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Review article

B lymphocytes in abdominal aortic aneurysms

Lili Zhang, Yi Wang*

Department of Cardiology, Shanghai General Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai, 200080, China

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ABSTRACT

Abdominal aortic aneurysm (AAA) is a progressive inflammatory disease of the artery walls. Immune cells, including B lymphocytes, are implicated in the pathogenesis of AAA through interconnected mechanisms. Many studies have shown that compared with normal abdominal aortic tissue, the amount of B lymphocytes that infiltrate the adventitia of AAAs was significantly higher. Activated B lymphocytes promote AAA by producing immunoglobulins, cytokines, and matrix metalloproteinases (MMPs), resulting in the activation of macrophages, mast cells (MCs) and complement pathways. Finally, all of these factors lead to the degradation of collagen and matrix proteins and to aortic wall remodeling, which are hallmarks of AAA. However, few studies focus on the relative function of B cells, and their precise mechanisms in AAA remain unclear. Thus, we summarize the current knowledge on the role of B cells in AAA and offer recommendations for further investigation of preventing the progression of AAA.

1. Introduction

Abdominal aortic aneurysm (AAA) is a multifactorial degenerative vascular disease that is a heavy burden on the health care system in many countries, especially in developed countries [1]. This disorder is the 10th leading cause of death in men aged over 60 years and is becoming more and more common in women [2–4]. Aneurysm can be defined as a permanent focal dilatation of an artery 1.5 times its expected dimension. Conventionally, AAA is defined as a maximum aorta diameter of 3 cm or larger, normally including the infrarenal aorta [5,6]. There is a strong clinical connection between tobacco smoking and aneurysm progression. Other risk factors for AAAs include male gender, advanced age, hypertension, hyperlipidemia, and family history [7–9]. AAA usually arises in the setting of generalized atherosclerosis [10], and numerous studies have demonstrated that AAA may progress from occlusive disease [11]. There is an autoimmune component to the aneurysm progression that is supported by the deposition of immunoglobulin G in the aorta wall [12]. Furthermore, infection by C pneumonia and oxidative stress also play important roles in the etio-pathogenesis of AAA. All of these factors increase inflammatory responses within the aortic wall.

Histopathological examination reveals that important features of aneurysms include elastin fragmentation and degeneration, infiltration of the aortic media and adventitia by inflammatory cells, and media degradation [13]. Activation of several types of inflammatory cells, for example, T cells, B cells, macrophages, mast cells, dendritic cells, and neutrophils, is important for the inflammatory response, an essential characteristic of both AAA and aortic occlusive disease. The predominant inflammatory cell types are T and B lymphocytes. T cells have been implicated in AAA progression by enhancing macrophage-derived matrix metalloproteinases (MMPs) production and vascular smooth muscle cell (VSMC) apoptosis [14–17]. Although the role of T lymphocytes in AAA formation has been fully investigated, the contribution of B cells or B-cell subsets in the development and progression of AAA remains elusive.

B cells have been found in human AAA for decades and are most frequently located in the adventitia. The potential mechanisms by which B cells may affect AAA include the production of immunoglobulins and cytokines, the regulation of T cells, and the concomitant formation of complement components, which may provide the necessary chemotactic signal that recruits neutrophils to the aortic wall [16,18–20]. These inflammatory components regulate macrophage-derived MMPs and cathepsins, mast cell chymase, and VSMC apoptosis. Finally, extensive extracellular matrix remodeling, degrading, and proteolysis give rise to the formation of AAA. In this review, we will discuss how B cells may affect the formation and development of AAA.

* Corresponding author.
E-mail address: wangyipublic@hotmail.com (Y. Wang).

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2. B lymphocytes in abdominal aortic aneurysms

The development of AAA starts with the infiltration of inflammatory cells into the wall of the aorta, followed by the secretion of cytokines, chemokines, and proteases. In turn, these inflammatory factors recruit more inflammatory cells, inducing vascular cell inflammation and apoptosis [21]. Lymphocytes have long been known to locate at sites of AAA formation. Koch et al. [22] found that $CD19^+$ B lymphocytes were mainly located in the adventitia of AAA. The percentage of B lymphocytes, ranging from 0% to 30%, was significantly higher in the abdominal aortic aneurysms compared with the occlusive aortas (Fig. 1). In inflammatory aortic aneurysm tissues, $CD19^+$ B lymphocytes constituted 20%–40% of the lymphocytes (Fig. 2). All of these consequences have proven that B lymphocytes are indeed located in the AAA, especially in the adventitia. Subsequently, lots of studies have shown that the majority of adventitial lymphocytes were CD19/22-positive (B-cell lineage) [23]. In an immunophenotype study, Bobryshev et al. [24] demonstrated that in some AAA cases, B cells represented 60%~80% of lymphocytes. Recently, muMT (mature B-cell deficient) mice were proven to be protected from elastase perfusion-induced AAA [19]. The authors thought that this protection might be the absence of IgG or IgM antibodies. In contrast to these findings, Akshaya KM et al. [25] proved that there is no difference between muMT and wild-type mice in experimental AAA models. They adoptively transferred isolated B2 cells to muMT to suppress AAA formation and found increased infiltration of splenic regulatory T cells. The B2 cells may have produced the formation of regulatory T cells that play a suppressed role in AAA formation. As noted above, the function of B cells in AAA remains controversial, and further studies are needed.

Other studies have found lymphoid follicles in the adventitia [16,26–28]. Within adventitial inflammatory infiltration, there are not only B lymphocytes but also lymphoid follicles called vascular-associated lymphoid tissue (VALT), which contain a germinative center(s) consisting of B cells [26]. Yuri VB et al. [26] used immunohistochemistry to discover that in some cases, the lymphoid follicles aggregated in lymphnode-like structures. The lymphoid follicles, where the selection of B cell subsets take place and both cellular and humoral immune responses are generated, are composed of a corona of B cells, follicular dendritic cells, a few T cells, and 'tingible body' macrophages [26,28]. In AAA, both infiltrating T- and B- lymphocytes highly express CXR4, with the capability of migrating to CXCL12. In the adventitia of AAA, experts found CXCL12-producing cells. This may explain why lymphocytes were recruited within the adventitia of the arterial wall in AAA [29]. Consistent with these findings, flow cytometry analysis of lymphocytes in human AAA walls identified activated memory B cells with specific homing properties [16]. Moreover, B cells also expressed T cell activation markers, indicating that B cells might act as antigen-presenting cells for T cells.

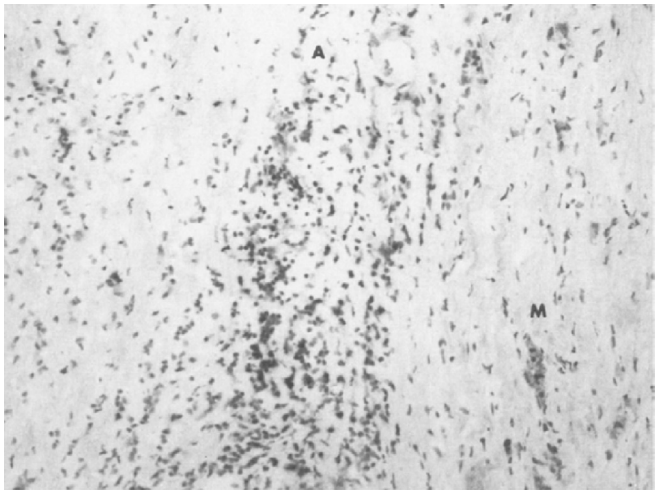

Fig. 1. Immunoperoxidase staining of a frozen section of an AAA: Anti-$CD19^+$ staining of a large number of B lymphocytes in the media. (M) and adventitia (A) of the aorta(200*) [22].

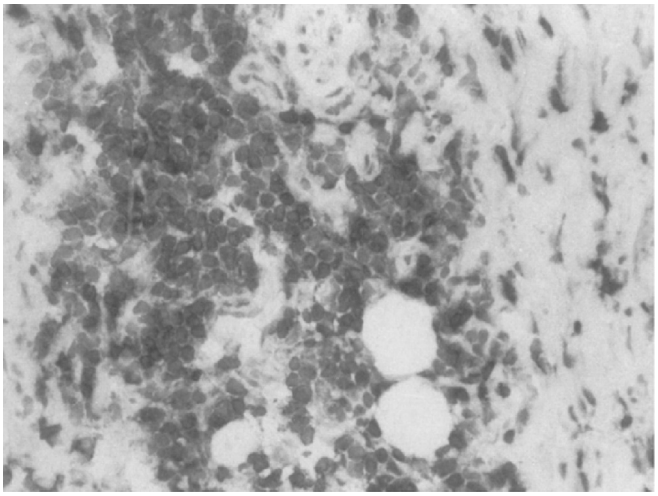

Fig. 2. Immunoperoxidase staining of a frozen section of an IAAA: Lymphoid aggregate in the adventitia showing preponderance of an anti-$CD19^+$ B cell staining [22].

3. The role of B cells in AAA

AAA lymphocytes are activated by either endogenous or exogenous antigens. Among these antigens, little is known about AAA-specific antigens. However, several studies have focused on autoantigens, including aortic aneurysm-associated protein-40 (AAAP-40) and carbonic anhydrase 1 (CA1). AAAP-40, which has homologies with elastin-associated microfibrils, has been shown to be similar to three chains of fibrinogen [30,31]. Zhou et al. [32] induced mice AAA with a natural IgG that binds to fibrinogen deposited in elastase-perfused aortic tissues. Furthermore, by using 2-dimensional electrophoresis and western blotting, Takashi et al. detected CA1 in AAA wall samples were modified to express neo-epitope(s) [33]. Additionally, in Chlamydia pneumonia (Cp) infection, molecular mimicry plays a role in the pathogenesis of AAA [34]. Molecular mimicry is defined as sharing similar epitopes between microorganisms and the normal aortic wall. Lindholt et al. [35] found a strong cross-reaction between Cp outer membrane proteins and the heavy chain of immunoglobulins in the wall of abdominal aortic aneurysms. While B cells (and/or dendritic cells) present antigens to T cells, activated T cells and B cells interact to promote the activation, proliferation, and differentiation of B cells. After activation, B cells in the germinal centers experience class switching and the affinity maturation of antibodies, producing IgA, IgM, IgE, and IgG. Elegant studies also found B-cell-bound immunoglobulins, such as IgG and IgM, in human AAA tissue [16,36]. Furthermore, B cells also produce a variety of cytokines, such as IL-6, TNF-alpha, and IL-10, which are also found in significantly high in human AAA tissue [37–40]. These cytokines might mediate the formation and development of human AAA via either promoting the activation of lymphocytes or promoting macrophages and mast cells that can produce MMPs and cathepsins (Fig. 3).