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Review

Implication of B lymphocytes in the pathogenesis of ANCA-associated vasculitides

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ABSTRACT

ANCA-associated vasculitis (AAV) is a subgroup of vasculitides characterized by the detection of anti-neutrophil cytoplasm antibodies (ANCA). Until recently, the pathogenesis of AAV mainly involved neutrophils, T cells, and ANCA. Importantly, data were recently published supporting B-cell implication in this setting. Thus, the identification of activated B lymphocytes in granulomatous lesions and the efficacy of B-cell depletion using rituximab in the treatment of patients with AAV changed our mind. However, the impact of B lymphocytes on disease activity and its specific role in the pathogenesis of AAV remains unclear, at least in part as the consequence of the limited number of patients investigated and the restricted number of studies investigating B-cell subsets. Perturbations of B-cell homeostasis have been identified in AAV with increased expression of CD38 and decreased expression of CD5 in active phase, contrasting with increased expression of CD25 and CD86 in remission state. Although decreased secretion of interleukin (IL)-10 has also been reported during disease flares, these data remain controversial and the cytokines secretion profile of B-cells needs to be further investigated. Herein, we summarize recent advances in the understanding of the implications of B-cells in the field of AAV and propose new fields of investigation for a better understanding of B lymphocytes in the pathogenesis of AAV.

Contents

Abbreviations: Aa, amino acid; AAV, ANCA-associated vasculitides; ANCA, anti-neutrophil cytoplasm antibodies; BAFF, B-cell activated factor; BAFF-R, BAFF receptor; BCR, B-cell receptor; c-ANCA, cytoplasmic ANCA; CLL, chronic lymphocytic leukemia; CTLA-4, cytotoxic T lymphocyte associated protein 4; EGPA, eosinophilic granulomatosis with polyangiitis; ENT, ear nose and throat; GPA, granulomatosis with polyangiitis; IL, interleukin; INF, interferon; IVIG, intravenous immunoglobulin; MPA, microscopic polyangiitis; MPO, myeloperoxidase; p-ANCA, perinuclear ANCA; PR3, proteinase 3; SLE, systemic lupus erythematosus; TACI, transmembrane activator and CAML interactor; TLR, toll-like receptor; TLS, tertiary lymphoid structures; TNF-α, tumor necrosis factor alpha.

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1. Introduction

Primary vasculitides constitute a heterogeneous group of diseases characterized by inflammation of blood vessels [1]. These rare diseases are characterized by distinct pathophysiological mechanisms and involve blood vessels of different sizes, resulting in a wide spectrum of clinical symptoms [1–4]. Anti-neutrophil cytoplasm antibodies (ANCA)-associated vasculitides (AAV) are pauci-immune necrotizing vasculitides involving small-sized vessels which include granulomatosis with polyangiitis (GPA) (formerly named Wegener's granulomatosis), eosinophilic granulomatosis with polyangiitis (EGPA) (formerly named Churg–Strauss syndrome), and microscopic polyangiitis (MPA) [5]. The immunofluorescence pattern of ANCA distinguishes cytoplasmic ANCA (c-ANCA), targeting proteinase 3 (PR3) in most cases, and perinuclear ANCA (p-ANCA), usually targeting myeloperoxidase (MPO). Inflammation of small-sized vessels is responsible for organ damage with granulomatous involvement of upper and lower respiratory tract in GPA and EGPA [6], and glomerulonephritis, intra-alveolar hemorrhage, and/or peripheral neuropathy in GPA, MPA, and EGPA [7].

Most of the research that has been conducted on AAV has focused on the production, secretion, and pathogenicity of ANCA and its impact on relapses [8]. Besides the pathogenic role of ANCA, previous studies have investigated the role of genetic predisposition [9], silica exposure [10] or autoimmune overlaps l11] and have demonstrated the implication of T cells in AAV, showing a predominant Th1 polarization in GPA contrasting with a predominant Th2 polarization in EGPA [12,13]. Only few studies were dedicated to analyze the potential role of B-cells in AAV. One of the first reports on the implication of B-cells in AAV focused on the analysis of B-cell infiltrates proximal to PR3-positive cells and plasma cells within endonasal inflammatory lesions of patients with GPA [14]. Within these lesions, Voswinkel et al. reported on the activation and maturation of aggregated B-cells [14,15], arguing for a key role of B lymphocytes in the pathogenesis of AAV. This concept was reinforced by the results of two prospective randomized trials demonstrating the efficacy of rituximab, an anti-CD20 monoclonal antibody, in the induction of remission in patients with GPA or MPA [16–18], and more recently for the maintenance of remission in the same diseases, with the superiority of rituximab compared to azathioprine [19].

The purposes of this systematic review are to summarize data supporting the role of B-cells in the pathogenesis of AAV and to explore new fields of investigation for the targeting of B-cells in the treatment of AAV.

2. Methods

Original and review articles in English or French with an abstract in the English language published from 1950 to January 15, 2015, were identified by completion of electronic database searching (Medline, ClinicalTrials.gov, Web of Science). Keyword combinations used included one of the following: anti-proteinase 3, anti-myeloperoxidase, ANCA-associated vasculitides, granulomatosis with polyangiitis, microscopic polyangiitis, eosinophilic granulomatosis with polyangiitis, together with one of the following: B lymphocytes, B-cells, regulatory B-cells, autoreactive B-cells, inflammatory B-cells, memory B-cells, naive B-cells, B-cells subsets, pathogenesis, plasmocytes, rituximab, anti-CD20, resulting in 408 unique references, including 357 original and 51 review articles.

3. General aspects on B-cells

B-cells derive from lymphoid precursors and are characterized by the membrane expression of the B-cell receptor (BCR) [20]. The BCR is composed of two identical heavy chains of immunoglobulins (Ig), which can be distinguished into five different isotypes (α, β, δ, γ, or μ), and two identical light chains (κ or λ), associated with co-receptors including CD19, CD21, CD79a, and CD79b. The heavy and light chains of Ig of the BCR form a tetramer connected by intra- and inter-disulfide bonds [21]. Specific Ig isotypes reflect the stage of differentiation of B-cells. Naive B-cells are characterized by high expression of IgM and IgD, whereas marginal zone B-cells (MZ B-cells) are characterized by high expression of IgM and low expression of IgD on the surface of $CD19^+$ B-cells [22]. BCR complex, in association with its co-receptors, recognizes the antigen by its tridimensional structure and promotes B-cell activation and differentiation into plasmablasts and plasma cells producing high-affinity antibodies (Fig. 1).

In mice, B-cells can be divided into two different subsets, including B1 and B2 cells [23]. B1 cells produce low affinity and T-independent polyreactive antibodies mainly directed against viruses and bacteria. These cells are restricted to pleural and abdominal cavities and excluded from secondary lymphoid organs (spleen and lymph nodes). These cells represent the first line of defense in mice by secreting high levels of IgM and low levels of IgG [24]. Recently, evidences of B1 cells exerting a protective effect in various inflammatory and/or autoimmune diseases, including atherosclerosis and multiple sclerosis, have been identified in humans [25,26]. In contrast, B2 cells require the presence of T cell signals to promote their activation and differentiation into antibody-producing cells, by inducing immunoglobulin class switching, acquisition of memory markers such as CD27, and antibody secretion [27,28]. These cells are predominantly found within secondary lymphoid organs and secrete high-affinity antibodies and are identified as MZ B-cells when they are found within the marginal zone of secondary lymphoid organs. However, the classification into B1 and B2 cells based on the expression of CD20, CD27, and CD43 is still controversial in humans [29,30].

4. ANCA production by B-cells

Detection and characterization of ANCA strongly support the implication of B-cells in the pathophysiology of AAV [31]. The prevalence of ANCA among patients with AAV differs according to the type of vasculitis. In GPA, PR3-ANCA are detected in 85% of patients while MPO-ANCA are identified in less than 10% of cases [12,32]. MPO-ANCA are detected in 60% of patients with MPA and in 31–38% of patients with EGPA [12,33,34].

In vitro studies demonstrated the induction of a respiratory burst in TNF-α primed neutrophils and monocytes after incubation with both