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Recent advancement in stem cell treatment of coronary artery lesion of kawasaki disease

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ABSTRACT

Kawasaki Disease (KD) is an acute, self-limited systemic vasculitis that affects the middle and small arteries, especially the coronary arteries. The incidence of KD is currently on the rise, with about 15 to 25 percent of children without systemic treatment, eventually developing coronary artery damage, Becoming the most common cause of child-acquired heart disease

in the developed countries. At present, stem cell therapy for Kawasaki Disease in mice model has made important progress. This article reviews stem cell treatment of coronary artery lesion of Kawasaki Disease.

Keywords: Coronary Artery Evaluation, Kawasaki Disease, Stem Cell.

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INTRODUCTION

Kawasaki disease (Kawasaki diseases, KD) is a autoimmune disease, also known as lymph node syndrome, skin and mucosa in 1967 by a pediatrician Kawasaki rich covered in Japan for the first time, develops in children under the age of five, the main is a kind of small artery inflammatory lesions in the body, the main pathological changes of acute febrile disease and systemic vasculitis [1], more invasion of the heart coronary artery and cause serious complications. Coronary Artery Injury (CAL) is a serious complication of Kawasaki disease, which has the risk of myocardial infarction and sudden death, and has become the primary pathogenic factor of acquired heart disease in children in developed countries. Up to 15-20% of patients with Kawasaki disease do not respond to high-dose intravenous immunoglobulin therapy, and these patients have a significantly increased incidence of coronary aneurysms [2]. So far, scholars on the pathogenesis and pathogenesis of Kawasaki disease is not very clear, but through nearly half a century of research support genetic factors play a key role in its occurrence and development, and emerged two university theories: infection theory and immunity theory. Kawasaki disease is a self-limited disease that causes inflammatory changes in blood vessels. It occurs most frequently in East Asian populations and occurs most frequently in winter and spring. The clinical manifestations of Kawasaki disease overlap with other infectious diseases [3], its clinical biochemical indicators, such as increased white blood cell/CRP and rapid erythrocyte sedimentation rate, are enough to prove that the underlying lesions are caused by inflammatory cells. During the acute onset of Kawasaki disease, a large number of inflammatory cytokines are released. After the activation of immune cells, the activated immune cells can release a

large number of inflammatory cytokines [4], is a vicious cycle, the formation of waterfall reaction, so that the body loses the control of the inflammatory response, resulting in endothelial damage. Secondly, a large amount of tumor necrosis factor (TNF) is produced to damage vascular endothelial cells, resulting in increased endothelial permeability, and then the vascular endothelial cells release chemokines, resulting in the aggregation of immune cells to the surface of the damaged vessels. The number of endothelial progenitor cells (EPCs) is reduced by tumor cells, thereby reducing the repair of damaged endothelial cells and leading to coronary artery damage. Thirdly, during the acute period of Kawasaki's disease, the body releases a large amount of interleukin, which enables cells to detect the toxic effect, inhibit the expression of P53 gene, reduce the apoptosis of lymphocytes, continuously produce more inflammatory factors and adhesion molecules, and mediate the damage of vascular endothelial cells [5]. Abnormal activation of T cells is the initial link and key step of immune system activation in Kawasaki disease, which leads to vascular immune injury [6]. A large number of T cells make the body in a state of immune activation. Activated T cells act on humoral immunity and induce vascular inflammatory response. Vascular endothelial growth factor (Vascular endothelial growth factor, VEGF) can cause excessive increased Vascular permeability, children with kawasaki disease can be detected in blood of Vascular endothelial growth factor, Vascular VEGF promote the white blood cells gathered in coronary inflammation of stimulation, the increased Vascular permeability, and stimulate the activation of peripheral blood mononuclear cell chemotaxis to endothelial injury and lead to local produce again producing VEGF, form a vicious circle, coronary blood vessels to participate in and lead to damage [7]. According to the study of Rao Xiao Hong et al., platelets are involved in vascular damage of Kawasaki disease. After thrombocytosis and enhanced activation, thrombocytosis causes thrombosis in the damaged coronary arteries, intima thickening, and release a variety of angioconstrictors and clotting substances, leading to myocardial function impairment, increased hypercoagulability and vascular blockage, resulting in ischemic necrosis of the myocardium.

At present, there are many studies on gene fragments such as ITPKC, Casp3, TGF-S, BLK, CD40 and FCGR2a at home and abroad, suggesting that many genes are involved in the occurrence of Kawasaki disease and the development of CAL[8]. In conclusion, the mechanism of KD disease is a complex process, but studies have shown that it is the abnormal activation of immune cells and the large release of various cytokines, leading to

vascular endothelial damage and dysfunction, and the occurrence of cascading damage of coronary arteries.

Pathological basis of coronary artery damage in Kawasaki disease

The coronary arteritis model was induced by Lactobacillus casei cell wall extract (LCWE) [9]. Pathological sections of the coronary artery showed thickening of the vascular wall and invasion of inflammatory cells around the heart tissue, and plaques may appear. LCWE induced Kawasaki disease vasculitis is characterized by inflammatory cell infiltration in the aortic root, necrotic coronary artery arteritis, and then complete coronary artery stenosis due to lumen occlusion caused by LMP [10, 11]. In 2004, through pig model, it was found that the coronary arteries of pig heart were dilated differently. Pathologically, it was found that the inner elastic membrane was broken and the intimal hyperplasia changed, and the perivascular inflammatory infiltration was observed. Through the analysis and observation of the clinical data of children with Kawasaki disease, combined with a large number of animal models of Kawasaki disease theoretical research basis and clinical research to improve the understanding of Kawasaki disease induced coronary artery damage. It shows that Kawasaki disease is an inflammation of small and medium blood vessels, and long-term vascular inflammation eventually leads to coronary atherosclerosis. The coronary artery wall was thickened, the inner diameter of the main artery was widened, the intima was thickened, the valve and the intima of the atrium were slightly swollen, the neutrophils were scattered and infiltrated, the coronary artery lumen was expanded and the cardiomyocytes were necrotic and dissolved, and local fibers replaced the calcium salt deposition of tissue hyperplasia. The extravascular interstitium of the heart is edema, with a few lymphocyte infiltrates and diffuse hyperplasia of fibrous connective tissue. The muscular layer of blood vessels was destroyed, and the adventitia showed focal fibrinoid necrosis and fibrosis. White thrombosis is seen in the lumen. Severe and persistent coronary thrombosis with endothelial cell damage and myocardial cell necrosis results in irreversible heart changes. Through the study of animal model and pathological changes, the inflammatory theory and immune theory of damage mechanism of coronary artery injury were confirmed.

Mechanism and effect of stem cell therapy

Functionally, stem cells have unique biological characteristics, such as the ability to self-renew, expand and limit the potential of differentiation, maintain and control cell regeneration, and then repair necrotic or damaged tissues. Through the theory of infection, as long as the inflammatory response caused by Kawasaki disease can be controlled or weakened, Kawasaki disease can be controlled or recovered. Therefore, a therapeutic measure is needed to inhibit or block the inflammatory response. In addition to promoting functional tissue regeneration and repair, stem cells also have a wide range of immunomodulatory and anti-fibrosis activities [12]. Macrophages in tissues are involved in the multiple roles of anti-inflammation and tissue repair in inflammatory injury. M1-type macrophages are dominant in the early stage of myocardial infarction, and M1-type macrophages lead to myocardial injury by phagocytosis, dissolution and digestion of necrotic myocardial tissue [13]. Type M2 macrophages participate in the anti-inflammatory response in the late stage of acute myocardial infarction and promote the effect of heart repair. Studies have shown that stem cell therapy can significantly increase the invasion of type M2 macrophages in the area of myocardial infarction, reduce fibrosis, increase angiogenesis, and improve cardiac function. A mouse model of myocardial infarction treated with stem cells showed that after one week of treatment, the number of M1 type in myocardial cells was less, the number of M2 type was increased, the number of residual myocardial cells was more, the infiltration of lymphocytes was reduced, the apoptotic index of myocardial cells and the deposition of myocardial collagen were decreased [14]. Peng Y [15-16] Studies have shown that stem cells reduce the expression of inflammatory factors and increase the expression of anti-inflammatory factors by adjusting the inflammatory response, so as to avoid excessive inflammatory response and tissue damage caused by inflammation. Mesenchymal stem cell-derived exosomes can enhance the M2 polarization effect of macrophages in myocardial tissue of myocardial infarction model, and inhibit the inflammation and apoptosis of myocardial tissue [17]. The transition from inflammatory injury tissue to pro-tissue repair in the inflammatory response is induced by the transformation of macrophages from M1 type to M2 type. The injection of mesenchymal stem cells induces the transformation of a large number of macrophages from M1 to M2, thereby reducing the inflammatory response of Kawasaki disease and promoting the repair of damaged heart tissue.

Stem cells have the ability to self-replicate, renew and effectively repair damaged tissues or organs [18]. Stem cells are a kind of relatively special cells, which are easy to obtain and do not involve many ethical issues [19-20] .Stem cells have homing properties and can be used as carrier tools to deliver biological agents in a directional manner, thus realizing the treatment of related diseases. The research of Zhao L et al. [21] demonstrated that stem cell DNA carries some gene points that determine the differentiation of muscle lines, thereby promoting the differentiation of stem cells into cardiomyocytes. Animal experiments have shown that the application of stem cells in the treatment of damaged myocardial cells can effectively improve the situation of myocardial blood supply and improve the body's cardiac function [22-23]. Human umbilical cord mesenchymal stem cells can differentiate into endothelium cardiomyocytes, and they have a wide range of sources with little immune response, so they have been used in the treatment of coronary artery damage caused by Kawasaki disease. After the injection of stem cells in animal models, the inner diameter of the main coronary artery was reduced, and a large amount of lymphocytes and eosinophils were infiltrated, but no obvious inflammatory response and injury changes were observed. Stem cells can successfully differentiate into vascular endothelial cells and some cardiomyocytes to repair heart tissue damaged by Kawasaki disease.

SUMMARY AND PROSPECT

Traditional treatments for Kawasaki disease are gamma globulin injections or oral aspirin. However, the 2004 American College of Cardiology guidelines state that the use of gamma globulin within five days of fever does not reduce the incidence of coronary damage, and there is a risk of developing resistance [24]; In addition, the price of gamma globulin is expensive, which increases the cost for the families of children. Stem cells play a key role in the regeneration and repair of coronary artery damage caused by Kawasaki disease, providing a new treatment method and idea to get rid of the limitations of traditional treatment, which is expected to successfully prevent the occurrence of CAL and improve the prognosis of patients with Kawasaki disease. However, it faces many problems. Stem cell therapy for coronary artery injury is still in the research stage, and the safety and

effectiveness of stem cell extraction need to be further studied and solved. However, with continuous efforts, stem cell therapy will become a more effective way to treat coronary artery damage.

DECLARATION OF COMPETING INTEREST

All authors declare no conflicts of interest.

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