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Perspective:

Interleukin-17 and acute coronary syndrome*

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Inflammation plays an important role in atherosclerosis, which is also crucial for acute coronary syndrome (ACS). Recent studies have revealed that interleukin (IL)-17, which was regarded as a pro-inflammatory cytokine, has a dual function in the progress of ACS. In this review, we sum up both experimental and clinical studies on the relevance of IL-17 to atherosclerosis and its complications, and summarize the research progress on the effect of IL-17 on the atherosclerotic plaque stability and ACS onset. Although the studies are controversial and the mechanism remains unclear, we highlight the knowledge of the role of IL-17 in ACS and elucidate its potential mechanism.

ACS is a clinical syndrome of coronary heart disease with a high risk of mortality, which includes unstable angina, non-ST elevation myocardial infarction, and ST elevation myocardial infarction. The atherosclerotic plaque rupture or erosion and platelet thrombus as the basis of pathogenesis could occlude the lumen of the atherosclerotic coronary artery completely or incompletely. Thus, the obstruction of flow would cause acute myocardial infarction or ischemia (Libby, 2013). Traditionally, inflammation was considered to play a vital role in the progression of atherosclerosis and its complication. Of late, a new inflammation marker IL-17 has drawn great attention, as several studies have reported its potential role in cardiovascular diseases such as atherosclerosis, myocardial ischemia/reperfusion injury, myocarditis, and dilated cardiomyopathy.

Inflammation is the core of atherosclerosis (AS), and is present throughout all stages of AS (Libby *et al.*, 2002). Notably, inflammation regulates the stability of atherosclerotic plaque, as well as the plaque's thrombogenic potential (Hansson, 2005; Crea and Liuzzo, 2013). Hyperlipidemia, hyperglycemia, smoking, and oxidized low-density lipoprotein (ox-LDL) activate endothelial cells expressing vascular cell-adhesion molecular 1 (VCAM-1), which leads to endothelial cell dysfunction. The VCAM-1-expressed endothelial cells could trigger the adherence of leukocytes, the recruitment of monocytes, and the migration of activated platelets into the endothelium. Then these monocytes differentiate into macrophages which express scavenger receptors. The macrophages regarded as a component of the innate immune system could swallow large amounts of lipid via scavenger receptors and become foam cells, leading to fatty-streak lesions (Cybulsky and Gimbrone, 1991; Nakashima *et al.*, 1998; Edfeldt *et al.*, 2002). During this process, the components of adaptive immune system T cells are also activated by ox-LDL, human leukocyte antigen (HLA)-DR, and other antigens. The activated T cells augment the inflammatory response by producing inflammatory mediators (Binder *et al.*, 2002; Lichtman *et al.*, 2013). With gradual accumulation of inflammatory cells and formation of the necrotic core, the lumen of the coronary artery progressively narrows. Meanwhile, the pro- and anti-inflammatory mediators regulate the fragility of the fibrous cap, as well as the vulnerability of the plaque by modulating apoptosis, smooth muscle cell content, and collagen production. In the late

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stage of AS, B cells are also involved into the deep layer of plaque (Houtkamp *et al.*, 2001). Release of matrix metalloproteinases (MMPs) and pro-inflammatory cytokines including IL-1, IL-6, and tumor necrosis factor (TNF)-α eventually triggers the plaque rupture, resulting in ACS onset (Chen *et al.*, 2010a).

To understand the mechanisms of inflammation in AS and its complications, several systemic inflammatory markers have been indicated as independent risk factors in cardiovascular events, especially in ACS (Drakopoulou *et al.*, 2009). Recently, a new potential marker IL-17 has drawn great attention. It is a signature cytokine produced by a new lineage of $CD4^+$ T cells, type 17 helper cells (Th17) (Harrington *et al.*, 2005). Potent evidence has shown that IL-17 plays critical roles in allergic reactions and the development of autoimmune disease such as multiple sclerosis, psoriasis, systemic lupus erythematosus, and inflammatory bowel disease. It also mediates a protective effect in host defense infection and participates in the chronic inflammatory processes of obesity and malignancy (Iwakura *et al.*, 2011). Lately, some studies have revealed the emerging role of IL-17 in AS and its complications (Ding *et al.*, 2012).

The currently known IL-17 cytokine family has six members, comprising IL-17A (IL-17), IL-17B, IL-17C, IL-17D, IL-17E, and IL-17F, respectively. Among these, IL-17F and IL-17 share 50% homologous sequences, and usually exist in the type of homodimer. Differently, the Th17-produced IL-17 mainly consists of IL-17/IL-17F heterodimeric form (Kolls and Linden, 2004; Chang and Dong, 2007). The cellular sources of IL-17 are aplenty. Besides Th17 cells, several types of hematopoietic cells can produce IL-17 as well as some types of immune cells like the γδT cell, natural killer cell, dendritic cell, macrophage, and neutrophil leucocyte. Those immunocytes can rapidly secrete IL-17 after being stimulated by several cytokines and may be the initial sources of IL-17 (Iwakura *et al.*, 2011).

IL-17 receptor (IL-17R) family has five members, namely IL-17RA–IL-17RE. IL-17RA is ubiquitously expressed through the body, which leads to the wide function spectrum of IL-17. According to the expressed downstream gene mediated by IL-17RA signaling, IL-17 is generally regarded as a pro-inflammatory cytokine: IL-17 and IL-17F primarily bind with IL-17RA- and IL-17RC-expressed cells, mainly epithelial cells, vascular endothelial cells, and fibroblasts. Then the common downstream signaling pathways, including nuclear factor (NF)-κB and mitogen-activated protein kinases (MAPKs), are activated. Eventually, the recipient cells are induced to express various types of pro-inflammatory mediators, like TNF, IL-1, IL-6, chemokines (CXCL1, IL-8, CCL2), MMP (MMP1, MMP3, MMP9), and C-reactive protein, resulting in the enhancement of inflammatory cells adhesion and recruitment of neutrophils, T cells, macrophages, and other types of cells to local inflammatory sites (Gaffen, 2009; Zhu and Qian, 2012). However, the ability to induce pro-inflammatory factors of IL-17F is weaker than that of IL-17 (Iwakura *et al.*, 2011). These effects show that IL-17 participates in the inflammatory progression and host defense bacterial infections, and also contributes to the surmise that IL-17 plays a role in atherosclerotic plaque stability and complications.

The plaque stability is closely related to inflammation of vessel walls, while rupture of unstable plaque is the pivotally initial step of ACS occurrence. The role of IL-17 playing in atherosclerotic plaque stability is still controversial. Erbel *et al.* (2009) showed that in the apolipoprotein E $(ApoE)^{-/-}$ mouse model, which is a classical model for atherosclerosis, giving the neutralizing antibody to block IL-17 could reduce the area of early plaque lesions and stabilize the plaque. They attributed this phenomenon to the ability of IL-17 to activate the downstream pro-inflammatory factors and chemokines, which promoted the expression level of MMP, the apoptotic rate of vascular smooth muscle cells, as well as induced pre-inflammatory transformation of macrophages, neutrophils, and several other immune cells. The research on the specimens of human atherosclerotic plaques (de Boer *et al.*, 2010) confirmed the finding that IL-17 could increase the plaque's vulnerability. van Es *et al.* (2009) used the technique of bone marrow cell transplantation to observe the relationship between IL-17 and AS. They implanted the myeloid cells originating from $IL\text{-}17R^{-/-}$ mice to $LDL^{-/-}$ mice, leading to a dramatic reduction in the IL-17R expression level in peripheral blood cells of $LDL^{-/-}$ mice. In this model, they discovered that the blockade of IL-17R signaling pathways could reduce

the atherosclerosis extent and prevent plaque progression. Since then, several studies have reported the proatherogenesis function of IL-17 (Eid *et al.*, 2009; Chen *et al.*, 2010b; Smith *et al.*, 2010; Xie *et al.*, 2010).

Interestingly, Danzaki *et al.* (2012) found that in ApoE and IL-17 gene double knockout mice, the deletion of IL-17 could accelerate the formation of atherosclerotic plaques, decrease the amount of type I collogen and vascular smooth muscle, eventually making the plaque open to instability. The results also proposed that IL-17 could stabilize the plaque partly by suppressing the levels of the Th1 cell activity marker interferon gamma (IFNγ) and promoting the levels of the Th2 cell activity marker IL-5. Taleb *et al.* (2009) reported that loss of the suppressor of cytokine signaling (SOCS)-3 in T cells of mice (SOCS-3 cKO) increased both IL-17 and IL-10 productions, polarized macrophages in an anti-inflammatory phenotype, and led to unexpected IL-17-dependent reduction in lesion development and vascular inflammation. However, the effective role of IL-17 in lesion development still needs identification as the potent anti-inflammatory cytokine IL-10 also increased, which may conceal the actual role of IL-17. The study also showed that over-expression of SOCS-3 in T cells reduced IL-17 production, which was in accordance with Romain *et al.* (2013), and accelerated atherosclerosis. Blocking IL-17 in SOCS-3-cKO mice by a neutralizing antibody resulted in increased VCAM-1 expression of endothelial cells, aggravating T cell infiltration, and accelerating lesion development. Therefore, Romain *et al.* (2013) proposed that the SOCS-3-negatively regulated IL-17 pathways had protective effects in atherosclerotic plaque stability.

In summary, IL-17 displays a dual character in the stability and vulnerability of the plaque; the conflicting results and concrete mechanism await further study.

Acute myocardial infarction (AMI) is serious and lasting myocardial ischemia and necrosis because of the obstruction of flow in the culprit coronary artery. The obstacle is usually the secondary thrombus after plaque rupture. Yamashita *et al.* (2011), Yan *et al.* (2011), Ávalos *et al.* (2012), and Liu *et al.* (2012) reported that as a pro-inflammatory factor, IL-17 production in rodents had no significant difference in the early stage after AMI compared with the normal, and did not affect the infarct size either. However, IL-17 was gradually elevated 1–2 weeks after AMI and peaked in the 4th week. An in-vitro study of Valente *et al.* (2012) verified that IL-17/IL-17R stimulated the proliferation and migration of primary cardiac fibroblasts through activating Akt/MKP-1-dependent p38 MAPK and Erk1/2 signaling pathways. These results suggest that IL-17 does not seem to participate in the acute inflammatory process in the early stage after AMI, but plays a role in the later chronic inflammation, and possibly affects the ventricular remodeling (Baldeviano *et al.*, 2010) and myocardial fibrosis in the late stage after AMI.

Some contrary results were also reported. Troitskaya *et al.* (2012) found that IL-17 reduced the production of C-C motif chemokine receptor-2 (CCR2) and CXC chemokine receptor 4 (CXCR4) in monocytes and limited the chemotaxia of monocytes. However, they detected the monocytes and IL-17 production from the spleen cells of mice on the 3rd day after AMI, so the comprehensiveness of the result needs further discussion. An in vitro study of Simon *et al.* (2013) reported a similar phenomenon that IL-17 reduced VCAM production in endothelial cells of mice, and limited monocytes adhering to human umbilical vein endothelial cells. These studies, together with Taleb *et al.* (2009), revealed that IL-17 may play a protective role in AMI through limiting the recruitment of monocytes to the ischemic area.

Zhang *et al.* (2012) explored the relationship between the serum IL-17 level and platelet aggregation in ACS patients. Both the concentration of serum IL-17 and platelet aggregation levels were obviously elevated in ACS patients compared with stable angina (SA) patients. The in vitro studies (Maione *et al.*, 2011; Zhang *et al.*, 2012) confirmed that IL-17 promoted ADP-induced platelet activation and aggregation through the MAPK/Erk2 signaling pathway, and accelerated thrombosis. de Boer *et al.* (2013) analyzed the structure of coronary thrombus in AMI patients and discovered that a large burden of neutrophils, neutrophil extracellular traps, and IL-17 were present in fresh thrombus (less than 1-d old after AMI) and lytic thrombus (between 1-d and 5-d old after AMI), but not in organized thrombus (more than 5-d old after AMI). The above studies exploring the role of IL-17 in thrombosis of ACS, proposed that IL-17 possibly had the effect of maintaining thrombus

stability and promoting thrombus growth in the early stage of ACS, which opens a new insight into the complex function spectrum of IL-17.

Notably, the cell source of IL-17 exhibits certain diversity and complexity. Besides neutrophils, monocytes, and Th17 cells as mentioned above, Eid *et al.* (2009) and Liao *et al.* (2012) also reported the increase of IL-17 originated from the γδT cell and IL-17/IFNγ dual-producing T cell in ACS. The complex cell sources of IL-17 possibly lead to the time and spatial pleiotropic effects, and are worthy of further research.

Based on the involvement of IL-17-mediated inflammation in ACS, many researches focused on the appreciable value of IL-17 to ACS progression and prognosis. Actually, the clinical studies have also led to disagreements. Research detecting 58 Chinese serum specimens (Hashmi and Zeng, 2006) showed a more significant increase in IL-17 levels in the ACS group than in the normal, which was also positively correlated with hypersensitive C-reactive protein (hs-CRP) and IL-6 levels. It proposed IL-17 as a potential predictor in ACS and was in conformity with an Iranian research (Jafarzadeh *et al.*, 2009). Another study with 85 Chinese serum samples indicated that the increased IL-17 level in ACS patients was due to the existence of Th17/Treg functional imbalance (Cheng *et al.*, 2008). However, these results were not replicated in Caucasians (Eid *et al.*, 2009). A study of 35 Caucasian serum specimens (Patel *et al.*, 2009) did not confirm any elevated expression of IL-17 in ACS patients. The author attributed the variant IL-17 expression levels to the difference in races, the time interval from ACS onset to serum sample collection, and the inhibitory effect of statins. And it seems that IL-17 is an unlikely marker of ACS.

The above-mentioned studies are retrospective with small sample sizes. Of late, a prospective study (Simon *et al.*, 2013) enrolled 981 Caucasian samples and observed the relevance of circulating IL-17 levels to cardiovascular outcomes in patients with AMI. It elucidated that serum levels of IL-17 were independently associated with the risk of all-cause death and recurrent myocardial infarction (MI) at two years in AMI patients. A low level of IL-17, less than the median, indicated a worse outcome. Furthermore, patients with low IL-17 levels and highly soluble VCAM-1 levels were at particularly increased risk of death and MI. These findings suggested that patients included in trials using IL-17 inhibitors, such as patients with autoimmune diseases, may be at a potentially high risk of adverse cardiovascular events and need to be closely monitored (Griffiths *et al.*, 2010; Lopez-Pedrera *et al.*, 2012).

In summary, IL-17 is a kind of cytokine with pleiotropic functions. The role of IL-17, in various stages of atherosclerosis and its complications, remains poorly understood. Both experimental and clinical studies have shown controversial results which suggest that IL-17 plays a dual role in atherosclerotic plaque stability and acute myocardial infarction. Thus, the function of IL-17 awaits more direct studies and needs deeper elucidation.

Compliance with ethics guidelines

Sheng-an SU, Hong MA, Li SHEN, Mei-xiang XIANG, and Jian-an WANG declare that they have no conflict of interest.

This article does not contain any studies with human or animal subjects performed by any of the authors.

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