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Pathogenesis of Atherosclerosis and Its Relationship with JAK / STAT Inflammatory Signaling Pathway

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Abstract: Atherosclerosis (as) is an important pathological basis of cardiovascular and cerebrovascular diseases such as coronary heart disease and stroke. In addition to risk factors such as lipid metabolism disorder, vascular smooth muscle cell (VSMC) activation and oxidative stress response, inflammatory response mediated by inflammatory signal pathway runs through the whole process of the formation and development of as as as a new risk factor, which has been recognized by the majority of researchers. This paper reviews the research progress of JAK / STAT inflammatory signaling pathway in as, in order to provide new ideas for the treatment of as by inhibiting inflammation.

1. Introduction

Atherosclerosis (as) is a chronic vascular inflammatory disease, with lipid metabolism disorder, inflammatory cell infiltration, bleeding and thrombosis, fibrous tissue hyperplasia as the main pathological changes. It is the pathological basis of cardiovascular and cerebrovascular diseases such as coronary heart disease, hyperten- sion and stroke, and poses a great threat to human health [1]. The pathogenesis of as has not been fully understood. At present, there are lipid infiltration theory, smooth muscle cloning theory, thrombosis theory, inflammatory response theory, etc. [2]. The inflammatory response theory explains the pathogenesis of as more comprehensively and has been widely recognized in the academic community. The author believes that the in-depth exploration of the pathophysiological mechanism and related signal path- ways of inflammatory response in as will help to find new drug targets and provide research ideas for the prevention and treatment of as.

2. Risk factors for atherosclerosis

There are many risk factors for AS. The more definite risk factors include hyper- lipidemia, hypertension, diabetes, obesity, alcoholism and smoking, which can promote the occurrence and development of AS in different degrees. Recent studies have found that, as is also affected by other factors, and these risk factors also play an important role in the occurrence and development of as.

2.1 Fibrinogen

In 1980, a study first published the relationship between fibrinogen (FIB) and coronary heart disease. Subsequent studies have shown that elevated fibrinogen levels have important implications for the occurrence of coronary heart disease and incid- ence rate and mortality of cardiovascular diseases. FIB is an independent risk factor for as. It is not only a reactive substance in acute phase, but also a coagulation factor. The possibility of as increases with the increase of FIB concentration in blood, which is in direct proportion [3]. FIB is an inducer of thrombin substrate and platelet aggregation. The change of FIB level can directly affect the thickness of arterial intimamedia. The pathological mechanisms of FIB induced as include the following: (1) promote the adhesion and aggregation between leukocytes and vascular endothelial cells, and further release inflammatory mediators. FIB, as a bridge between leukocytes and vascular endothelial cells, promotes the adhesion and cohesion between them, induces the release of inflammatory mediators, damages vascular endothelium, leads to plaque rupture and increases the incidence of cardiovascular and cerebrovascular events. (2) Participate in the regulation of inflammatory response. FIB is an acute phase protein of inflammatory response, which can lead to vascular endothelial cell injury, increase the permeability of vascular endothelium, cause smooth muscle cell proliferation and hypertrophy, accelerate the migration and degeneration of vascular endothelial cells, and then induce the accumulation of lipids in the arterial intima to form plaque, and finally as [4]. (3) Effect on hemodynamics. FIB can accelerate platelet aggregation, activate and regulate fibrin stabilizing factor, accelerate the reactive degranulation of platelets to adenosine diphosphate, and then increase the blood viscosity, make the blood in a hypercoagulable state, and finally form thrombosis.

2.2 Uric acid

Studies have confirmed that the degree of as is positively correlated with the increase of uric acid (UA) in serum [5]. The level of serum UA can be determined by the uric acid transport related protein GLUT9 (encoded by SLC2A9 gene) in human body. In the kidney, when the GLUT9 gene is mutated, the excretion of urate in vitro will be greatly reduced, resulting in a large amount of urate stored in the body, which will lead to hyperuricemia. The solubility of UA in blood is very low. The salt crystals formed by UA in blood can deposit on the blood vessel wall and directly damage the vascular endothelial cells. In addition, UA can also promote the release of inflamma- tory mediators such as C-reactive protein, increase the generation of oxygen free radicals, accelerate the oxidation of low-density lipoprotein and lipid peroxidation, further damage vascular endothelial cells and induce the formation of as.

2.3 Homocysteine

Homocysteine (Hcy) is an intermediate metabolite of methionine. McCully first proposed that Hcy may play an important role in the process of as in 1969 [6]. Studies have shown that compared with the general population, the level of serum Hcy in stroke patients is significantly increased, suggesting that Hcy is involved in all stages of as formation [7]. The mechanism of Hcy involved in as may include the following: (1) toxic effect on vascular endothelial cells. Hcy can promote the degradation of nitric oxide (no) through reactive oxygen intermediates such as hydroxyl, peroxide and superoxide anion free radical, inhibit the synthesis of no, and damage the vasodil- ation function mediated by no, resulting in as. (2) Promote the proliferation of vascular smooth muscle. Vascular mesomembrane smooth muscle cells can proliferate and accelerate plaque formation under Hcy mediated inflammatory response. (3) Break the balance between coagulation and fibrinolysis system. Hcy, as a thrombogenic agent, can change the coagulation function by up regulating the secretion and expression of

interleukin-8 and nuclear cell chemokine-1; In addition, Hcy can selectively inhibit the expression of thrombomodulin in vivo, reduce the activities of antithrombotic factors VI and VII and vascular endothelial cell related protein C, and increase the activity of coagulation factor V. At the same time, platelet thromboxane (TXA2) can be produced under the promotion of Hcy, activate coagulation factors and platelet adhesion factors, lead to as and thrombosis [8] (4) and affect lipid metabolism. Low density lipoprotein (LDL) is a lipoprotein particle that transports cholesterol to peripheral tissue cells. LDL can be oxidized into oxidized low density lipoprotein (ox-LDL). When LDL is oxidized excessively, the cholesterol it carries will deposit on the arterial wall, causing a series of inflammatory reactions and finally as. Hcy can not only increase the oxidation reaction of LDL, but also bind to LDL to form foam cell complexes and promote AS[9].

2.4 C-reactive protein

C-reactive protein (CRP), as a pro-inflammatory factor, when the tissue is damaged or the body is infected, the level of CRP in plasma will increase significantly, which can be used as an indicator protein of various acute and chronic inflammation. As is an inflammatory disease of vascular intima. Therefore, the change of CRP level can affect the occurrence and development of as and is closely related to the forma- tion of thrombosis [5]. CRP can mediate the inflammatory response of vascular endothelial cells by promoting phagocytosis of necrotic cells, activating complement and releasing inflammatory mediators, leading to the occurrence or acceleration of as. Relevant studies have shown that CRP, mediated by active oxidants, can directly act on the endothelial cells of arterioles, produce toxic damage to vascular endothelial cells, and make the vascular wall more prone to plaque and thrombosis. In the healthy population, the baseline level of CRP is an important factor for strongly predicting future stroke, myocardial infarction, peripheral vascular disease and vascular death events [10].

3. Inflammatory response and the mechanism of as

As was once considered to be a process of slow accumulation of lipid substances in the blood vessel wall. At the end of the 20th century, foreign expert Ross put forward the "injury response" theory of as, indicating that as is a chronic inflamma-tory disease induced by multiple factors [11]. Subsequently, a large number of research results confirmed this view. As involves complex circulating blood cells (such as platelets and monocytes) and plasma components (such as lipoprotein), which interact with vascular wall cells (such as endothelial cells) stimulated by external factors such as high fat and high sugar to mediate as.

The early mechanism of as is the destruction of the permeability barrier function of endothelial cells in the arterial intima, which makes the deposition of lipoproteins and other substances in the circulating blood and finally adhere to the arterial wall, and then oxidized and modified into low-density lipoprotein cholesterol, which leads to local inflammatory reaction. At the same time, the secretion of vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1) increases, and leukocytes migrate and adhere to the endothelial injury mediated by a variety of chemotactic factors, so as to gather under the endothelium. It and the inflammatory mediators secreted by endothelial cells trigger the local chronic inflammatory reaction of blood vessels and mediate the formation of as plaque [12].

Once the white blood cells are attached to the arterial wall, monocyte chemoat- tractant protein-1 (MCP-1) promotes monocyte differentiation into macrophages. Oxidized low density lipoprotein (OX-LDL) can be rapidly identified and phagocy- tosed by macrophage scavenger receptor (SR), and chemotaxis macrophages are transformed into foam cells. Foam cells are filled with lipid droplets and form a "lipid streak" on each other [13]. At the same time, lipoprotein phagocytic macrophages

and damaged endothelial cells synthesize and secrete interleukin-6 and tumor necrosis factor- α (TNF-α), Matrix metalloproteinases (MMPs), platelet-derived growth factor (PDGF), fibroblast growth factor (FGF) and other pro-inflammatory factors and growth factors promote immune cell infiltration, form lipid pools locally, and promote inflammatory response and plaque growth.

Under the co-chemotaxis of PDGF and FGF, arterial media smooth muscle cells (SMC) migrate to the subintima and proliferate. SMC derived collagen and other extracellular matrix proteins form a protective fiber cap to cover the plaque, making the plaque more stable. Activated macrophages can secrete a variety of MMPs, and extracellular matrix proteins and interstitial collagen can be degraded, resulting in thinning of fiber cap and easy rupture of plaque; At the same time, activated leukocytes can inhibit the renewal of interstitial collagen, increase the fragility of plaque and further increase the possibility of plaque rupture [12].

Once as plaque ruptures, platelet activation, activation of coagulation cascade and multicellular activation in circulation will participate in thrombosis, block blood vessels and lead to malignant ischemic events. Recent studies have shown that platelets not only mediate as thrombosis, but also participate in inflammatory immune response. When the blood flow shear stress changes, platelets in circulating blood respond to blood flow changes through surface receptors, bind adhesion proteins and extracellular matrix, make platelets adhere and activate, and immune by expressing integrin, P-selectin and toll like receptors. The interaction between platelet P-selectin and leukocyte expressed ligand 1 (PSGL-1) mediates the formation of platelet leukocyte aggregates and promotes the occurrence of as. At the same time, activated platelet activated granules release, and dense granules secrete neurotransmitters (5-HT), adenosine phosphate (ATP / ADP) and other mediators; α Particles release adhesion proteins, chemokines, cytokines, etc. These secretions participate in the development of as through positive / negative regulation of endothelial cells, smooth muscle cells and leukocytes [9-10].

In conclusion, as contains complex matrix mediators, and a variety of cytokines run through the whole process of its occurrence and development.

4. Relationship between atherosclerosis and tyrosine kinase / signal transducer and activator of transcription (JAK / STAT) signaling pathway

JAK / STAT is a cytokine mediated signal transduction pathway, which can be activated by a variety of cytokines and regulate the expression of a variety of cytokines. It is the main way for cells to transmit signals. JAK /STAT is mainly composed of tyrosine kinase Jak and STAT protein. JAK / STAT family has four Janus kinases (jak1-3, Tyk2) and seven stats (1,2,3, 4,5a, 5b, 6). The process of pathway activation is as follows: firstly, cytokines combine with the corresponding receptors on the cell membrane to drive the dimerization of receptor molecules and recruit receptor coupled JAK kinases, which are phosphorylated and activated through interactive tyrosine. After JAK kinase is activated, it can catalyze the phosphorylation of tyrosine residues on the receptor. The receptor recruits stat, JAK kinase phosphorylates stat to activate it, and the activated stat is separated from the receptor to form dimer in the cytoplasm, it enters the nucleus and binds to the target gene to regulate gene transcription and protein expression. Activated JAK / STAT protein can increase the expression of various inflammatory factors, such as VCAM-1 and MCP-1, accelerate cell proliferation and migration, and chemotactic adhesion and infiltration of inflammatory cells to arterial endothelial cells [14].

JAK / STAT signaling pathway mediates the formation of as from the dysfunction of vascular endothelial cells (VECs), the proliferation and migration of vascular smooth muscle (VSMC), inflammatory cell infiltration and so on. The activation, proliferation and migration of endothelial cells are the basis for the formation of new blood vessels. The immature neovascularization can cause

the instability and even rupture of as plaque. The proliferation and migration of endothelial cells are induced by vascular endothelial factor (VEGF), and JAK / STAT signal pathway is the main pathway of VEGF signal transduction in cells. Chen Jianfang et al [15] found that inhibition of JAK / STAT signaling pathway can reduce high glucose induced vascular endothelial injury in human umbilical vein. SMC cells in vascular mesomembrane are in a static state under normal conditions. When as occurs, tissue synthesis and expression of a variety of inflammatory mediators stimulate VSMC from static to proliferative and migratory state. Studies have shown that VSMC proliferation and migration can be inhibited by inhibiting JAK / STAT signaling pathway [16]. Inflammatory infiltration is an important factor in as lesions. A large number of studies have shown that the regulation of inflammatory cell prolifera- tion and differentiation is closely related to JAK / STAT signal pathway. Huang Zhi min et al [17] found that blocking JAK / STAT signaling pathway can reduce the level of inflammatory factors in adriamycin renal fibrosis rats.

5. Summary and Prospect

With the development of modern molecular biology, the research on the patho- genesis of as has gradually penetrated into the micro fields of cells, molecules and so on. The formation of as is a complex process with multiple mechanisms. It is gener- ally believed that as lesions are a chronic inflammatory process caused by VECs damage and endothelial dysfunction. The signal pathways related to the inflammatory response of VECs are complex, far from the above one. These pathways are interrel- ated and affect each other, and jointly participate in the formation and development of as. Theoretically, blocking the related inflammatory signaling pathway can block the process of as. In fact, this conjecture has been confirmed in many clinical studies and animal experiments; The recent study on the thrombosis results of canakinumab anti-inflammatory drugs (Cantos) changed the inflammation in as from speculation to clinical reality [18]. This study takes IL-1, a specific proinflammatory cytokine that has played an important role in the formation of as after a lot of research β As a target, it has successfully broken through the inflammatory body as a promising way for further therapeutic intervention, NLRP3 inflammatory body and downstream cytokine IL-1 β, IL-18 and IL-6 are attractive intervention candidate targets. Studies have shown that taking anti-il-1 β Antibodies can reduce the recurrence of myocardial infarction in patients with cardiovascular stability after myocardial infarction and the occurrence of major cardiovascular adverse events in patients treated according to guidelines (including statins). With the success of Cantos, there have been interfer- ence with IL-1 by inhibiting the activation of inflammatory body β and the strategy of its production process, and the selective neutralization of some chemokines are also worth considering in this regard. In addition, there are several promising pathways that have not yet entered the stage of clinical trials, but are in the stage of active exploration [19-20]. As is a complex disease mediated by many factors. In practice, it is difficult to achieve the ideal effect if only anti-inflammatory treatment is carried out for a single target. Therefore, exploring the relationship between inflammatory response and as and the relationship between various signal pathways will help to clarify the pathogenesis of as, find the target of new drugs and design a more reasonable scheme for the prevention and treatment of as.

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