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Prospect on the Therapeutic Effect of Vascular Endothelial Growth Factor from the Perspective of the Pathogenesis of Pancreatitis

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Abstract

Many theories on the pathogenesis of severe acute pancreatitis (SAP) cannot fully explain the pathophysiological mechanism of SAP, with many unexplainable contradictions, hence the need for further investigation. Vascular Endothelial Growth Factor (VEGF), the most effective proangiogenic and vascular endothelial protective agent found by far, plays critical roles in the processes of angiogenesis, vascular development and vascular protection. In recent years, many scholars have investigated the therapeutic effect of VEGF on pancreatitis, but the results are inconclusive. This study intends to explore the prospects of VEGF on the treatment of SAP from the perspective of the pathogenesis of pancreatitis.

Keywords: Acute pancreatitis; Pathogenesis; Vascular endothelial growth factor

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Background

Between the two types of Acute Pancreatitis (AP), Severe Acute Pancreatitis (SAP) accounts for approximately 20% and tends to cause Multiple Organ Dysfunction Syndrome (MODS). In spite of continuous improvements in medical conditions, the mortality rate of SAP is still as high as 20% to 40% [1,2]. This situation is mainly due to an insufficient understanding of the pathogenesis of SAP, which also leads to the lack of substantial progress in its clinical treatment. Further exploring the pathogenesis of SAP and then carrying out an intervention on the key steps from the disease onset may lead to therapeutic breakthroughs.

As the most effective proangiogenic and vascular endothelial protective agent found by far, Vascular Endothelial Growth Factor (VEGF) specifically acts on endothelial cells to promote the proliferation and differentiation of vascular endothelial cells and facilitate angiogenesis. VEGF plays crucial roles in the processes of vascular development and formation and vascular protection. VEGF is often widely used as a specific factor of vascular endothelial cells in the studies on tumorigenesis, progression and metastasis, and treatment of ischemic diseases [3]. Due to its powerful roles in promoting angiogenesis and vascular protection, scientists have started to study the therapeutic effect of VEGF on AP in recent years and have obtained preliminary research results. This review intends to focus on the therapeutic effect of VEGF on AP from the perspective of the pathogenesis of AP, to address the gap in the understanding of AP, in order to provide a new clinical treatment concept.

Current Research Status and Inadequate Understanding of Acute Pancreatitis

Self-digestion of pancreatic enzymes

In 1896, Chari proposed that pancreatitis was caused by the ectopic activation of pancreatic enzymes; this has been considered the classic theory of AP pathogenesis ever since. Under normal circumstances, trypsin is activated in the duodenum. However, in AP, the normal isolation mechanism of lysosomal enzymes and trypsinogen is disrupted, causing the ectopic activation of trypsinogen in the pancreas and leading to the self-digestion of pancreatic tissues. Coelho et al. confirmed that the blood levels of TNF-α and IL-6 were positively correlated with the blood concentration of proteases during SAP, and decreasing the blood concentration of proteases significantly reduced the degree of liver injury [3]. This finding suggests that trypsin plays an important role in AP and the

associated multiple organ damage. In 2000, Lundeberg [4] reported that trypsin is the most important mediator of the inflammatory response in SAP. Meanwhile, Leonhardt et al. [5,6] also confirmed Lundeberg's conclusion. In fact, the discovery by Lundeberg et al. is an extension of Chari's pancreatic enzyme theory. However, Chari's theory is limited to the pathological changes of the pancreas itself and lacks a reasonable explanation for the damage to the organs other than the pancreas. Therefore, Chari's theory has certain limitations. Foitzik and others proposed that SAP-activated pancreatic enzymes not only digest the pancreas itself but also continue to exert their destructive effects as they enter the blood circulation with blood flow, triggering a series of pathological changes, such as microcirculatory disturbances, excessive activation of leukocytes and inflammatory factors, and secondary infections. However, how does trypsin cause these pathological phenomena? What is their specific mechanism of action? Further research is needed to address these questions.

Excessive release of inflammatory mediators and cytokines

The theory of inflammatory factors and cell mediators was first proposed by Ringerknecht et al. in 1988 [7]. Since its introduction, this theory has become a hot topic for research in the field around the world. In recent years, substantial research results have been achieved, which suggest that the overstimulation of neutrophils causes the increased production of toxic substances such as oxygen free radicals and TNF-α, resulting in varying degrees of Systemic Inflammatory Response Syndrome (SIRS), which in turn leads to multiple organ failure. The main idea of this theory is that the over activation of leukocytes leads to the release of large amounts of cytokines and inflammatory mediators into the blood upon the onset of AP, resulting in a respiratory burst, the production of oxygen free radicals, and the initiation of a cascade of inflammatory cytokine activation. These events lead to microcirculatory disorders, which further aggravates pancreatic tissue injury and triggers SIRS and MODS [8].

Microcirculatory dysfunction

The occurrence and development of AP are believed to have a crucial association with circulation. Thromboxane A_2 (TXA_2) is a potent capillary vasoconstrictor and platelet contraction enhancer that can cause tissue ischemia; coagulation disorders, leukocyte activation, and the release of oxygen free radicals, resulting in damage to the vascular endothelium and in turn microcirculatory dysfunction. Endo Thelin (ET) can cause vasospasm, promote calcium influx, damage tissue cells, and reduce cardiac output, leading to ischemia and oxygen free radical production. Ischemia, hypoxia, and increased oxygen free radicals also promote ET production in endothelial cells, resulting in a vicious cycle [9].

However, the role of blood circulation in the pathogenesis and progression of AP remains controversial. Some scholars believe that the changes in pancreatic blood flow is only a secondary manifestation of AP, and studies have demonstrated that changes in pancreatic blood flow and systemic hemodynamics are caused by hypovolemia after the onset of AP. Therefore, the role of blood circulation in the pathogenesis and progression of AP and its exact mechanism await further research.

Bacterial infection and the "Second Strike" theory

Infections in pancreatic and para pancreatic tissues following AP are one of the major causes of mortality in the late stage of AP. A large number of studies have shown that the barrier function of the intestinal epithelium is seriously impaired in AP, resulting in the translocation of bacteria and toxins in the intestinal tract and thus infections in pancreatic and para pancreatic tissues and even sepsis [10]. Endotoxins also promote the second cascade of cytokine activation, causing the body to suffer a second strike, aggravating organ damage and further worsening the symptoms.

The above theory explains to some extent some phenomena in the pathogenesis of AP. However, many special phenomena cannot be reasonably explained by existing theories. (1) What are the criteria to distinguish between the two pathological types of AP? In the two types of pancreatitis, the pathological changes of edematous pancreatitis are mainly edema and inflammatory cell infiltration in pancreatic tissues. In addition to hemorrhage and necrosis in the pancreas itself, SAP also causes serious damage to other organs. According to the current theory of the "waterfall-like" cascade effect, and in the absence of specific treatment measures, there should be only one type of AP, which is SAP. In fact, less than 20% of all pancreatitis patients fall into this category. This phenomenon cannot be explained by the current theories. (2) Why are the pathological changes of other organs similar to those of the pancreas itself? We know that the pathological changes of the pancreas in AP mainly include necrosis, hemorrhage, and inflammatory cell infiltration in pancreatic tissue. In fact, the pathological changes in the liver, kidney, lung, intestine and brain tissues are consistent with those in the pancreas in AP [11,12]. This phenomenon is also currently unexplainable using the existing theories. (3) Why does the occurrence of multiple organ damage have an obvious decreasing trend along the pancreatic blood flow circuit? Our literature review clearly found that the incidence of organ damage has a close relationship with the location of the involved organ on the route of pancreatic venous drainage, namely, liver (80-100%) >heart (48.9-60.7%) >lung (15-50%) >kidney (15-35.8%) >brain (9-20%). What causes this phenomenon?

Establishment of a Medical Hypothesis

With the above questions in mind, we developed the following hypothesis after long-term animal experiments and an extensive review of the literature: a large amount of pancreatic proteases are ectopically activated upon AP, especially SAP, and enter the blood circulation through venous blood flow while destroying the structure of the pancreas itself. These proteases can destroy the protein skeleton structure on vascular wall, causing impaired vascular wall integrity and increased vascular permeability. Therefore, large amounts of vascular contents pass through the damaged vascular wall and enter the interstitial space or body cavity. This leads to early circulatory dysfunction in AP patients, which is an important cause of early death in AP patients. Because the liver is the first recipient organ in pancreatic venous drainage, the concentration of activated pancreatic protease is the highest in the liver, where the extent of damage caused by these proteases is also the most serious. With the consumption of these pancreatic enzymes in the liver, the concentrations of these proteases in post hepatic venous blood are significantly lower than the prehepatic concentrations, and thus, the degree of damage to other organs along this venous drainage circuit shows a decreasing trend. According to this hypothesis, we can easily explain the questions we raised earlier. Distinguishing between AP and SAP, the two types of pancreatitis, mainly depends on the amount of activated pancreatic proteases and whether they enter the blood circulation and then cause a wider range of damage.

According to our inference, from the current point of view on AP treatment, once the vascular wall is damaged, it is apparently impossible to fundamentally address the issue using the current traditional treatment measures. This is also the main reason why the mortality rate of AP patients remains high. Therefore, it is only possible to achieve better therapeutic effects when we start from the root cause of the disease and repair the damaged vascular endothelium as soon as possible, to maintain the stability of the circulatory function and then improve the impaired organ functions. This treatment strategy is likely to become a breakthrough for AP treatment in the future.

Prospect on the effect of vascular endothelial growth factor on the treatment of pancreatitis

As the most potent substance that promotes angiogenesis and vascular endothelial protection, VEGF specifically acts on endothelial cells to promote the proliferation and differentiation of vascular endothelial cells, thus promoting angiogenesis. VEGF plays important roles in the process of vascular development, formation, and myocardial and cerebral ischemia. VEGF is often widely used as a vascular endothelial-specific factor in research on tumorigenesis, tumor progression and metastasis, and the treatment of various ischemic diseases [13]. Recent studies have found that VEGF has the following functions: 1) Promote endothelial cell proliferation: VEGF stimulates vascular endothelial cell division and proliferation, with a chemotactic effect. VEGF activates phospholipase C, hydrolyzes phosphatidylinositol, and induces calcium release to promote endothelial cell proliferation and inhibit endothelial cell apoptosis. 2) Promote angiogenesis: VEGF promotes mitosis in vascular endothelial cells and regulates the factors involved in angiogenesis. VEGF has the functions of stimulating cell migration, blood vessel formation, and intimal repair and thus maintaining vascular integrity. In addition, VEGF induces the activation of fibrinogen and the expression of metalloproteinase and interstitial collagenase in endothelial cells. These proteases stimulate matrix degradation, which is an important step in angiogenesis. VEGF also promotes the growth of endothelial cells derived from arteries, veins, and lymphatic vessels. 3) Vascular protection: (1) Vascular maintenance function: VEGF dose-dependently stimulates the production of Nitric Oxide (NO) in animal or human endothelial cells to exert its vascular maintenance function. (2) Inhibition of Smooth Muscle Cell (SMC) overgrowth: VEGF promotes SMC proliferation and inhibits endothelial cell apoptosis and thus has protective effects on endothelial cells. (3) Protection of endothelial cells: VEGF induces the expression of survivin and X-linked Inhibitor of Apoptosis Protein (XIAP) through inducing the expression of anti-apoptotic protein Bcl-2 and its family member A1 and suppresses the upstream pathway of the caspase family and inhibits endothelial cell apoptosis. (4) Alteration of extracellular matrix: In endothelial cells, VEGF induces the expression of plasminogen activator and plasminogen activator inhibitor, as well as the expression of other proteases, matrix collagenase and the tissue factor. VEGF also stimulates the release of factor VIII from endothelial cells. These effects change the extracellular matrix, which is conducive to the bud growth of blood vessels to the surrounding areas [13]. (5) Anti-inflammatory effect: Inflammation is a defensive response characterized by exuding circulating leukocytes and plasma proteins to the site of tissue damage. Adhesion of leukocytes to the surface of the vascular endothelium is the starting step of the chemotactic migration of leukocytes, their crossing of the vascular wall and forming inflammatory foci. VEGF weakens the interaction between leukocytes and the endothelium, performing anti-inflammatory activities. (6) Inhibition of thrombosis: VEGF inhibits platelet aggregation and adhesion and thus has an antithrombotic effect. The specific mechanisms of VEGF are shown in (Figure 1).

Based on the therapeutic effect of VEGF, we believe that the use of VEGF in AP patients to promote neovascularization and vascular endothelial protection and intervene in AP from the onset may have unexpected therapeutic effects. Therefore, in subsequent studies, we will use VEGF as a therapeutic drug to observe the therapeutic effect of VEGF on SAP in rats and further explore the associated mechanisms. Based on the experimental results, we will strive to conduct clinical studies, in the hopes of finding new effective treatment options for AP and improving patient prognosis.

Fortunately, the therapeutic effect of VEGF on SAP has already received some attention and has been preliminarily confirmed in experiments. As early as 2006, Ueda et al. demonstrated that VEGF alleviated the degree of organ damage during SAP by inhibiting apoptosis in liver and kidney tissues via the examination of serum VEGF levels in SAP patients and VEGF intervention in animal experiments [14]. Nakajima et al. also demonstrated in animal experiments in 2007 that VEGF mitigated intestinal mucosal functional impairment and the resulting shift in bacterial colonization in SAP rats through improving microcirculation and inhibiting intestinal mucosal cell apoptosis [15]. Unfortunately, these studies were limited to studying the conditions, without further exploration on the related mechanisms. With progress in relevant research, VEGF will have a new breakthrough in the treatment of pancreatitis in the near future.

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