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Review

What do we know about memory B cells in primary Sjögren's syndrome?

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ABSTRACT

Abnormalities of memory B cells seem to be closely involved in the pathogenesis of primary Sjögrens Syndrome (pSS) and its malignant complication, B cell lymphoma. Recent studies on B cells in pSS add to our understanding of the distinct memory B cell subsets in pSS. Reduction of peripheral memory $CD27^+$ B cells, most strikingly of the $CD27^+IgM^+$ subset, may indicate a lack of appropriate censoring mechanisms and incomplete differentiation processes within the ectopic lymphoid tissues in pSS. This ectopically formed lymphoid tissue might protect autoreactive memory B cells from deletion by physiological check-points and, thereby, may contribute to the perpetuation of the disease as well as to an enhanced lymphoma risk. Thus, B cells may be potential targets of direct or indirect treatment in pSS.

Contents

1. Introduction

Primary Sjögren´s syndrome (pSS) is a chronic inflammatory autoimmune disease of as yet unknown origin [1,2]. Preferentially, pSS affects exocrine glands such as salivary and lacrimal glands resulting in keratoconjunctivitis sicca and xerostomia. But, there is also a wide range of clinical and laboratory manifestations, emphasizing that pSS is a systemic disorder [1,2]. Although the process that underlies the autoimmune response in pSS is not known, it is well established that close interactions of salivary gland epithelial cells, endothelial cells and dendritic cells with the infiltrating lymphoid cells contribute to the perpetuation and progression of the disease as well as to systemic lymphocyte derangement [3]. In this regard, hallmarks of pSS are B cell hyperactivity and B cell disturbances as manifested by hypergammaglobulinemia, circulating autoantibodies and/or immune complexes, changes in the distribution of peripheral B cell subsets [4–6], formation of germinal center (GC)-like structures within the inflamed tissues, and, finally, an enhanced risk to develop B cell lymphoma [1,7]. More detailed analyses of B cell subsets in pSS [8–10] as well as first data on B cell repopulation following B cell depletion therapy with rituximab in pSS patients [11] have underlined the central role of B cells, especially of the memory B cell compartment, in the immunopathogenesis of pSS.

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2. Memory B cell subsets in pSS

A considerably heterogeneity is apparent among human memory B cells which account for about 40 to 60% of all peripheral blood B cells in human adults [9,12–17]. Notably, the circulating peripheral blood memory B cell repertoire may reflect complex influences on differentiation, activation, selection, homing and recirculation of B cells from lymphoid organs and tissues. Altered B cell differentiation and priming, shedding of surface CD27 molecules, accumulation of $CD27^+$ memory B cells in inflamed tissues and altered recirculation of B cell subsets from these sites may all contribute to disturbed B cell homeostasis in pSS [3]. In this regard, early immunophenotyping studies in pSS indicated normal total B cell counts but characteristic B cell disturbances with a predominance of $CD27^-$ naive B cells and diminished peripheral $CD27^+$ memory B cells [4–6]. Of note, this included a markedly diminished circulating $CD27^+IgM^+$ subpopulation [10].

2.1. $CD27^+IgD^+IgM^+$ B cells

Based on a flow cytometric multicolor approach analyzing the major surface markers CD19, CD27 and IgD, more than a half of all human $CD27^+$ memory B cells have not undergone isotype switch but still express surface IgM and various levels of surface IgD [12–14]. Remarkably, a relevant proportion of circulating IgM^+CD27^+ B cells display a similar phenotype to the vast majority of splenic marginal-zone (MZ) B cells in humans, $IgM^{high}IgD^{low}CD23^-CD21^+$, and, therefore, have been suggested to correspond with this splenic B cell subset [15,16]. Notably, an early prominent reduction of peripheral $CD27^+IgM^+IgD^+$ B cells has been found in individuals who underwent splenectomy for medical reasons, e.g., following trauma or because of autoimmune thrombocytopenia [18]. However, both the putative differentiation pathway and function of $CD27^+IgM^+IgD^+$ "MZ-like" B cells are still under discussion [15,16]. In particular, it is not yet clear where these cells encounter their Ig gene mutations and whether they represent innate effectors to T cell-independent antigens or "true" memory B cells [15,16]. At least, $CD27^+IgM^+$ B cells may encompass B cells of different origin. Early studies in pSS have detected significant reduction of peripheral $CD27^+IgM^+$ and $CD27^+IgD^+$ B cells [6]. Recently, a significant reduction of peripheral $CD27^+IgD^+IgM^+$ B cells along with an enhanced surface-expression of HLA-DR, CD38, and CD95, as well as a reduced surface-expression of CD21, CXCR5 and ICOS-L has been identified in pSS patients when compared to healthy individuals [10]. In addition, in pSS patients, individual single-sorted peripheral $CD27^+IgD^+$ B cells exhibited significantly lower mutational frequencies of their cμ-transcripts compared to those from healthy donors [10]. Thus, compared to healthy controls, circulating $CD27^+IgD^+IgM^+$ B cells in patients with pSS are significantly reduced but exhibit signs of abnormal activation and differentiation. This may reflect impaired differentiation and censoring mechanisms within secondary lymphoid organs and/or ectopic "tertiary" lymphoid tissues in pSS [3]. In accordance, recent immunohistological studies have detected both transitional (T)2 B cells and marginal-zone (MZ)-like B cells within lymphoid tissue infiltrates of the minor salivary glands of patients with pSS [8,11]. Although the degree of T cell-independent immune response in pSS remains unclear, excess BAFF, APRIL and IL-21 may be central in the progression of the entire autoimmune process in pSS by triggering B cell survival and autoantibody production.

2.2. $CD27^+IgD^-IgM^-$ B cells

In humans, "classical" memory B cells are generated in germinal centers (GCs) in response to T cell-dependent antigens (Ag), where they mutate their immunoglobulin (Ig) variable (V) region genes, express surface CD27 and can switch their Ig class [19]. As a result, class-switched memory B cells express a $CD27^+IgD^-IgM^-$ phenotype and mutated IgV genes. Memory B cells, yielded by GC reaction, require lower concentrations of Ag and T cell help for their activation than naïve B cells and rapidly differentiate into high-affinity plasma cells following re-encounter with the immunizing Ag [20]. Under physiological conditions, the B cell development is tightly regulated by central and peripheral self-tolerance mechanisms, i.e., by several "check-points" against autoreactivity [21,22]. By contrast, in autoimmune conditions, the occurrence of high-affinity, class-switched autoantibodies, such as anti-Ro and anti-La in pSS [23], represent a break of B cell tolerance [24]. In this regard, circulating $CD27^+$ memory B cells are markedly reduced in the peripheral blood of pSS patients, whereas preferential accumulation of memory B cells in their inflamed salivary glands has been indicated by IgV analysis [6,25] and analysis of chemokine receptor-ligand interactions [26]. Especially, CXCL12–CXCR4 and CXCL13–CXCR5 interactions have been strongly suggested to be of special importance in B cell disturbances in pSS and may be closely associated with the entire inflammatory process, the development of ectopic GC-like structures [27,28] as well as with peripheral memory B cell disturbances [4–6,29]. The detection of both autoantigen-specific T and B cells, evidence of antigen-driven clonal B cell expansions by analyzing the mutations of IgV genes [30], a linkage between local autoantibody production and ectopic GC development as well as the occurrence of class-switched autoantibodies in the patients saliva strongly indicate that T cell-dependent immune responses may occur to some extent in lymphoid tissue infiltrates, especially in those containing ectopic GC-like structures [3]. More recent data on activation-induced deaminase (AID) expression in ectopic GC structures support the suggestion that the humoral immune response involving autoreactive B cells may mature in such ectopic GCs, although "true" ectopic GCs are rarely detected in pSS salivary glands. [11]. Altogether, this data indicates that the microenvironment of ectopic lymphoid tissues in pSS represents a niche were autoreactive memory B cells are escaped from deletion by the regular peripheral "check-points" against autoreactivity. Other sites, e.g., secondary lymphoid tissues may be also important in maintaining the autoimmune B cell memory in pSS, especially when the pSS salivary glands have been destructed by the chronic lymphocytic inflammation process.

2.3. $CD27^-IgD^-$ B cells

More recently, the role of CD27 as a general memory B cell marker in humans has been questioned by the detection of a peripheral CD27-negative B cell subpopulation expressing mutated IgG genes in healthy donors [20]. The mutational pattern of their IgG genes showed antigenic selection characteristics but with lower mutation frequencies than that of $CD27^+IgG^+$ B cells. $CD27^-IgG^+$ B cells may represent up to 4% of all peripheral B cells in healthy individuals [20] but might be activated and/or expanded in autoimmune conditions, such as in systemic lupus erythematosus (SLE) [31] or pSS [6,29]. As has been reported in SLE, $CD27^-$ memory cells are comparable to conventional $CD27^+$ cells in their isotype expression (e.g., they express either IgM, IgG or IgA) [13,14]. In pSS, combined immunophenotypic and molecular studies also revealed a significant proportion (~10%) of peripheral $CD27^-$ B cells expressing mutated IgV genes [6,29]. Most recent analysis in pSS revealed that this subset almost exclusively belongs to the $CD27^-IgD^-$ B cell population and encompasses both class-switched and non-class-switched B cells (unpublished observation). Thus, memory B cells in pSS may also partly masquerade as $CD27^-$ B cells. Their functional capacity and potential pathological role in pSS warrants further investigations. For example, these cells might be derived from extra-follicular responses or incomplete germinal center reactions. Alternatively, they could represent activated $CD27^+$ memory cells which have shedded surface CD27 [13,31].

2.4. IgD-only B cells

Whether IgD-only B cells which represent a minor fraction of all B cells in healthy humans [12,13] play a role in pSS pathogenesis remains to be elucidated.