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Review

Cytokines in aortic dissection

Tao Zeng[a,1], Lei Shi[a,1], Qingwei Ji[a,c], Ying Shi[a], Ying Huang[b], Yu Liu[a], Jianting Gan[a], Jun Yuan[a], Zhengde Lu[a], Yan Xue[a], Haiying Hu[d], Ling Liu[a,*], Yingzhong Lin[a,*]

[a] Department of Cardiology, the People's Hospital of Guangxi Zhuang Autonomous Region, Nanning, China
[b] Department of Ultrasound, the People's Hospital of Guangxi Zhuang Autonomous Region, Nanning 530021, China
[c] Emergency & Critical Care Center, Beijing Anzhen Hospital, Capital Medical University, Beijing Institute of Heart, Lung, and Blood Vessel Diseases, Beijing 100029, China.
[d] Department of Cardiology, Handan First Hospital, Handan 056002, China

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ABSTRACT

Aortic dissection (AD) is one of the most dangerous forms of vascular disease, characterized by endometrial rupture and intramural hematoma formation. Generally, the pathological process is complicated and closely related to the infiltration of inflammatory cells into the aortic wall and apoptosis of vascular smooth muscle cells. Currently, multiple cytokines, including interleukins, interferon, the tumor necrosis factor superfamily, colony stimulating factor, chemotactic factor, growth factor and so on, have all been demonstrated to play a critical role in AD. Additionally, studies of the link between cytokines and AD could deepen our understanding of the disease and may guide future treatment therapies; therefore, this review focuses on the role of cytokines in AD.

1. Introduction

Aortic dissection (AD) is a rare cardiovascular disease with high mortality, the incidence of which has increased, affecting progressively younger patients in recent years. The promotion of aortic replacement and interventional therapy in clinical practice has significantly reduced the mortality rate of patients with AD [1, 2]; however, both treatments have certain limitations. Aortic replacement is traumatic, costly, and can lead to a variety of serious clinical complications, bringing heavy psychological pressure and financial burden to patients and families. However, complications from interventional therapy are relatively rare and treatment is less expensive, but it is mostly suitable for Stanford B type cases and has a narrow range of adaptability. Therefore, an in-depth understanding of the pathogenesis of AD and the search for more effective and safe intervention targets are required for AD prevention and treatment and will have great clinical value and social significance.

Vascular smooth muscle cells (SMCs) are an important component of aortic structure and play a vital role in maintaining normal structure and function of the aorta. In addition to maintaining vasoconstriction and diastolic function, SMCs can continuously synthesize and degrade the extracellular matrix (ECM) and maintain its dynamic balance [3]. In addition, vascular SMCs can also feel hemodynamic pressure and maintain cytoskeleton and ECM reconstruction [4]. Excessive loss of SMCs can lead to a variety of severe vascular diseases, including atherosclerosis, aortic aneurysm, and AD [5–7]. Significant reduction of SMCs was observed in human AD vascular tissues, and this change was associated with AD progression [8, 9]. Once AD occurred, the heavy chain of SMCs could be released into the blood and was found to be elevated in comparison with control subjects; this increase was of high value and specificity for the diagnosis of AD [10, 11]. In addition, evidence suggested that AD is pathologically related to degeneration of aortic media, characterized by loss, breakage and failure of SMCs [2, 12]. Therefore, excessive loss of SMCs in the aorta is an important cause of AD.

Cytokines are small secreted proteins that mediate and regulate immunity, inflammation, and hematopoiesis. They are produced in response to an immune stimulus. Cytokines regulate the intensity and duration of the immune response by stimulating or inhibiting the activation, proliferation, and/or differentiation of various cells and by regulating the secretion of antibodies or other cytokines. Cytokines can be divided into 6 categories according to their function, including the interleukins (ILS), interferon (IFN), tumor necrosis factor (TNF) superfamily, colony stimulating factor (CSF), chemokines and growth factors (GF), and they play an important role in the regulation of proliferation, apoptosis, differentiation, inflammation and immunity. Among them, the apoptosis mediated by the inflammatory response is

* Corresponding authors.
E-mail addresses: gxliu@126.com (L. Liu), yingzhonglin@126.com, gxliu@126.com (Y. Lin).
[1] These authors contributed equally to this work.

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closely related to the occurrence and development of aortic dissection [4, 5, 8].

2. The role of cytokines and AD

All 6 families of cytokines have been shown to be involved in AD. We have summarized the current knowledge regarding each cytokine family member and AD, such as changes in expression, action and mechanism. Below, we describe them in turn, according to the classification of different cytokines.

3. ILs and AD

At the second international symposium on lymphocytes in 1979, some non-specific factors secreted by monocytes/macrophages and lymphocytes that play a role in immune regulation and inflammation were uniformly named interleukins (ILs). So far, a total of 40 IL members have been discovered, named IL-1 to IL-40 in the order in which they were discovered [13]. According to biological function, ILs can be divided into the IL-1, IL-6, IL-10, IL-12, and IL-17 families.

The IL-1 family is the general name for ILs that can bind to a group of related receptors, the receptor accessory protein (RAcP). As of now, 12 IL-1 family members have been found, including IL-1α, IL-1β, IL-1 receptor antagonist (RA), IL-18, IL-18 binding protein, IL-33, IL-36α, IL-36β, IL-36γ, IL-36RA, IL-37 and IL-38 [14]. In the pig AD model of suprarenal aortic cross-clamping, IL-1β levels were increased [15]. In an earlier study, Zhang L et al. reported that IL-1β mRNA levels were increased in human type A thoracic AD and that IL-1β may participate in AD via up-regulation of matrix metalloproteinase-9 and apoptosis of media cells [16]. In another study, Cheuk BL. et al. found that circulating IL-1β levels were significantly decreased in patients who suffered from Stanford B AD and who received endovascular stents [17]. In an angiotensin II (Ang II)-induced mouse AD model, mercaptoethanol protected the aorta from dissection and reduced aortic IL-1β mRNA levels [18]. In addition, IL-1β mRNA levels increased in a time-dependent manner when AD formation was induced by b-aminopropionitrile monofumarate (BAPN) administration [19]. A recently published study reported that the IL-33/sST2 axis had some value in the diagnosis of AD [20]. No studies of other IL-1 family members and AD have been reported.

The IL-2 family is also named the γ-chain (γc) family because the receptors for these cytokines share γc (also known as IL-2Rγ and CD132), which consists of IL-2, IL-4, IL-5, IL-7, IL-9, IL-15 and IL-21 [21]. Both circulating IL-2 and aortic IL-2 receptor are reported to increase in type A AD when compared with control subjects, and the IL-2 receptor negatively correlated with the follow-up period after repair [22, 23]. Our recent study showed that both circulating Th2/Th9 cells and their functional cytokines IL-4/IL-9 were reduced in human AD [24]. IL-5, IL-7, IL-15 and IL-21 were not reported to be involved in AD.

Members of the IL-6 superfamily include IL-6, IL-11, IL-30, IL-31 and non-IL molecules, such as leukemia inhibitory factor (LIF), oncostatin M (OSM), ciliary neurotrophic factor (CNTF), cardiotrophin-1 (CT-1), cardiotrophin-2 (CT-2) and cardiotrophin-like cytokine (CLC) [25, 26]. The IL-6 family is characterized by their receptors, which share the GP130 subunit [26]. Data from clinical experiments and animal studies showed that both circulating and aortic IL-6 mRNA levels were elevated with AD [15, 17, 23, 27–30]. In addition, IL-6 could activate the signal transducer and activator of the transcription-3 pathway, promote Th17 infiltration of the aorta and enhance Ang II-induced AD in mice [31]. In another study, the authors found that IL-6 expression was significantly increased when compared to the controls and was accompanied by up-regulated autophagy in the human TAD aortic wall; down-regulation of IL-6 expression could repress expression of the VSMC contractile proteins α-SMA and SM22α via enhancement of autophagy-related 4B cysteine peptidase (ATG4B)-mediated autophagy in vitro [32]. In our recent study, we found that IL-11 was elevated in both plasma and the aortas of AD patients and that macrophages were the source of IL-11; this IL-11 may participate in AD via promotion of IFN-γ and IL-17 secretion [33]. Studies between other IL-11 members and AD have not yet been reported.

The IL-10 family consists of nine related molecules: IL-10, IL-19, IL-20, IL-22, IL-24, IL-26, IL-28α, IL-28β, and IL-29 [34]. These molecules have a somewhat conserved primary structure and contain a core of hydrophobic amino acids and two pairs of disulfide bonds in the chain, giving them a similar spatial conformation and thus enabling them to bind type II cytokine receptors [35]. Among these IL-10 family members, IL-10 and IL-22 were reported to be closely related to AD. The expression of IL-10 in AD is controversial. There was only one early article that reported that IL-10 was decreased in a pig AD model [15], while an opposing trend was observed in human AD among other studies [23, 36–41]. In addition, using an Ang II-induced mouse AD model, IL-10 could play an anti-inflammatory role and alleviate the progression and development of AD [42]. In our previous study, we found that plasma IL-22 levels were increased in AD patients, and higher aortic IL-22 levels were also observed in the torn section [30]. In another recently published paper, we found that both Th22 and IL-22 levels were increased in AD patients and were positively correlated with the occurrence of AD [21].

All IL-12 superfamily members are heterogenous dimers composed of two subunits, each of which has structural homology. These superfamily members include IL-12, IL-23, IL-27, IL-35 and IL-39 [43, 44]. There are less studies of these superfamily members not only with regard to AD but also other vascular diseases. Our previous study is the only one to observe that both the Treg cell and its functional cytokine IL-35 decrease in AD patients, and this decrease was negatively correlated with the onset of AD [21].

The IL-17 superfamily includes six members, IL-17A, IL-18B, IL-17C, IL-17D, IL-17E (also named IL-25) and IL-17F. IL-17A was the first member of the IL-17 superfamily to be discovered and is commonly known as IL-17 [45]. Of these superfamily members, only IL-17 was found to be critically related to AD. A previous study reported that IL-6 aggravated Ang II-induced mouse AD via the promotion of Th17/IL-17 secretion [31]. Our recent study found that circulating Th17/IL-17 levels were elevated in AD patients [21, 30].

There are other ILs that are not included in these six superfamilies, including IL-3, IL-8, IL-13, IL-14, IL-16, IL-32, IL-34 and IL-40. IL-3 is a colony stimulating factor and is also named multi-colony stimulating factor (multi-CSF) and hemopoietic cell growth factor (HCGF). In a recent study, Liu C et al. reported that IL-3 expression was up-regulated in a BAPN-induced mouse AD model and that SMCs were the main course of action. IL-3 activated the c-Jun N-terminal kinase (JNK)- and extracellular regulated protein kinases (ERK)-dependent activator protein 1 (AP-1) pathway in macrophages, stimulated matrix metalloproteinase (MMP) 12 production and contributed to TAAD formation. Knockout of IL-3 significantly reduced MMP12 expression in the aortic wall and reduced protease activity; this was associated with protection against AD [46, 47]. IL-8 is an important chemokine and has been demonstrated to be involved in AD [48]. Increased IL-8 expression was observed in both blood and aorta samples from AD patients [23, 36, 49, 50]. Plasma IL-16 levels were reported to be elevated in AD patients [51]. The role of IL-13, IL-14, IL-32, IL-34 and IL-40 in AD has not yet been observed.

4. The role of IFNs and AD

IFNs can be divided into three distinct types, namely, type-I, type-II and type-III [52]. Type-I IFN members include 14 genes, such as the well-known IFN-α and FN-β and the lesser understood IFN-ε, IFN-κ, and IFN-ω. Type-II IFN consists of one member-IFN-γ, which is biologically and genetically distinct from other IFNs. Type-III IFNs were more recently described, and the members include IFN-λ1, IFN-λ2, IFN-λ3 (which are also named IL-29, IL-28α, and IL-28β, respectively) and IFN-