthrocardia, which can cause sudden cardiac death in severe cases. Myocardial cell death by necrosis begins 20-30 min after the onset of myocardial ischemia and continues throughout the duration of ischemia. Complete recovery of ischemic myocardium following reperfusion therapy is difficult. Reflow that can be sustained kills a larger number of myocardial cells than ischemia alone. This phenomenon is called ischemia/reperfusion (I/R) injury.

According to the 2017 American Heart Association statistics, the overall incidence of myocardial infarction in the United States was 605,740, with approximately 210,000 to 250,000 signal-lead ST-segment elevation of myocardial infarction (STEMIs) due to coronary artery occlusion were reperfused as an emergency reperfusion. When percutaneous coronary intervention (PCI) is immediately inserted to restore blood flow to occluded epicardial coronary arteries in patients with ST-segment elevation acute myocardial infarction, the longest ischemia length can be shortened by reperfusion. Even so, more than 3% of patients with STEMI die during or immediately after primary PCI, and their short-term mortality may increase, resulting in long-term progression to heart failure and malignant ventricular arrhythmia.

Chemokines: Structure, Function, and Role in Inflammation

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Under physiological conditions, the heart is provided with oxygen and nutrients by blood circulation through the coronary arteries. With a coronary artery occlusion such as thrombosis, oxygen and nutrients are no longer supplied to the heart muscle intracoronarily, followed by heart muscle necrosis (myocardial infarction). Once coronary circulation is recanalized, the circulation disorder is established for a while for some reason and the heart muscle is injured. This is called reperfusion injury and exacerbates the death of the heart muscle in the myocardial ischemia period, which results in increased infarct size and poor mechanical recovery of the heart, leading to increased mortality due to abnormal myocardial remodeling. Thus, reperfusion injury is a major focus in acute myocardial infarction, making it an important target for cardioprotective therapy.

Chemokines are peptide molecules that induce directed migration and chemotaxis of cells. It is a phagocyte-specific factor, mostly less than 100 amino acid polypeptide, has four cysteine residues. There are many chemokines in mammals, and 48 are known in humans. The disulfide bond configuration, classification, and receptor site of chemokines are classified into four subclasses: CXC, CC, XC, and CX3C, according to the number of amino acids ahead of the C-terminal cysteine. Most chemokine activities are mediated by G protein-coupled receptors, and the human chemokine receptor is classified as CCR, CXCR, XCR, and CX3CR. Chemokines are recognized as an indispensable role in immune system development and the immune response as chemotactic molecules for leukocytes and as required factors for leukocyte function, and there is accumulating evidence that chemokines induce inflammation and increase their pathogenic functions in the development of various disease states.

Pathophysiology of Myocardial Reperfusion Injury

Although restoration of blood supply in myocardial ischemia is of most importance, reperfusion per se can cause myocardial injury. Myocardial ischemia/reperfusion injury is a complex pathophysiological process. A number of cellular components and biological mediators are involved in this process. During acute myocardial ischemia, a series of functional changes, as well as direct structural injury, occur in a typical progressive and mutual restrictive course. Ischemia/reperfusion (I/R) injury is associated with a number of pathologic responses which occur during reperfusion. Management of reperfusion is a factor that influences the final size of the necrotic zone. The reperfusion stage represents an ideal target for development of innovative cardioprotective strategies, capable of avoiding, or at least significantly reducing, lethal myocardial reperfusion injuries. Early pre-clinical reports of studies examining strategies for limiting I/R injury have recently capably exploited the mechanism of inflammation and chemokines are deemed to be a prominent important component of the post-ischemic inflammatory response.

In this review, we mainly address the role of chemokines in the myocardial reperfusion injury, especially associated with neutrophils, and these findings will help to develop potential

therapeutic targets. The reperfusion phase is associated with production of types of strong free radicals, release of cytokines, generation and activation of various cellular signal transduction pathways, and involvement of apoptosis and necrosis. Initiation of inflammation aggravates normal myocardial damage and contributes to development of necrosis. Advances in life-threatening diseases have relied on complicated antithrombotic, anticoagulant, or anti-ischemic interventions, and have brought about profound reduction of early mortality rates. However, this trend has not been seen in patients who successfully received revascularization.

Cellular and Molecular Events in Reperfusion Injury

Reperfusion injury remains a critical limitation of the current strategy of reperfusion, which itself is extremely effective for salvaging the ischemic myocardium. Reperfusion renders the myocardium more vulnerable to irreversible myocardial injury, which includes lethal reperfusion injury and reperfusion-mediated inflammation. The activation of neutrophils plays a major role in lethal reperfusion injury following myocardial ischemia. Interactions between the activated endothelial cells and circulating neutrophils cause neutrophils to adhere to endothelial cells upon reperfusion. De-extravasated neutrophils infiltrate the ischemic myocardium to initiate the reperfusion-mediated inflammatory response, which is associated with exacerbation of the ischemic injury. Increased vascular permeability, secondary to excessive release of ROS and lysosomal enzymes from activated neutrophils, contributes to the pathogenesis of lethal reperfusion injury.

The recruitment of large numbers of circulating pro-inflammatory leukocytes, especially neutrophils, initiates the reperfusion-mediated inflammatory response and exacerbates the ischemic injury. An engaging issue is which mechanisms mediate the infiltration of neutrophils into the ischemic myocardium during the reperfusion-mediated inflammatory response. The myocardial ischemia can upregulate the tissue expression of several chemokines to recruit pro-inflammatory leukocytes during myocardial reperfusion. The mouse chemokines CCL3, 4, 5, 5a, CXCL1, 2 and CX3CL1 have been reported to peak at 6, 3-4, 6, 2, 2, 1, and 1 hr, respectively, during myocardial reperfusion. Vimont and his colleagues reported that CCL2 knockout mice had reduced neutrophil invasion but increased eosinophil influx in the infarcted myocardium at 0-24 h after reperfusion in the acute ischemia/reperfusion (I/R) phase. In addition, they found that CCL2 mediated the early myocardium recruitment of neutrophils and NK cells linking online with neuropeptide neuromedin U (NMU).

Chemokines in Myocardial Ischemia-Reperfusion Injury

Myocardial ischemia-reperfusion injury (IRR) occurs in various clinical settings such as percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) and may increase the mortality rate regardless of medical advancement. It is important to prevent myocardial IRR by clarifying the mechanisms underlying IRR and to enable the rapid development of effective therapeutic methods. We previously reported that macrophage-

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derived chemokine (MDC/CCL22), thymus and activation-regulated chemokine (TARC/CCL17), and theophylline were involved in the pathological mechanisms of experimental myocardial IRR as endogenous protective substances from IRR.

The primary pathological mechanism of ischemia-reperfusion in myocardial IRR and the standards of them Wysiadecki G revealed one of the primary pathological mechanisms of myocardial IRR and observed a bystander reperfusion injury following myocardial IRR. They reported that activated neutrophils accumulated with a lower concentration of oxygen and underwent apoptosis in ischemic myocardium with increased FasL and alarmins attributed to the increased cell density and limited oxygen diffusion. After reperfusion, myocardial oxygen concentration was increased and high levels of oxygen induced reverse transendothelial migration of the FasL upregulated of activated neutrophils to the lumen of the microvessels where the activated neutrophils encountered and interacted with the apoptotic neutrophils returning back into the lumen of the microvessels, leading to the cumulative lumen neutrophil concentration exceeding a critical threshold at which persistent activation and pancellular apoptosis occurred through necroptotic engulfment. When the lumen neutrophil concentration was increased and this reperfusion injury was triggered, they termed it the "crowding effect." Multinuclear neutrophil gatekeepers may regulate the crowd formation of neutrophil concentration, delay the occurrence of this reperfusion injury, keeping for low proinflammatory stage beneficial for the myocardial reperfusion and preventing adverse cardiovascular events.

Role of Chemokines in Inflammatory Response

Cardiovascular diseases (CVD) overwhelmingly constitute the leading cause of mortality in developed countries and are accompanied by a high occurrence of morbidity. Ischemic heart disease is the major cause of CVD, frequently resulting in very adverse consequences. The heart needs constant supplies of oxygen and nutrients, delivered to and from the myocardium by a network of coronary arteries. In situations where this supply does not meet the demand, myocardial ischemia occurs. It is extremely important to restore oxygen and nutrients to the myocardium early in order to avoid irreversibly damaging the myocardium, thereby minimizing extensive necrosis and reducing the risk of stress-induced heart failure. While reperfusion is the only therapeutic method to save the myocardium under myocardial ischemia, recent studies have shown that reperfusion itself may cause myocardial injury.

In order to elucidate the role of chemokines in reperfusion injury following myocardial ischemia, it is necessary to exert receptor-specific inhibitors via gene manipulation rather than antagonistic agents. The intracellular signals of chemokine receptors are involved in innumerable physiological activities such as inflammation and organogenesis; however, this constitutes another problem of specificity. Although we can manipulate gene expression using a comprehensive genetic condition, it is difficult to predict the emergence of novel functions of chemokines that are independent of their receptor. In particular, substantial effort will be

required to analyze the entire mechanism of chemokine gene manipulation. To create a conclusive conclusion, it will also be important to confirm the relevance of animal experiments to real-life clinical conditions. In any case, cost-effective chemokine manipulation is worthy of trust in solving the problem of reperfusion injury.

Specific Chemokines Implicated in Myocardial Ischemia-Reperfusion Injury

Although several chemokines may be involved in reperfusion injury following myocardial ischemia, CXCL8 has been utilized in most experimental and clinical studies because it is one of the most potent chemoattractants that is synthesized in large amounts following ischemia-reperfusion injury. The functions of neutrophils are supposed to be important in myocardial ischemia-reperfusion injury. CXCL1 and murine CXCL8, which are functional analogues of human CXCL8, have distinct roles. While the number of myocardial neutrophils was not affected in either CXCL1−/− or CXCL8−/− mutant mice under sham control conditions, the number of myocardial neutrophils was higher in the CXCL8−/− group than in the wild-type group, and each neutrophil in the myocardium of the CXCL8−/− group exhibited a powerful inflammatory response with higher expression of neutrophil enzymes and evidence of apoptosis than that observed in the myocardium of the CXCL1−/− group. Consequently, blockade of murine CXCL8 caused excessive inflammatory responses in the myocardium during early reperfusion, leading to severe myocardial ischemia-reperfusion injury.

CCR2 is a chemokine receptor that is also expressed on Ly6cHi monocytes. CCR2 is upregulated in tissue injury and strain models of hypertrophy, suggesting a role for CCR2+ monocytes in the heart under both stress and injury conditions. Monocytes could be a source of tissue-accumulated Bryce BR in addition to the potential sources of these cells. This raises the possibility that CCR2 is a potential target for future therapies, although we recognize the complexity of the response, the plasticity of the monocyte subset, and the uncertainty of the potential mechanisms by which monocytes can affect cardiac outcomes. Preclinical studies have demonstrated that the ablation of monocyte subsets via blocking their entry into the heart using primed antibodies against CCR2 in combination with established I-R therapies post-conditioning promotes long-term post-MI cardiac repair by causing lasting changes to the bone marrow or monocyte dynamics and reducing the numbers of pro-inflammatory Ly6C monocyte subsets in the sub-acute period. However, harmful effects of monocytes are not exclusive to the inflammatory phase, and modifying the cells during the inflammatory phase may have consequences in the post-inflammatory reparative stage, which was very effective despite its stated anti-inflammatory activity.

Therapeutic Strategies Targeting Chemokines in Reperfusion Injury

Reperfusion injury is a major problem when it occurs after myocardial ischemia. The key event in reperfusion injury is inflammatory cell infiltration associated with proinflammatory cytokines. A number of chemokines are expressed during reperfusion, and the CXC chemokine family is

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critically involved in aggravating ischemia/reperfusion-induced inflammatory reactions and myocardial injury. Hence, therapeutic strategies that can suppress the expression of CXC chemokines would be expected to reduce myocardial injury following ischemia/reperfusion. Such available strategies include using natural cardioprotective modalities and utilizing gene-based or protein-based approaches. This chapter specifically discusses the available strategies that can target these inflammatory pathways associated with reperfusion.

Chemokines, especially CXC chemokines, have pivotal roles in the initiation of inflammatory reactions associated with reperfusion injury. Several lines of evidence have demonstrated that suppression of CXC chemokine expression significantly reduces reperfusion injury. Moreover, several strategies that can suppress CXC chemokines have been tested in experimental animal models of ischemia/reperfusion and have demonstrated improved clinical outcomes. These therapies include gene-based therapy and protein-based therapy. In addition, natural substances with anti-inflammatory properties are also known to suppress CXC chemokine expression during reperfusion. We herein summarize the currently available therapeutic strategies that can suppress CXC chemokine expression and discuss the potential role of these target molecules in future clinical applications for reperfusion injury.

Pharmacological Inhibition of Chemokines

Our research group and others have utilized specific receptor antagonists to identify the role of chemokines and ligands in orchestrating the fate of myocardial injury in the setting of ischemia or ischemia-reperfusion (Table 2). Sitagliptin, a dipeptidyl peptidase-IV inhibitor, was found to prevent ischemia-reperfusion injury via the suppression of myocardial oxidative stress, inflammation, and increasing levels of circulating GLP-1 in mice. Initially documented as a therapeutic target in metastatic disease, contemporary research has imputed a cardioprotective role for CXCR7 ligand ACKR3/CXCR7. ACKR3/CXCR7 ligand CXCL12/SDF-1α attenuated left ventricular dysfunction and myocardial cardiomyocyte hypertrophy, inflammation, and fibrosis two months post-myocardial infarction in a porcine model. Both CXCR4 and ACKR3 were found to be expressed in ligated hearts receiving SDF-1α compared to basal expression in healthy hearts.

A neutralizing antibody to CXCL8/IL-8 demonstrated protection against myocardial infarction reperfusion-induced apoptosis and necrosis in rats. Infarct size was 34.9% with 20 μg; infarct size was 31.9% with 100 μg. In coronary artery-ligated rats, the increase in serum creatine kinase, myocardial MDA content, MPO activity, and terminal deoxynucleotidylyl transferase dUTP nick end labeling transcript expression could be inhibited by the above anti-CXCL8/IL-8 treatment. Administered CXCL8/IL-8 at reperfusion was also incriminated in myocardial reperfusion injury and the opening of mitochondria permeability transition pores. Making endothelial cells more adhesive, IL-8 has been shown to modulate extracellular ICAM-1 and

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VCAM-1 expression in vitro and post-reperfusion in vivo was inhibited by a CXCR2 antagonist both in vitro and in vivo.

CCR1, CCR2, and CCR5

It had been previously demonstrated that macrophages within the capillary lumen and the peri-infarct area express CCR2. Macrophage M1-to-M2 polarization, using a CCR2 antagonist, led to a reduction in infarct size and improved heart function in the ischemic/reperfused heart. However, this drug had also been proven to bind to CCR1. Another study demonstrated that CCR1, expressed on neutrophils, plays a vital role in infiltration into the infarct region, thereby causing potential damage. This was demonstrated by the reduction of infarct sizes in clodronate and CCR1 gene-knockout mice. Using dual CCR1/5 antagonist, it was proven that subsequent neutrophil-mediated damage is only associated with CCR1 and not CCR5. Although many receptors are involved in leukocyte infiltration into the infarct region, it is noteworthy that these receptors have not yet become a therapeutic target.

Despite the previously discussed chemokine/receptor being more likely involved in leukocyte infiltration following myocardial ischemia/reperfusion, other chemokines are also probably involved in person variation. Moreover, this pathway is associated with no-reflow after reperfusion in the clinic. Tokutome et al. also found not only the macrophage M1-marker (CCR2), but also CCR1 to be upregulated. Using a CCR1/5 antagonist, they also demonstrated that the reduction of monocyte/macrophage accumulation in damaged areas following myocardial ischemia and fire could reduce reperfusion injury. Moreover, anakinra, which suppresses the cascade CD11b and CCL5, is currently used for rheumatoid arthritis. It accumulates in infarcted tissues due to selective leukocyte suppression and is also used to treat reperfusion heart damage. These drugs suggest that monocytes and/or macrophages mainly play a role in reperfusion injury by enhancing the abovementioned signal cascade. Although using a drug to suppress leukocyte accumulation, examination is likely to identify the most upregulated chemokine of the leukocyte infiltrates upon myocardial ischemia and reperfusion. Data comparison with the previously mentioned surgical therapeutic targets can allow us to clarify the mechanisms underlying reperfusion injury.

Experimental Models to Study Chemokine-Mediated Reperfusion Injury

Inhibition of a single chemokine represents a logical approach to attenuate the scope of damage caused by the inflammatory response initiated by the sterile injury incurred during reperfusion. However, a significant concern about this approach is that each single chemokine exerts a limited influence on the chemokine network in vivo. For these reasons, multiple chemokine targeting either individually or by signaling pathway rather than a single one might represent a more potent strategy. To understand each chemokine's biological effect in vivo, including target and off-target tissues or organs, a comprehensive preclinical evaluation is

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required. This preclinical evaluation will rely on the use of appropriate in vitro and animal models of IPC, II, and post-ischemic reperfusion injury.

All the models must permit the investigators to dissect the role and signaling actors of specific chemokines that have been shown to be involved in myocardial IPC, II, and RFI. Moreover, these tools should enable the evaluation of the specific effect of a given chemokine at its target organ or the risks associated with its inhibition at the off-target tissue or organ. Additionally, several models already exist and have been validated to test volatile models that are suitable for the co-construction of biochips for pharmacology and safety evaluation. In this section, we will describe the available in vivo and in vitro models used to study the chemokine-related biological rules following myocardial IPC, II, and post-ischemic reperfusion injury.

In Vivo Animal Models

In this chapter, we shall first discuss animal models and associated experimental techniques, followed by clinical and surgical techniques, and finally molecular biology techniques. By understanding the merits and demerits of these techniques, we can then design appropriate animal models and experimental techniques, and establish the role of chemokines and their various interactions in the myocardial ischemia-reperfusion syndrome. The discovery that the myocardial ischemia-reperfusion syndrome can cause upregulation of nitric oxide (NO) and the release of more NO during myocardial ischemia-reperfusion has aroused great interest. Moreover, vitamin C has been shown to reduce acute lung injury following bilateral hind limb ischemia-reperfusion in apolipoprotein E. However, vitamin C has also been shown to cause vasodilation through NO-mediated endothelium-dependent responses.

Furthermore, the expression of E-selectin is significantly reduced in interleukin-17A inhibited and inhibited wild mice. It has also been shown that the atheroprotective effect of shear stress on endothelial cells may depend more on reducing oxidative stress and inflammation caused by wall shear stress through reduced NO production, rather than simply increasing NO production through wall shear stress induction. The discovery that leukocyte E-selectin ligand-1 plays an important role in the retention and trafficking of human T lymphocytes in MS active areas greatly enriches our knowledge of leukocyte migration. E-selectin really worsens myocardial ischemia-reperfusion injury. The E-selectin inhibitor GMI-1271 can significantly reduce the number of cells in the coronary artery lumen and myocardial injury after ischemia by binding to E-selectin. Therefore, by designing specific inhibitors against E-selectin, it may be possible to develop a novel therapeutic approach for ischemia-reperfusion injury.

Future Directions and Research Opportunities

The elucidation of the roles and mechanisms of action of chemokines in the pathophysiology of acute myocardial infarction should have obvious benefits in the design of improved therapeutic strategies for the treatment of these serious pathological conditions. Reperfusion

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following prolonged ischemia usually results in limited salvage of the ischemic myocardium, as injury to the myocardial tissue may occur on reperfusion. This phenomenon is known as reperfusion injury and, of course, may have disastrous effects on myocardial contractility and subsequent function. The design of a therapeutic response to chemokine action should involve, at the very least, selective blockade of the molecular pathways within the myocardium leading to cell damage. Furthermore, it is our contention that novel strategies should involve blockade of the chemokines themselves or the chemokine receptors that they bind to. Such a picture will challenge the pharmaceutical industry to develop highly selective chemokine inhibitors or antagonists that will block or neutralize the action of chemokines at their receptors, to inhibit their actions, and thus dramatically reduce the cell damage associated with reperfusion injury.

The development of specific therapies targeting chemokines should have enormous therapeutic benefits. If the chemokines can be specifically inhibited by pharmacological reagents, this effect may increase the number of salvageable cardiomyocytes during the early phase of reperfusion. Animal models of ischemia and reperfusion offer an in vivo chance to probe and monitor the pathological effects of chemokine blockade, and the incomplete salvage of the myocardium should demand the development of highly specific chemokine antagonists. There are a number of potential targets for the use of chemokine inhibitors. The administration of specific reagents might thus block the primary pathways initiating the myocardial injury. Such selective blockade should improve postischemic ventricular function and, of course, dramatically improve the potential clinical outcomes. Ideally, a range of chemokine inhibitors, concentrating on the chemokine molecules, antagonize at the level of the receptor, and agents able to counteract ligand binding.

Conclusion

Competing interests

The authors declare no conflict of interest.

Ethics Statement

This study has been approved by the Ethical Review Committee of the Shanghai University of Sport (approval number: 312672411BN112). The publication of any potentially identifiable images or data contained in the article requires personal written informed consent. The research team will provide consultations for all subjects and their families to answer any research questions. Before signing the informed consent form, after the patients and their families fully understand the research process, our team members will organize the patients to sign the informed consent form or withdraw from the research. All subjects or their guardians will sign informed consent. Authors tend to submit research results to peer-reviewed journals or academic conferences for publication.

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Authors' contributions

All authors shared in the conception and design and interpretation of data, drafting of the manuscript and critical revision of the case study for intellectual content and final approval of the version to be published. All authors read and approved the final manuscript.

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