

# *Progress of macrophage polarization in the treatment of aortic dissection*

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**Abstract:** Aortic dissection is one of the most devastating cardiovascular diseases. One of the most important pathological features of aortic dissection is local inflammatory response, including the infiltration of inflammatory cells, extracellular matrix degradation, and smooth muscle cell phenotype switch. Macrophages which are the core of the inflammatory response play an extremely pivotal role in the progression of inflammation and tissue remodeling. Macrophages can be artificially divided into M1 and M2 types, of which the M1-type promotes inflammation while the M2-type is associated with the regression of inflammation and tissue healing. Mastering the switch of phenotypic transformation of macrophages may be of great help in inhibiting the inflammation of aortic tissue and facilitating tissue healing, as well as the treatment of aortic dissection. In this paper, we focus on the polarization of macrophages and discuss the role of macrophages in aortic dissection, the polarization pathway and the effect of related polarizing agents on the treatment of aortic dissection.

## **1. Introduction**

Aortic dissection (AD) is a serious illness caused by the rupture of the aorta's intermediate layer, which allows blood to penetrate the inner membrane and cause the aortic wall to separate. Its onset is abrupt, and the death rate is significant [1]. Although open surgery or minimally invasive endovascular surgery can treat the majority of cases of aortic dissection, there are still many patients in clinical practice with early-stage dissection who only show inflammatory exudation around the aorta and filling defects in the aortic intima on imaging, with no indication for surgery or endovascular treatment at this time. There are no specific medicines for treating AD in clinical practice, and the condition is likely to progress to normal AD. As a result, early management for this group of patients and the quest for viable drug-targeted interventions for aortic inflammatory damage are critical. In recent years, research on changes in inflammatory indicators during the progression of AD has suggested a tight link between inflammation and AD, which is extremely important. Various inflammatory cells play a significant role in the early development of the aorta, with macrophages being the most prevalent and one of the most promising therapeutic targets [2]. For starters, aortic macrophages live in the aorta and are highly adaptable. Diverse macrophage morphologies serve

diverse functions in inflammation, with M1 cells causing inflammation and M2 cells suppressing inflammation and aiding in aortic tissue repair [3]. As a result, early activation of local macrophage polarization towards the M2 type may help to reduce aortic tissue inflammation and promote tissue healing.

## 2. Macrophage phenotype and its role in aortic dissection

Macrophages have strong plasticity and are present in almost all tissues, playing important roles in body development, homeostasis, tissue repair, inflammation, and immunity. Activated macrophages are usually divided into two types, including M1 macrophages and M2 macrophages. Both M1 and M2 macrophages are closely related to inflammatory response, with M1 mainly involved in pro-inflammatory response and M2 involved in anti-inflammatory response[4]. The specific pathological mechanism of AD is not yet clear, but a large amount of evidence suggests that macrophages play an important role in the formation of AD. Recent studies have proven that there is a high level of macrophage infiltration in the tissue sections of AD patients, and that their aggregation is critical for the development of early AD. The study found that the two phenotypes of macrophages play completely different roles in the formation of dissection, with M1 type macrophages secreting tumor necrosis factor- $\alpha$  (Tumor necrosis factor- $\alpha$ , TNF- $\alpha$ )[5]. Various inflammatory factors such as reactive nitrogen and matrix metalloproteinases drive the initial response of AD, including inflammatory cell infiltration, extracellular matrix degradation, and other aortic instability tendencies [6]. During the tissue healing stage, M2 macrophages can reduce inflammatory factor production, increase the formation of new extracellular matrix, and aid in tissue repair [7]. As a result, macrophages play a vital role as a "switch" and "hub" in the sandwich's shift from injury to healing. Early phenotypic change of M1 to M2 macrophages is extremely important for correcting inflammatory damage and sandwich repair before sandwich formation.

## 3. Polarizers and the treatment of AD.

Many drugs have been shown to have the ability to prevent aortic inflammation and repair dissection, but they have not been widely used in clinical practice. Macrophages offer substantial advantages in targeted therapy. First, they exhibit two extreme phenotypes. One is persistent inflammatory activation, which destroys the dissection, while the other promotes dissection repair, acting as a switch in the path of dissection from destruction to repair. Second, macrophages are highly capable of phagocytosis[8]. Based on the hallmarks of AD inflammation progression, our goal is to identify polarizers that can increase M2 macrophage polarization or inhibit M1 macrophage polarization, which can then be used in clinical practice to achieve early repair and treatment of dissection.

### 3.1 Interleukin

Interleukin-4 and IL-10 can convert monocytes to M2 macrophages by activating STAT 3 and STAT 6, respectively. According to research [9], the expression of STAT6 in susceptible atherosclerotic plaques increased dramatically following IL-4 stimulation, facilitating macrophage differentiation into the M2 type. Similar to IL-4, IL-10 and IL-13 help macrophages polarize towards the M2 type. IL-10 is an anti-inflammatory immune regulating factor. In a mouse model of arterial aneurysm, the number of M2 macrophages in the aorta tissue transfected with IL-10 dramatically increased, and the incidence of AD was also significantly reduced [10]. In Alzheimer's disease, IL-10 regulates vascular remodeling through transforming growth factor- $\beta$  pathways [11]. IL-10 can trigger the production of M2 macrophages via a variety of mechanisms, and its polarization impact

is both durable and effective. In conclusion, vascular anti-inflammatory cytokines IL-10, IL-13 can drive macrophage polarization toward the M2 type and may be employed to treat early AD damage.

### 3.2 Glucocorticoid

Corticosteroids are conventional anti-inflammatory agents that may slow the progression of Alzheimer's disease. Proteomics confirms that stimulation of glucocorticoid receptors can cause monocyte differentiation into M2 macrophages. Glucocorticoids, which stimulate the formation of M2 macrophages, can considerably reduce acute lung damage and acute respiratory distress syndrome [12]. A study [13] found that antibody-guided glucocorticoid treatment can reduce liver inflammation by targeting M2 macrophages. Corticosteroids can also suppress inflammatory cell proliferation and migration, making them potentially useful in the treatment of lower limb arterial restenosis [14]. However, glucocorticoids' influence on Alzheimer's disease is complex. Many studies have demonstrated that glucocorticoids and their receptors increase the risk of cardiovascular disease, particularly atherosclerosis. The difficulty in precisely targeting the inflammatory site may be a significant reason why glucocorticoids cannot be used in clinical therapy of vascular inflammation. Targeting macrophages may avoid the impact of glucocorticoids on other cells and maximize their anti-inflammatory effects.

### 3.3 Platelet endothelial cell adhesion molecules

The platelet endothelial cell adhesion protein CD31 has several roles in vascular biology, including angiogenesis, platelet activation, and mechanical sensibility of endothelial cells in response to shear stress [15]. All of these pathways are intimately related to Alzheimer's disease etiology. A study using nanoparticles to treat chronic wounds in diabetic rats [16] found that increasing the expression of the vascular endothelial marker CD31 during wound healing increased the polarization of M2 macrophages considerably. Recent research [17] has demonstrated that CD31, a crucial switch for M1 to M2 transformation, and its agonist can aid in the repair of AD lesions. Promoting M2 macrophage polarization via intravenous or subcutaneous treatment of a CD31 agonist (P8RI) can result in early healing of acute arterial dissection and limit the formation of potential aneurysms after dissection. Although more research is needed to validate their toxicity and pharmacokinetics, CD31 agonist peptides may represent a novel class of medicines that can be used in the clinical treatment of atherosclerosis and Alzheimer's disease.

### 3.4 MiRNAs

MicroRNAs (miRNAs) are small non-coding RNA molecules that influence gene expression after transcription. The differential expression of certain miRNAs in macrophages has a major effect on macrophage polarization, currently, miR-21 inhibitors are utilized to treat aneurysms [18]. MiR-223 is also thought to play a significant role in inflammation, and studies [19] have demonstrated that the expression or lack of long-chain non-coding RNA (lncRNA) MEG 3 upregulates miR-223 production, encouraging polarization of M2 macrophages. MiR-223 can inhibit TNF receptor-related factor 6 and NF- $\kappa$ . The B signaling pathway and M1 macrophage polarization reduce myocarditis-related damage. MiR-181b is considerably elevated during the formation of human aneurysms, and studies [20] have revealed that reducing miR-181b expression can prevent mice aneurysm formation and even slow the progression of pre-existing aneurysmal illnesses. In addition to the aforementioned miRNAs, miR-124, miR-34a, let-7c, miR-132, miR-146a, and miR-125a-5p can induce M2 macrophage polarization by targeting several transcription factors and adaptor proteins [21]. However, research on their role in vascular inflammation is sparse, and their efficacy and targeting approaches

require additional investigation

### 3.5 1, 25-Dihydroxyvitamin D3

Vitamin D3 is a cholesterol derivative. The most active form is 1,25-dihydroxyvitamin D3, 25 (OH) 2D3, which is primarily generated by hydroxylation of liver microsomes and renal mitochondrial hydroxylase [22]. One  $\alpha$ , 25 (OH) 2D3 regulates bone metabolism, calcium, and phosphorus balance, and promotes cell differentiation. According to studies [23], 1  $\alpha$ , 25 (OH) 2D3 regulates chicken macrophage development significantly. 1  $\alpha$ , The lack of 25 (OH) 2D3 is associated with increased expression of inflammatory cytokines, which may result in abnormal differentiation of M2 macrophages and dysfunction of endothelial cells and vascular smooth muscle cells, increasing the risk of cardiovascular diseases such as atherosclerosis, aneurysms, and Alzheimer's disease [24]. Research demonstrates that 1  $\alpha$ , 25 (OH) 2D3 can be metabolized through PPAR  $\gamma$  Pathways, promoting the conversion of M1 macrophages to M2 macrophage. In addition to increasing polarization of M2 macrophages, 1  $\alpha$ , 25 (OH) 2D3 can quiet NF- $\kappa$ B. The B route decreases M1 macrophage polarization, which reduces vascular inflammation [25]. Although 1  $\alpha$ , 25 (OH) 2D3 has a definite anti-inflammatory and repair effect, it is less widely utilized in the treatment of cardiovascular illnesses in clinical practice. This is due to its systemic effects, which can induce calcium and phosphorus metabolism issues. Macrophages targeting vascular inflammation with antibodies or nanoparticles can lessen the negative effects of 25 (OH) 2D3, allowing for early and accurate treatment.

## 4. Conclusion

In recent decades, AD has transitioned from "giant innovation" to "minimally invasive". However, open surgery and minimally invasive intracavitary treatment have not solved all problems, and many early patients do not meet the surgical indications and do not have specific drugs for treating Alzheimer's disease. Adverse events such as postoperative aortic leakage and reverse tearing continue to pose a serious threat to the patient's survival. In recent years, innovative strategies for treating macrophage-targeted disorders have gained popularity. Studies have used customized nanoparticles or antibody-loaded polarizers to limit tumor development and spread by targeting tumor-associated macrophages. According to research, AD is intimately associated to macrophage infiltration and differentiation, and blocking or promoting macrophage polarization toward M1 or M2 type may result in tailored therapy for dissection. Polarizers have been shown to decrease the progression of vascular inflammation while also promoting tissue healing. However, there has been limited research on the use of macrophage polarizers in the treatment of Alzheimer's. With a better understanding of macrophage polarization pathways and novel intervention strategies, macrophage polarizers could become one of the most important targets for future AD treatment. Macrophage polarizers are also predicted to be fully employed in clinical treatment of Alzheimer's disease.

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