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Research Progress on the Formation Mechanism and DNA Methylation of Autologous Arteriovenous Fistula Stenosis

Zhi Zou[1], Yanlong Zhao[2,*]

[1]Shaanxi University of Chinese Medicine, Xianyang 712046, Shaanxi, China
[2]Shaanxi Provincial Hospital of Chinese Medicine, Xi'an 710003, Shaanxi, China
**Correspondence Author*

Abstract: ***Arteriovenous fistula (AVF), as the most commonly used vascular pathway for end-stage renal failure hemodialysis patients, is also the premise for hemodialysis patients to start and maintain dialysis, but its complications have become the main factors affecting hospitalization and death of dialysis patients. The most common complication of AVF is intimal hyperplasia resulting in stenosis. In order to better prevent and treat AVF stenosis, it is of great significance to further study the mechanism of its occurrence and development for HD patients. The mechanism of AVF stenosis is the result of the interaction of multiple factors, and a deeper understanding of these mechanisms can help to develop more effective diagnostic and treatment strategies to improve the patency of AVF in HD patients. This article briefly describes the mechanism of AVF formation and the progress of DNA methylation research, hoping to provide new prevention and treatment ideas for further clinical research and practice, and finally achieve the purpose of improving the quality of life of HD patients.***

Keywords: Autogenous arteriovenous fistula stenosis, DNA methylation, Epigenetics, Hemodialysis**.**

1. Introduction

When chronic kidney Disease reaches the End Stage Renal Disease (ESRD), the normal kidney function must be replaced by kidney transplantation or blood purification to maintain life. maintenance hemodialysis (MHD) is the most commonly used life-sustaining treatment for patients with chronic renal failure. Clinical practice guidelines for vascular access recommend AVF as the preferred vascular access for end-stage renal failure hemodialysis patients [1], and the consensus of Chinese experts on vascular access for hemodialysis also believes that AVF should be the preferred vascular access for MHD patients. AVF has the advantages of high surgical maturity, high tolerance, and low infection rate. Only when AVF cannot be established, Arteriovenous Graft (AVG) is selected as the secondary option. As the most commonly used vascular pathway for end-stage renal failure hemodialysis patients, AVF is also the premise for hemodialysis patients to start and maintain dialysis, but its complications have become the main factor affecting hospitalization and death of dialysis patients. Stenosis caused by intimal hyperplasia is the most common complication of AVF. Studies have reported that the incidence of stenosis is as high as 90%, and the incidence of proximal anastomotic stenosis is the highest [2]. The loss of vascular access due to stenosis has become the main reason for hospitalization and operation of hemodialysis patients, which has caused huge medical and mental burden to a considerable number of patients. However, the formation mechanism of AVF stenosis is a very complex process. In recent decades, many studies have been devoted to revealing the mechanism of AVF stenosis. Although some progress has been made, the mechanism of internal fistula stenosis is still not very clear. In order to better prevent and treat AVF stenosis, it is of great significance to further study the mechanism of its occurrence and development for HD patients. Therefore, this paper briefly describes the formation mechanism of AVF and the research progress of DNA methylation, hoping to provide new prevention and treatment ideas for further clinical research and practice, and ultimately achieve the purpose of improving the quality of life of HD patients.

2. The Formation Mechanism of AVF Stenosis

2.1 Proliferation of Vascular Smooth Muscle Cells

Studies have shown that [3], vascular intimal hyperplasia is mainly caused by the proliferation and migration of vascular smooth muscle cells (VSMCs). In the rat model of autologous arteriovenous fistula, significant thickening of the intima near the anastomotic end was observed, and a large number of smooth muscle cells and collagen deposition were found in the hyperplasia tissue. After phenotypic changes, smooth muscle cells in the vascular media migrate to the intima and proliferate abnormally, eventually leading to intima thickening and lumen stenosis. VSMCs play a central role in the process of intima hyperplasia and vascular wall remodeling. Abnormal proliferation of VSMCs can be activated by many different bioactive substances. The factors that promote the proliferation of smooth muscle cells include PDGF, TGF-β, FGF, angiotensinII (AngII), thrombin, endothelin-1 (ET-1), tumor necrosis factor-α (TNF-α), etc. They may participate in the proliferation of VSMCs through their own mechanisms [4]. After abnormal activation, smooth muscle cells proliferate excessively, and can secrete a variety of vasoactive substances and extracellular matrix, causing hypertrophy of blood vessel wall and neovascular intima. Arteriovenous fistula puncture can induce local inflammatory response, act on vascular intima, induce high expression of oxidative stress, and phagocytes accumulate at the puncture site, aggravate vascular endothelial injury and release a large number of chemokines, change the phenotype of VSMCs, and promote their proliferation and migration. At the same time, a large amount of extracellular matrix (ECM) is produced and secreted, which leads to abnormal endometrial hyperplasia and vascular wall remodeling, further reducing the AVF tube

diameter, leading to the occurrence of stenosis and loss of AVF function [5].

2.2 Inflammatory Response Occurs

As one of the mechanisms of AVF stenosis, inflammatory response has been confirmed in a large number of experiments and clinical studies that inflammatory factors can cause AVF stenosis. For patients with end-stage renal failure, a variety of factors and mechanisms may lead to inflammatory responses, resulting in increased levels of inflammatory factors in the body, which further aggravate the narrowing of intra-arteriovenous fistulas. Liu et al. [8] found that compared with hemodialysis patients without vascular dysfunction, the expression of inflammatory factors such as C-reactive protein, interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF-α) in the blood of hemodialysis patients with AVF loss is significantly increased. The construction of AVF is itself a pathological process due to the operation of arteriovenous fistula, and post-traumatic repair often stimulates an inflammatory response, as does the formation of scar tissue or blood clots. When macrophages infiltrate the blood vessel wall, the production of monocyte chemoattractant protein-1 (MCP 1) can be increased, the local inflammatory response can be aggravated, the cells can be recruited to the intima, and the intima hyperplasia can be promoted [6], Thus, aggravating the formation of arteriovenous fistula. Other inflammatory factors and corresponding inflammatory cells, such as hypersensitive C-reactive protein (hs-CRP), IL-6, TNF-α, FGF, etc., may be involved in the process of endometrial hyperplasia [7]. Relevant studies have shown that CKD can activate the YAP/TAZ signaling pathway of vascular endothelial cells and promote the infiltration of AVF endometrial inflammatory cells, thus promoting the proliferation of vascular smooth muscle cells and participating in the occurrence and development of AVF internal fistula hyperplasia [8].

2.3 Vascular Endothelial Dysfunction

Endothelial cell (EC) is a cell component that is in direct contact with blood. Once any changes occur in the blood, including changes in composition and dynamics, EC will first be felt, and then activate pathophysiological activities to affect surrounding cells. For example, high shear stress induces KLF2 activation in EC, prompting EC to secrete extracellular phospholipid vesicles containing microRNA (miR) of the Mir-143/145 cluster. These vesicles promote the differentiation of VSMCs into an anti-atherosclerotic phenotype, reducing the extent of atherosclerotic lesions [9]. Under the influence of low shear stress and oscillatory shear stress, EC can feel pressure and secrete factors pathologically to promote the proliferation and migration of VSMCs [10], Further aggravated endometrial hyperplasia resulting in stenosis of internal fistula. The results of animal experiments confirmed that CKD can up-regulate the expression of YAP of EC in the internal fistula tissue, and the subsequent changes of EC may be one of the reasons for the stenosis of internal fistula caused by endometrial hyperplasia [8].

3. DNA Methylation

As one of the more mature epigenetic modification methods studied at present, DNA methylation means that s-adenosyl methionine (SAM) provides methyl groups under the catalysis of DNA methyltransferases (DNMTs). The process of selectively adding methyl groups to cytosine in two nucleotides of DNA, CG (cytosine guanine), to form 5'methylcy tosine (5mC), which causes heritable changes in cell phenotype and gene expression. DNMTs in animals are divided into maintenance methyltransferase (DNMT1), DNA methyltransferases 3a (DNMT3a), and DNA methyltransferases 3b (DNMT3b). DNA methylation is an important epigenetic modification that regulates cell function by silencing the expression of related expressed genes. A large number of studies have shown that [11, 12], DNA methylation is involved in smooth muscle cell proliferation, inflammatory response regulation, vascular endothelial dysfunction and other related reactions. These reactions are directly or indirectly involved in the formation mechanism of AVF stenosis caused by intimal hyperplasia, and ultimately lead to AVF loss [12].

3.1 DNA Methylation is Involved in Regulating the Proliferation of Vascular Smooth Muscle Cells

Relevant studies show that [13], DNA methylation controls certain genes associated with proliferative differentiation of VSMCs, such as serum response factor, PDGF, and VSMCS-specific SM22α. In addition, DNA methylation inhibitors inhibit the proliferation and migration of VSMCs induced by platelet-derived growth factor (PDGF) [14]. Meanwhile, matrix metalloproteinases (MMP) are also associated with the proliferation and migration of VSMCs [15, 16]. MMP1 expression and protein secretion of VSMCs increased under the action of DNA methylation inhibitors [17]. The result of research shows that [18] DNMTs gene knockout or inhibition can induce the loss of hypermethylation in ten-eleven translocation-2 (TET2) gene promoter and promote its expression, thereby inhibiting the proliferation of vascular smooth muscle cells in vitro. In addition, it can be concluded from the study results [19] that the increased expression of DNMT3b down-regulates the expression of p53 by increasing the methylation degree of p53, thus promoting the proliferation of VSMCs. The above studies demonstrated that DNA methylation deficiency, decreased activity of DNMT1 or increased expression of DNMT3b in vascular smooth muscle cells were closely related to the proliferation and migration of VSMCs, which further led to the formation of AVF stenosis.

3.2 DNA Methylation is Involved in Regulating Inflammation

As one of the mechanisms of AVF stenosis, inflammatory response has been recognized by many scholars. DNA methylation is closely related to inflammation. Studies have shown that only scattered CpG dinucleotides exist in the TNF-α gene promoter region, and their methylation status plays an important role in gene expression regulation. When the methylation level of CpG dinucleotide scattered in the TNF-α gene promoter region was high, the gene was not expressed or had low expression. When the methylation level is low, the gene is highly expressed [20]. In fibroblast-like synoviocytes associated with rheumatoid arthritis, miR-124a gene methylation promotes IL-1β-mediated cell proliferation

and also upregulates TNF-α expression, accelerating inflammatory responses [21]. In addition, DNA methylation inhibitors up-regulate the expression of IL-6 and TNF-α genes in lipopolysaccharide-stimulated broiler peripheral blood mononuclear cells, which can promote inflammatory response. At the same time, methyl-donor methionine increased the methylation level of IL-6 promoter region 191 and TNF-α promoter region 419, and down-regulated the expression levels of IL-6 and TNF-α, thereby inhibiting the inflammatory response [22]. In different types of inflammation, DNA methylation has a regulatory effect on the inflammatory response, such as the methylation level of the promoter region of inflammatory factors such as TNF-α and IL-1β, which has a certain impact on its expression. At the same time, some inflammatory factors can also promote the expression of DNMTs and increase its activity, thereby causing abnormal DNA methylation [23, 24]. It [25] is concluded that DNA methylation may also regulate inflammatory response through some mirnas. For example, inhibition of DNMT1 expression may lead to hypomethylation of the promoter region of miR-193a-5p gene, resulting in upregulation of hsa-miR-193a-5p expression, thereby reducing the expression of pro-inflammatory factor IL-12 and inhibiting inflammatory response. At the same time, miR-203 is regulated by DNA methylation, and Mir-203 also influences inflammation by regulating IL-6 expression through the NF-κB signaling pathway [26]. In addition, under the catalyst of enhancer of zeste, trithorax 9, (SET9), TNF-α and IL-1β can induce the methylation of p65 protein, inhibit the binding of p65 promoter to transcription factors, down-regulate the expression of p65, and inhibit the NF-κB signaling pathway. To reduce the inflammatory response [27]. In summary, it can be seen that DNA methylation can regulate inflammatory response through miRNA and inflammatory signaling pathways, increase the content of inflammation factors in blood vessels, and further cause AVF stenosis, resulting in its loss of function.

3.3 DNA Methylation is Involved in the Regulation of Vascular Endothelial Dysfunction

Some studies have shown that compared with non-uremic patients, uremic patients have a reduced ability to regulate vasodilation through blood flow, an increase in endogenous nitric oxide synthase (eNOS), and a decrease in the number and function of endothelial progenitor cells, all of which increase the occurrence of oxidative stress [28], This leads to vascular endothelial dysfunction. eNOS expression is regulated in part by epigenetic modifications, including methylation of gene promoter regions. For example, in cells with low eNOS expression, the eNOS promoter region is highly methylated, while in cell types with high eNOS expression, the eNOS promoter region is almost entirely demethylated. At the same time, in vitro experiments showed that eNOS gene was highly methylated in undifferentiated early endothelial progenitor cells, but very low methylated in differentiated endothelial cells (including umbilical vein endothelial cells, microvascular endothelial cells, etc.) [29]; Demethylation treatment can improve the expression of eNOS in cells with low eNOS expression [30]. Judging from the vascular endothelial dysfunction caused by DNA methylation mediated inflammatory response, DNMT1, as a key catalytic enzyme of DNA methylation, can participate in vascular endothelial dysfunction by regulating inflammatory response [31]. Elevated levels of Kruppel-like transcription factor 2, a transcription factor in the zinc finger transcription factor family, activate anti-inflammatory responses in vascular endothelial cells. Studies have shown that the up-regulation of DNMT1 expression can promote the methylation of the promoter region of Kruppel-like transcription factor 2 gene, inhibit the transcription of Kruppel-like transcription factor 2 gene and silence its expression, thus accelerating the inflammatory response and further leading to vascular endothelial dysfunction [32-33]. In addition, there are numerous studies showing that [34-35], DNA methylation is involved in the regulation of NF-κB mediated signaling pathway, and NF-κB can up-regulate the release of pro-inflammatory cytokines and adhesion molecules in vascular endothelial cell (VEC), such as IL-6, TNF-α, ICAM-1, VCAM-1, etc. The enhanced expression of proinflammatory gene cytochrome C oxidase subunit II is closely related to the enhanced expression of proinflammatory cytokines and adhesion molecules, thus accelerating vascular endothelial dysfunction.

4. The Unique Advantages of Chinese Medicine in Preventing and Treating AVF Stenosis

Modern medical studies on arteriovenous fistula intimal hyperplasia and stenosis focus on single target and single mechanism intervention, such as inhibiting platelet aggregation, reducing blood viscosity, regulating lipids, inhibiting cell proliferation, cracking vascular elastic fibers, etc., but no significant effect has been obtained. The 2019 updated version of the KDOQI Guidelines for Vascular Access considers it necessary to develop new drugs, devices and/or new methods or materials to facilitate the maturation of internal fistula and prevent stenosis, reduce endometrial hyperplasia and improve the patency rate of internal fistula [36-37]. Traditional Chinese medicine has unique advantages in preventing and treating AVF stenosis: (1) In terms of pathogenesis, traditional Chinese medicine, especially compound medicine, has the characteristics of multi-target, multi-gene and multi-link interaction in the intervention of diseases, and the combined compatibility has the synergistic effect. The combination of different Chinese medicines may act on the human microenvironment by changing the epigenetic mechanism of the disease, and thus play a therapeutic role, which provides an optimistic prospect for the treatment of AVF. (2) In terms of treatment principles, Chinese medicine follows the holistic concept, emphasizing the corresponding nature and human and three reasons (according to the time, local measures and individualized measures), attaches importance to the impact of environmental factors on the human body, and intervenes in the human body as a whole to restore the internal balance of the body by improving diet and living, regulating emotions and various characteristics of traditional Chinese medicine therapy, so as to play a therapeutic role. Epigenetics is also a combination of genetic and environmental factors, so that the genome is not only stable, but also has accurate responsiveness and adaptability to the external environment [38], These coincide with the whole concept of TCM and the corresponding theory of heaven and man. In addition, modern studies have confirmed that blood-activating and blood-stasis removing drugs can change hemorheology to improve

patients' own vascular conditions, improve the success rate of arteriovenous fistula surgery, and its anti-inflammatory and anti-thrombotic effects can also prevent thrombosis in the short term after arteriovenous fistula and inhibit vascular intimal inflammation [39].

In summary, DNA methylation may be involved in the occurrence and development of AVF stenosis through regulation of vascular smooth muscle cell proliferation, inflammatory response, and vascular endothelial function. In other words, when arteriovenous fistula in hemodialysis patients maturates, cell and molecule regulation of related gene expression through DNA methylation may be one of the important mechanisms of AVF stenosis. The pathogenic process of abnormal DNA methylation is reversible, and the function and characteristics of genetic genes can be fully regulated by environmental intervention. Therefore, based on the DNA methylation mechanism of AVF stenosis and combined with Chinese medicine intervention to reverse the methylation abnormality of target genes, it is a very promising research direction.

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