Editorial Commentary: Top Five Stories of the Cellular Landscape and Therapies of Atherosclerosis: Current Knowledge and Future Perspectives*

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Atherosclerosis (AS) is the main underlying pathology of atherosclerotic cardiovascular disease (ASCVD), which is the leading cause of mortality in the worldwide[1, 2]. Since the 19th century, Virchow has already stated that AS is a chronic inflammatory state induced by cholesterol. After that, it took at least three decades' worth of study to establish the multiple inflammatory pathways related to AS.

Nevertheless, the mechanism of inflammation in AS is complex and requires further exploration. In the current issue of Current Medical Science, Pan *et al* provides new perspectives for cellular landscapes during the initiation and progression of AS: (1) novel regulated cell death (RCD) forms in plaques; (2) novel functions of focal myeloid cells; (3) transdifferentiation of vascular smooth muscle cells (VSMCs); (4) stem cell-based therapy; (5) clinical translation of nanomedicine for AS[3]. In this editorial commentary, we interpreted these new viewpoints from the perspective of inflammation in AS.

1 Novel RCD and inflammation in AS

The novel RCD including ferroptosis, pyroptosis, and cuproptosis promotes local inflammatory response, which is strongly correlated with the development of AS[3]. NOD-like receptor protein 3 (NLRP3)/interleukin (IL)-1β pathway plays an important role in novel RCD induced inflammation. Ferroptosis is induced by the interaction of intracellular free iron with reactive oxygen species (ROS). NLRP3 activation is strongly associated with ferroptosis due to the increased level of ROS[4]. During pyroptosis in macrophages, NLRP3 induces the release of bioactive IL-1β, leading to cell swelling and lytic death[5]. The toxicity of copper oxide nanoparticle also activates the NLRP3 inflammasome in macrophages in addition to cuproptosis[6].

NLRP3/IL-1β pathway is the important target of anti-inflammatory treatment in ASCVD[7]. Although the treatment for novel RCD is still in preclinical models, the approved anti-inflammatory agent colchicine in ASCVD may exert its effect by inhibiting NLRP3/IL-1β pathway associated novel RCD. Yang *et al* found that colchicine could alleviate cholesterol crystal-induced endothelial cell pyroptosis[8]. Colchicine could reduce ROS formation that is the key molecule in the pathological processes of ferroptosis and cuproptosis[3, 9]. Thus, the potential effect of colchicine on novel RCD may provide new mechanisms for its anti-inflammatory efficacy in ASCVD.

2 Focal myeloid cells and inflammation in AS

Efferocytosis and extracellular traps (ETs) involving focal myeloid cells reveal new mechanisms in AS. Efferocytosis is a process of quick phagocytic clearance and highly effective turnover of apoptotic cells[3]. Removal of apoptotic cells from atherosclerotic plaques by efferocytosis inhibits arterial inflammation[10]. CD47 expression levels are increased in human atherosclerotic arteries, and global CD47 inhibition could stimulate efferocytosis and attenuate cellular inflammation[11]. CD47 is considered as the downstream of tumor necrosis factor (TNF)-α[12]. Anti-inflammatory treatment with antibodies against TNF-α (Infliximab or Etanercept) could reduce the CD47 expression, suggesting the potential effects on efferocytosis in AS[13].

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ETs are a complex structure composed of nuclear chromatin, nuclear proteins, cytoplasmatic, and granular proteins[14]. The process of ETs formation is also known as ETosis, which is mainly used to describe a new form of neutrophil death[3]. The released DNA and neutrophil-derived granule proteins stimulate a strong type I interferon (IFN) response, which accelerates leukocytes recruitment, foam cells potentiation, endothelial cells impairment, and thrombosis in AS[3]. Anti-inflammatory treatment with colchicine suppresses neutrophils ETs formation by restoring cytoskeletal dynamics in patients with acute coronary syndrome post-percutaneous coronary intervention[15]. Treatment with IL-1β antibody canakinumab could reduce NETosis, which may provide a mechanistic explanation to reduced adverse cardiovascular events as observed in CANTOS[16]. These studies provide the potential approach to target ETosis in AS.

3 VSMCs and inflammation in AS

VSMCs, an important component of the media tunica of arteries, display a high degree of plasticity with the switch between the differentiated (contractile) and de-differentiated (synthetic) state under various physiological exposure[17]. VSMCs transform into foam cells under exposure to lipid overload and inflammation, and the major source of foam cell seems to be the transdifferentiated VSMCs[3]. VSMCs release matrix metalloproteinase (MMP) and inflammatory factors, reducing the plaque stability by aggravating the necrotic core and thinning the fibrous cap[18]. Administration of anti-IL-1β antibody could inhibit AS progression by attenuating VSMCs migration and extracellular matrix production[19, 20]. The roles of VSMCs in AS have been undervalued, and the interplays between VSMCs and inflammation in the pathogenesis of AS remain further explored.

4 Stem cell-based therapy and inflammation

Mesenchymal stem cells (MSCs) are the most extensively studied stem cells in AS[3]. MSCs could stabilize coronary plaques and avoid thrombosis by down-regulating the TNF-α/IL-6 expression and up-regulating the IL-10 expression[21]. Transplantation of MSC derived from bone marrow (BMSC) could significantly reduce the levels of circulating monocytes, and promote differentiation of T cells into regulatory T cells rather than pro-inflammatory subpopulations[22, 23]. Adipose tissue-derived MSCs exerted greater anti-inflammatory capabilities than BMSCs through regulating the macrophage immune function[24]. The clinical translation of stem cell therapy for AS is full of challenges, and further study is needed to clarify its effectiveness and safety.

5 Nanomedicine and inflammation

Nanoparticles (NPs) are considered as promising candidates for AS treatment[3]. NPs-based RNA interference could effectively silence 5 key adhesion molecules and curtail neutrophil and monocyte recruitment into atherosclerotic lesions[25]. NPs-mediated delivery of pioglitazone demonstrated its effects of inhibiting macrophage activation and atherosclerotic plaque rupture in hyperlipidemic ApoE(-/-) mice[26]. A novel delivery nano-system encapsulated with colchicine targeting inflammatory endothelial cells could alleviate atherosclerotic plaque accumulation[27]. CD47- and integrin α4/β1-comodified-macrophage-membrane-moated NPs enabled delivery of colchicine to atherosclerotic plaque, which reduced the lipid plaque load and improve the plaque stability[28]. This strategy could provide a potential therapeutic approach for the targeted delivery of anti-inflammatory drugs to the local atherosclerotic site for the treatment of AS.

In summary, inflammation is a fundamental mechanism that interacts with these new directions such as RCD, focal myeloid cells, VSMCs transdifferentiation, stem cell-based therapy, and nanomedicine in AS. Further exploration of these new perspectives may help us to develop an integrated strategy for AS treatment.

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