

Understanding B Cell Biology

**Martin S. Naradikian, Jean L. Scholz, Michael A. Oropallo,
and Michael P. Cancro**

Abstract Humoral autoimmunity reflects failures in B cell tolerance and regulation. Accordingly, B cells have long been proposed as targets for treating autoimmune disease. The last decade has witnessed substantial growth in the number of therapeutic agents that target B cells themselves, or molecules key to B cell survival or function. In order to understand, develop, and eventually predict the outcomes of B cell targeted therapies, a thorough understating of the mechanisms underlying B cell development, activation, and regulation is necessary. Here we summarize B cell genesis, differentiation, and tolerance, and illustrate how an understanding of basic B cell biology can afford insight into the design and action of therapeutic agents.

1 Introduction and Overview

During the last decade, therapeutics targeting B cells have emerged as attractive candidates for treating autoimmune diseases. In addition to making antibodies, B cells perform several other roles critical to normal immune system function, including antigen presentation and regulatory cytokine production. Further, the extent and nature of each function varies based on the B cell subset involved, the anatomic context, and the nature of inducing stimuli. Thus, unraveling—and eventually predicting—the basis for B cell targeted therapeutic activity requires understanding the developmental, selective, and homeostatic mechanisms governing naïve, activated, and antigen experienced B cell pools. Accordingly, this chapter focuses on current understanding of these processes in both mouse models and humans. First, an overview of B lineage commitment, subsets and primary B cell development is provided, followed by considerations of the selective

M.S. Naradikian • J.L. Scholz • M.A. Oropallo • M.P. Cancro (✉)
Department of Pathology & Laboratory Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA 19104-6082, USA
e-mail: smartin@mail.med.upenn.edu; jeanl@mail.med.upenn.edu; mant@mail.med.upenn.edu; cancro@mail.med.upenn.edu

and homeostatic processes active in establishing and maintaining pre-immune B cell pools. In subsequent sections, we discuss alternative routes of B cell activation, as well as the generation of effector and memory B cell subsets. Finally, we briefly discuss the relevance of these considerations to current thought and practice in B cell targeted therapies.

2 B Cell Commitment, Lineages, and Development

B cells are produced continuously throughout life, initially arising from the fetal liver and then from hematopoietic stem cells in the bone marrow (BM) (reviewed in Busslinger 2004; Dorshkind 2002; Georgopoulos 2002). As with all eukaryotic cells, B lineage commitment is based on transcription factor competition and cross-regulation (Warren and Rothenberg 2003). Accordingly, acquiring B cell identity involves both the onset of a B cell transcriptional program and the loss of other immune cell potentials (Rothenberg and Pant 2004). Key features of B lineage commitment are tied to the initiation of gene rearrangements at the immunoglobulin (Ig) heavy and light chain loci and the expression of several “master” transcription factors, notably Pax5 (Nutt and Kee 2007; Cobaleda et al. 2007). Once common lymphoid progenitors commit to the B lineage, the transcription factor E2A modifies chromatin marks to activate EBF and Pax5, which in turn activate a cascade of B cell-specific genes (Allman et al. 1999; Li et al. 1996; Nutt and Kee 2007; Medvedovic et al. 2011; Singh et al. 2007; Johnson et al. 2009). More recently, several studies have highlighted regulatory aspects of microRNAs (MiRs) in B cell development, particularly MiR-150 (Xiao et al. 2007; Li et al. 2013). While epigenetic regulation of B cell development is beyond the scope of this chapter, details of this topic and its link to lymphoma are discussed elsewhere (Xiao and Rajewsky 2009; Fernando et al. 2012).

B cells can be separated into two lineages: B-1 and B-2. Debate remains as to whether B-1 and B-2 cells derive from a common progenitor and diverge based on antigen-driven selection, or instead reflect the products of distinct, lineage-restricted progenitors (Ghosn et al. 2007; Berland and Wortis 2002; Montecino-Rodriguez and Dorshkind 2012). Regardless of their exact origins, each lineage plays distinct yet overlapping roles in humoral immunity, reflecting differences in their generation, antigen receptor diversity, and anatomic niche (Table 1). The phenotypic and functional characteristics of B-1 cells are well established in mice, but their likely human counterpart was only recently revealed (Griffin et al. 2011). In contrast, the characterization of B-2 cells is well advanced in both human and mice, affording more extensive comparisons.

Murine B-1 cells are derived primarily from the fetal liver and are sustained largely by self-renewal in the periphery (Hardy 2006; Berland and Wortis 2002; Ghosn et al. 2007). In contrast, B-2 cells arise mostly from the bone marrow and are produced throughout life, albeit at reduced output rates with advanced age. Thus, despite the early production and brief predominance of B-1 cells in fetal and

Table 1 Overview of B-1 and B-2 B cells

Ontogeny and function	B-1	B-2
Major roles	Immune barrier; rapid, early immune responses; natural Abs; TI responses	Surveillance; adaptive immune responses; memory; produce Ab targeted to pathogens; secondary immune responses; TI and TD responses
Anatomic locations	Coelomic cavities Mucosal interfaces Spleen	Secondary lymphoid organs Lymphatics blood
Development	Fetal liver; adult bone marrow; self-renewal in periphery	Continuous generation from bone marrow HSC pool
Major subsets	B-1a, B-1b	Transitional (TR), follicular (FO), marginal zone (MZ), germinal center (GC), memory B (MBC)
Pool size	Small	Large overall; FO B cells comprise the majority in young adult life
Primary antibody isotype(s) secreted	IgM, IgA	IgM, IgG
BCR/repertoire	Generated by somatic recombination J-proximal V _H segments Lack junctional diversity	Generated by somatic recombination; random use of entire V _H cluster; high junctional diversity Somatic mutation in GC, memory B

Key differences between B-1 and B-2 B cells in the context of this chapter are shown. These are extensively reviewed in Montecino-Rodriguez and Dorshkind (2012) and Herzenberg (2000)

neonatal life (Haughton et al. 1993), continuous B-2 cell production yields a much larger steady-state B-2 pool in secondary lymphoid organs (Krop et al. 1996).

2.1 BCR Expression and Early B Cell Differentiation

The expression of a functional B cell antigen receptor (BCR) is fundamental to B cell identity. Further, because BCRs are clonally distributed—each mature B cell expresses only one combining site specificity—a large repertoire of BCRs must be established in the pre-immune B cell compartment to afford the selectivity and specificity associated with adaptive immune responses. In mammals, this diverse array of BCRs is established through the rearrangement of V, D, and J gene segments at the Ig heavy and light chain loci (Tonegawa 1983; Alt et al. 1984). In addition to the considerable permutations provided by the random splicing of multiple gene segments and independent Ig heavy-light chain pairing, nucleotide insertion mechanisms at gene segment junctions further amplify the breadth of BCR diversity (Komori et al. 1993). Notably, while both B-1 and B-2 lineages undergo VDJ rearrangement, the B-1 repertoire is comparatively restricted in terms of heavy chain V segment use, and most B-1 cells lack junctional insertions

(Pennell et al. 1989a, b; Pennell 1995; Seidl et al. 1999; Gu et al. 1990; Kantor et al. 1997; Griffin et al. 2011; Alugupalli et al. 2004; Stoel et al. 2005).

The discrete, sequential steps of VDJ recombination provide the basis for current nomenclatures describing the developmental stages of BM-derived B-2 cells (Melchers 1997; Melchers et al. 1989; Hardy 1989). The three most commonly used nomenclatures are outlined and compared in Table 2. The pro-B cell (Hardy fractions A–C) is the earliest of these developmental stages, where recombinase activating genes 1 and 2 (RAG1/2) join a D and J_H segment at the Ig heavy chain (*IgH*) locus, followed by a V_H to DJ_H rearrangement (Oettinger et al. 1990; Schatz et al. 1989). After a successful V_HDJ_H recombination event at *IgH*, the resulting heavy chain gene product pairs with surrogate light chain ($\lambda 5$ -Vpre-B) to form the pre-BCR. Reflecting the order of Ig heavy chain constant region genes, this initially expressed heavy chain utilizes the J_H-proximal μ constant region. The pre-BCR complex, which includes the signaling components Ig- α and Ig- β , is trafficked to the cell surface (Pillai and Baltimore 1987; Karasuyama et al. 1994). Signaling through the pre-BCR is critical for continued B cell differentiation, presumably as a checkpoint for successful Ig heavy chain expression (Kitamura et al. 1992). Pre-BCR signals lead to reduced RAG1/2 protein levels (Jung et al. 2006), as well as a proliferative burst in these so-called large pre-B cells (Hardy fraction C'). The RAG1/2 proteins are then re-expressed, commencing light chain rearrangement and marking the small pre-B cell stage (Hardy fraction D). Productive light chain rearrangement at either the Ig kappa or lambda light chain locus yields expression of a complete BCR, demarcating the immature (IMM) BM B cell stage (Hardy fraction E).

While most details of B-2 cell differentiation and Ig gene rearrangement were established from studies in mice, human B cell development is strikingly similar. A decade after Cooper and colleagues suggested that different lymphoid lineages mediate antibody production versus delayed-type hypersensitivity in animal models, B cell precursors were described in human fetal liver (Cooper et al. 1965, 1966; Gathings et al. 1977). While these studies were largely geared towards diagnosing and characterizing leukemia (Preud'homme and Seligmann 1972; Vogler et al. 1978), they initiated work leading to an understanding of human B cell development. As in mice, human B cells arise in the fetal liver or bone marrow and are continuously generated throughout life (Nunez et al. 1996). Furthermore, the molecular mechanisms and temporal sequence of events underlying human BCR expression mirror the processes described in mice (LeBien 2000). One apparent difference between mouse and human B cell development is the contribution of the common γ chain cytokine interleukin 7 (IL-7). While murine pro- and pre-B cells rely on IL-7 for survival and differentiation, human B cell progenitors are IL-7 independent (Namen et al. 1988; Prieyl and LeBien 1996; Puel et al. 1998; Noguchi et al. 1993).

Table 2 B-2 developmental stages in the bone marrow

Developmental stages			
Osmond	Melchers and Rolink	Hardy	Status of Ig loci
Pro-B	Pre-pro B	A	Germline
	Pro-B	B	D–J _H rearrangement
		C	V _H –DJ _H rearrangement
Pre-B	Large pre B	C'	V _H DJ _H pairs with λ5-Vpre-B Pre-BCR surface expression
	Small pre B	D	V _κ –J _κ or V _λ –J _λ rearrangement
Immature B	Immature B	E	Complete BCR (receptor editing can occur)

Comparison of the nomenclatures used to identify developmental B cell subsets and how they relate to key VDJ recombination events (comprehensively reviewed in Osmond et al. 1998; Hardy et al. 2000)

2.2 *Peripheral B-2 Cell Maturation and Homeostasis in Pre-Immune Pools*

Once developing B cells reach the IMM stage, they will exit the BM within several days, entering the circulation as transitional (TR) B cells. The TR B cell pool can be further divided into numbered subsets, T1, T2, and T3, according to surface marker and functional criteria (Allman et al. 2001; Carsetti et al. 1995; Loder et al. 1999). TR cells are found in the blood and spleen, but rarely enter the lymphatics. Moreover, they are the last stage before developing cells enter one of the two mature pre-immune B-2 pools: the follicular (FO) or marginal zone (MZ) B subsets (Pillai and Cariappa 2009). Whereas FO B cells are recirculating and thus found in the blood and secondary lymphoid organs, MZ B cells—at least in mice—are sessile and instead home to and reside within the marginal zone of the splenic white pulp (Gray et al. 1982; Pillai et al. 2005; Lu and Cyster 2002). Besides occupying different physical niches, FO and MZ B cells display different BCR signaling characteristics and serve distinct functions (Martin and Kearney 2002; Pillai and Cariappa 2009; MacLennan et al. 1982; Oliver et al. 1997). While the mechanisms dictating which mature subset TR B cells will enter are not fully understood, BCR specificity, cytokine availability, and competition with preexisting mature B cells are all contributors (Martin and Kearney 2002; Thien et al. 2004; Allman and Pillai 2008). For example, MZ B cells express a skewed repertoire of BCR specificities, sharing some features with the B-1 repertoire. Further, under normal homeostatic conditions most TR B cells enter the FO pool, but under B lymphopenic conditions the MZ fate is favored (Agenes and Freitas 1999; Srivastava et al. 2005).

While not absolutely congruent with the analogously named subsets in mice, four B cell subsets are defined among human peripheral blood B cells, based on the differential expression of CD19, CD38, CD27, CD24, and IgD (Table 3). These include TR, FO, MZ-like, and memory B cell populations. A more detailed discussion of subset demarcation, and comparisons with the corresponding mouse

Table 3 Comparison of mouse and human peripheral B cell subset phenotypes

Subsets	Mouse	Human
Transitional	B220 ⁺ AA4.1 ⁺ CD24 ^{hi} IgM ⁺ BR3 ⁺ TACI ⁺	CD20 ⁺ CD27 ⁻ CD38 ^{hi} IgM ⁺ CD24 ^{hi} BR3 ⁺
Mature pre-immune	CD23 ⁺ CD21/35 ⁺ IgD ^{hi} IgM ^{lo} (FO ⁺) CD23 ⁻ CD21/35 ^{hi} IgD ^{lo} IgM ^{hi} CD1d ⁺ (MZ ⁺) BR3 ⁺ TACI ⁺	CD20 ⁺ CD27 ⁻ CD38 ⁺ IgM ⁺ IgD ⁺ (Naïve ⁺) CD20 ⁺ CD23 ⁻ CD21 ^{hi} IgD ^{lo} IgM ^{hi} CD1d ⁺ (MZ ⁺ -like) BR3 ⁺ TACI ⁺
Germinal center	B220 ⁺ GL7 ⁺ Fas ⁺ PNA ⁺ IgD ⁻ IgM ⁻ BR3 ⁺	CD20 ⁺ CD38 ⁺ IgD ⁻ BR3 ⁺
Plasma cell	IgD ⁻ B220 ^{lo} , CD138 ^{hi} TACI ⁺ and/or BCMA ⁺	CD20 ⁻ CD38 ^{hi} CD27 ^{hi} CD138 ⁺ TACI ⁺ and/or BCMA ⁺
Memory B cell	B220 ⁺ CD80 ⁺ CD73 ⁺ PD-L2 ⁺	CD20 ⁺ CD38 ⁻ CD27 ⁺

Major surface marker differences between pre-immune and antigen experienced B cell subsets including BLyS receptor expression are shown. Memory B cell BLyS receptor profiles remain poorly defined (Tangye et al. 2006; Scholz et al. 2011; Tomayko et al. 2010)

subsets, can be found elsewhere (Scholz et al. 2011). Recent studies of human B cell reconstitution after B cell depletion indicate that these peripheral subsets and their differentiative order largely recapitulate murine B cell ontogeny; BM émigrés initially seed the TR B cell pool, followed by appearance of the more mature FO and MZ-like subsets (Anolik et al. 2007; Roll et al. 2006; Leandro et al. 2006; Palanichamy et al. 2009; Suryani et al. 2010).

Once established, the maintenance of mature pre-immune B cell pools relies on signals from survival cytokines, primarily those in the BLyS family of ligands and receptors. This subfamily of the tumor necrosis factor (TNF) superfamily consists of two cytokines, BLyS (B Lymphocyte Stimulator a.k.a. BAFF) and A proliferation-inducing ligand (APRIL); and three receptors, BLyS receptor 3 (BR3, a.k.a. BAFF-R), trans-membrane activator and cyclophilin ligand interactor (TACI), and B cell maturation antigen (BCMA) (Hahne et al. 1998; Kelly et al. 2000; Madry et al. 1998; Moore et al. 1999; von Bulow and Bram 1997). BLyS binds with the greatest affinity to BR3, less strongly to TACI, and with low affinity to BCMA (Bossen and Schneider 2006; Day et al. 2005). In contrast, APRIL binds with high affinity to both TACI and BCMA, but negligibly to BR3.

Within the pre-immune B-2 cell pools, TR, FO, and MZ B cells express BR3 (Stadanlick et al. 2008; Hsu et al. 2002) and require signals via this receptor for their survival. Accordingly, both BLyS and BR3 deficiencies independently yield profound reductions in TR and mature B cell numbers (Harless et al. 2001; Lentz et al. 1996, 1998; Miller and Hayes 1991; Miller et al. 1992; Yan et al. 2001). Conversely, BLyS transgenics or mice given exogenous BLyS show increased FO and MZ B cell numbers (Mackay et al. 1999; Thien et al. 2004). The current models for peripheral B cell homeostasis posit that B cells fill the mature pre-immune pools until most of the available BLyS is bound to cell surface BR3 and TACI; and at that point B cell

capacity is maximal so the pool size remains constant unless B_{LyS} levels change substantially.

Far less is understood about the homeostatic mechanisms operating in B-1 B cells. However, B-1 cell homeostasis differs fundamentally from B-2 cells in two ways. First, unlike B-2 cells, the B-1 compartment is maintained largely by self-renewal, rather than by the continuous influx of new cells generated from HSC-derived progenitors. Second, B-1 B cells are largely independent of B_{LyS}, since B_{LyS} depletion in mice has little or no effect on B-1 pools, despite the profound depletion of B-2 cells (Scholz et al. 2008).

Though human B cell homeostasis is less extensively characterized, evidence suggests mechanisms parallel to those in mice. For example, human B cells also bind B_{LyS} and express BR3 in both TR and naïve pools (Darce et al. 2007; Palanichamy et al. 2009; Ng et al. 2004; Sims et al. 2005; Carter et al. 2005). Furthermore, homozygous BR3 deletion results in a B cell developmental block at the TR stage, severely reducing numbers of mature pools—as has long been appreciated in BR3- or B_{LyS}-deficient mice (Warnatz et al. 2009; Thompson et al. 2001; Schiemann et al. 2001). These observations imply an inverse relationship between total B cells and B_{LyS} levels, conceptually consistent with the notion that B_{LyS} signals via BR3 are key homeostatic regulators of the pre-immune B cell pools. Indeed, BR3 deficiency, B cell lymphopenia, or B cell depletion therapy leads to elevated serum B_{LyS} levels (Cambridge et al. 2006; Kreuzaler et al. 2012). Nevertheless, there is also evidence that human and nonhuman primate B cells are somewhat less sensitive to B_{LyS} depletion than murine B cells. In contrast to murine FO B cells, a higher percentage of human B cells survive in culture without B_{LyS} and show only small improvements in survival with added B_{LyS} (Avery et al. 2003; Sims et al. 2005; Tangye et al. 2006). Furthermore, antibody-mediated B_{LyS} depletion partially ablates late TR and mature naïve B cell subsets in humans and nonhuman primates, but to a lesser degree than in mice (Scholz et al. 2008; Calero et al. 2010; Halpern et al. 2006; Vugmeyster et al. 2006; Baker et al. 2003). Differences in B cell sensitivity to B_{LyS} may reflect differences in B_{LyS} receptor expression levels and/or B_{LyS} availability within different anatomic locales: for example, splenic MZ B cells of both mice and nonhuman primates are highly sensitive to B_{LyS} (Scholz et al. 2008; Vugmeyster et al. 2006). In toto, these studies indicate a critical role for B_{LyS} ligands and receptors in the size and content of the primary human B cell repertoire.

3 Immune Tolerance and the Selection of Pre-Immune B Cell Pools

Early demonstrations of acquired tolerance led to the clonal selection paradigm, which posits the selective elimination of clones bearing autoreactive antigen receptors (Billingham et al. 1953; Owen 1945; Burnet 1976). Indeed, the random recombination and nucleotide insertion mechanisms underlying Ig gene expression unavoidably

yield self-reactive BCRs, necessitating mechanisms to eliminate or silence potential autoreactivity. In accord with this idea, multiple checkpoints are imposed during B cell development that reduce the likelihood that self-reactive B cells will enter the mature FO and MZ pools.

3.1 Deletion and Receptor Editing in the Bone Marrow

While some losses occur among developing B cells at the pre-B stage, the first point at which a complete BCR specificity can be leveraged for selection is at the IMM BM stage. Several powerful transgenic mouse models have identified two general mechanisms through which autoreactive specificities are eliminated or altered at this stage. Following the seminal findings of Nossal and Pike, compelling evidence has accumulated for the selective elimination of IMM B cells bearing self-reactive BCRs, driven by strong BCR ligation (Nossal and Pike 1975; Goodnow 2007; Nemazee and Weigert 2000). In addition, avid BCR signaling at the IMM B cell stage can lead to continued RAG expression and successive light chain gene rearrangements, thus altering BCR specificity via a process dubbed receptor editing (Tiegs et al. 1993; Gay et al. 1993; Luning Prak et al. 2011). This specificity-based central tolerance checkpoint is stringent, as only about 10 % of IMM B cells proceed through this checkpoint and exit the BM (Allman et al. 1993; Forster and Rajewsky 1990).

Evidence for similar processes in humans was established through single cloning and re-expression of Igs from human B cell subsets. In these studies, Nussenzweig and colleagues showed that nearly 75 % of BM precursors express autoreactive or polyreactive BCRs, and that these are purged from the repertoire as cells transit successive maturation stages (Wardemann et al. 2003). Interestingly, in some autoimmune patients these checkpoints were faulty (Meffre and Wardemann 2008; Yurasov and Nussenzweig 2007; Yurasov et al. 2005).

3.2 Transitional B Cell Selection

Despite the ~ 90 % losses due to negative selection in the BM, autoreactive and polyreactive clones nonetheless enter TR pools. While no longer capable of RAG reactivation and editing, TR cells remain subject to deletional tolerance mechanisms (Allman et al. 2001; Fulcher and Basten 1994; Goodnow et al. 1988; Rolink et al. 1998; Carsetti et al. 1995). Moreover, in addition to negative selection mediated by avid BCR signals, cells at the TR checkpoint also undergo a form of positive selection, whereby a minimal level of so-called tonic BCR signaling is required for survival and ultimate maturation (Monroe 2006). Thus, under normal physiological conditions, only about 30 % of TR B cells—and thus about 3 % of the original IMM B cell cohort—successfully continue to the mature FO or MZ pools (Allman et al. 1993). Importantly, and in contrast to BM selection, the stringency of peripheral tolerance is flexible and determined through interclonal competition

based on BCR signal strength and the ability to acquire BLyS (Cyster et al. 1994; Thien et al. 2004; Hondowicz et al. 2007). Thus, excess BLyS relaxes peripheral selection, allows autoreactive clones to enter otherwise forbidden mature pre-immune pools, and is associated with development of humoral autoimmunity in mice (Groom et al. 2002; Khare et al. 2000; Mackay et al. 1999).

In accordance with this relationship, BLyS levels correlate with serum autoantibody titers in Sjogren's syndrome and other systemic rheumatic diseases (Mariette et al. 2003; Cheema et al. 2001; Stohl et al. 2003). Despite the effectiveness of negative and peripheral selection, autoreactive B cells are found in mature pools in a quiescent state, suggesting the presence of additional poorly understood regulatory mechanisms (Wardemann et al. 2003). Finally, studies in humans receiving B cell ablation therapies such as rituximab or stem cell transplantation have provided not only detailed kinetics of human TR maturation but also novel surface markers to identify these immature B cell subsets (Palanichamy et al. 2009; Suryani et al. 2010; Anolik et al. 2007; Roll et al. 2006; Leandro et al. 2006). Further phenotypic marker studies, as well as functional and gene expression analyses, should help to further discriminate human B cell subsets (Anolik et al. 2009). Lastly, studies of human BCRs at the IMM and TR stages of development suggest that selection is based on specificity, and that either or both of these tolerogenic checkpoints are defective in humoral autoimmune diseases (von Boehmer and Melchers 2010; Meffre and Wardemann 2008; Wardemann et al. 2003; Yurasov et al. 2005; Wardemann and Nussenzweig 2007).

4 B Cell Activation and Humoral Immune Responses

BCR ligation initiates downstream signaling systems that foster activation. Characteristics of the subsequent humoral immune response are dictated by the type of antigen, the B cell differentiative subset(s) involved, the avidity of BCR cross linking, and intercellular interactions. In general, B cell responses follow the two-signal paradigm (Bretscher and Cohn 1970), whereby BCR ligation (signal 1) must be followed by additional activation and differentiation cues (signal 2) that are delivered via other cells or molecules. Two broad categories of humoral responses are defined based on the source of the second signal. The thymus-dependent (TD) response involves second signals that are delivered when B cells internalize, process, and present protein antigens to CD4 helper T cells. In contrast, the second signal in thymus-independent (TI) responses is delivered through innate immune receptors such as Toll like receptors (TLRs) expressed by the B cells themselves (TI-1), or through exceptionally intense BCR cross linking alone (TI-2).

Important differences between TD and TI responses include the pre-immune B cell populations that participate, the antibody isotypes generated, the response duration, the ultimate antibody affinity, and the extent of immunological memory established. In general, B-2 cells, particularly those in the FO compartment, are the major contributors to TD responses. In contrast, TI responses arise primarily from

either B-1 cells or the B-2 lineage MZ subset. These differences likely reflect the BCR signaling characteristics and differentiative potential of these pools, as well as the nature of inducing signals. TI responses are of short duration and skewed towards IgM production, whereas TD responses are more protracted and usually culminate in substantial class switched antibody of the IgG isotypes. Moreover, TD responses display a gradual but profound increase in average antibody affinity—a process termed affinity maturation. Finally, while both types of response can generate relatively long-lived antibody forming cells and memory B cells, TD responses are substantially more robust in this regard.

4.1 T-Independent Responses and Natural Antibodies

Within days after TI antigen challenge, substantial numbers of antibody secreting plasma cells (PCs) appear in splenic extrafollicular regions (Tarlinton 2008; Gourley et al. 2004). The antibodies made by this extrafollicular response are largely IgM and display comparatively low affinity for antigen. Within 2–3 weeks, the vast majority of these PCs die, although recent evidence indicates some long-term PC persistence and memory B cell (MBC) formation (Bortnick et al. 2012; Obukhanych and Nussenzweig 2006).

In addition to participating in responses to overt TI antigenic stimuli, some B-1 B cells are apparently constitutively activated and produce so-called natural antibodies (Bos et al. 1989; Baumgarth 2011). These polyreactive antibodies of the IgM and IgA isotypes bind epitopes on pathogens and commensals, as well as self-components such as cellular debris and phospholipids (Haas et al. 2005; Binder and Silverman 2005; Griffin et al. 2011). In conjunction with their use of a restricted set of IgH and IgL variable regions that do not include junctional insertions, these features suggest that B-1 B cells are “innate-like,” serving both barrier and house-keeping functions with a limited and relatively invariable set of ligand receptors (Herzenberg 2000).

Several autoimmune prone mice highlight a role for TI activation of autoreactive B cells; particularly from the standpoint of antigens containing TLR7, 8, and 9 ligands (Pisitkun et al. 2006; Leadbetter et al. 2002; Herlands et al. 2008). How these activation cues lead to sustained autoantibody production nonetheless remains unclear and is an active area of investigation.

4.2 T-Dependent Responses, Germinal Centers, and Affinity Maturation

As with TI responses, within days of TD antigen challenge, substantial numbers of PCs that generate low-affinity IgM appear in splenic extrafollicular regions.

However, a few days later clusters of proliferating B cells appear at the borders of B cell follicles and T cell zones in the lymph nodes and spleen (Nieuwenhuis and Opstelten 1984; Jacob et al. 1991). These are germinal centers (GCs); transient structures wherein the unique functional features of TD responses emerge, including affinity maturation as well as efficient memory B cell (MBC) and long-lived plasma cell generation.

GC formation requires a series of cognate, bi-directional interactions between activated CD4 T cells and activated, antigen-presenting B cells. Detailed discussions of these interactions are found elsewhere (Victora and Nussenzweig 2012), but they include MHCII-restricted presentation by the B cell, costimulation via CD40-CD40L, and key cytokines such as IL-21. Together, these interactions result in the adoption of a GC B cell transcriptional program driven largely by Bcl-6 (Allman et al. 1996; Dent et al. 1997; Shaffer et al. 2000; Basso and Dalla-Favera 2010). A key gene upregulated in GC B cells is activation-induced deaminase (AID), which creates point mutations in Ig V regions (Muramatsu et al. 2000; Pavri et al. 2010). This so-called somatic hypermutation (SHM) mechanism results in clonal variants of GC B cells with altered antigen affinity and specificity (Pavri and Nussenzweig 2011). Through selective competition and survival, clonal variants with higher affinity for antigen are selectively preserved, whereas those with lower affinity are at a selective disadvantage and die (Zotos and Tarlinton 2012). The details surrounding preferential survival remain an area of intense investigation, but clearly involve competition for antigen as well as survival signals. Currently popular models posit that the anatomically defined GC light zones are where competition for antigen and T helper cell survival factors occurs; whereas proliferation and AID-mediated SHM occur in GC dark zones (MacLennan 1994). AID also mediates class switch recombination (Muramatsu et al. 2000). Regulation of GC formation and resolution, light and dark zone designations and functions, and outcomes are broadly similar between mice and humans (Victora et al. 2012; Schmidlin et al. 2009; Diehl et al. 2012; Durandy et al. 2007; Peron et al. 2007).

Since GC B cells undergo a random BCR diversification process, the formation of autoreactive specificities is an unavoidable consequence (Diamond and Scharff 1984; Alabyev et al. 2007). Accordingly, active selection against incipient autoreactive GC B cell clones must also occur, although the mechanisms remain debated (Zou and Diamond 2013). Current models include direct death signaling through Fas–FasL interactions, as well as an inability to access survival cytokines due to loss of cognate antigen-presenting ability. Nonetheless, there is clear evidence for GC and/or post-GC selective checkpoints in both mice and humans (Wong et al. 2012; Yan et al. 2012; Tiller et al. 2007). Moreover, there is evidence for defects in this tolerance checkpoint in some SLE patients (Cappione et al. 2005).

4.3 Long-Lived Plasma Cells and Memory B Cells

Humoral responses, particularly TD responses, culminate in the establishment of long-lived PCs and MBC. Long-lived PCs can persist for the life of the organism; however, the basis for their longevity and precise differentiative origin remain an

area of intense investigation. Commitment to the PC fate involves the expression of B lymphocyte induced maturation protein 1 (Blimp1), which extinguishes the mature B cell gene expression program (Shaffer et al. 2002). Blimp1 initiates the PC transcriptional program in part through repression of both Bcl6 and Pax5 (Angelini-Duclos et al. 2000; Martins and Calame 2008). In addition, a plethora of stress response genes, presumably to cope with sustained antibody secretion (Oracki et al. 2010), are upregulated via the transcription factor Xbp1 (Reimold et al. 2001). Long-lived PCs home to and reside in the BM, affording stable and high antibody titers for the lifetime of the host (Schitteck and Rajewsky 1990; Manz et al. 1997). For example, TD responses from vaccines or pathogens confer protection for years or decades in humans (Pinna et al. 2009; Plotkin 2008; Amanna et al. 2007). Accordingly, given their robust nature and remarkable lifespan, long-lived BM PCs are of particular concern in the context of autoimmunity. Indeed, among patients where long-lived PCs are the source of pathogenic autoantibodies, ablative therapies targeting pre-immune and MBC pools may have little impact (Slifka et al. 1998). Thus, specifically targeting PCs is an important yet comparatively unexplored area in therapeutics for humoral autoimmune disorders.

MBCs are the result of antigen-driven clonal expansion long after an immunological challenge (Crotty et al. 2003). They remain in the host at elevated frequencies and are less dependent on T cell help for their reactivation (Maruyama et al. 2000). Whether antigen persistence plays a role in their maintenance remains debated, but at least some MBCs endure in the apparent absence of antigen (Vieira and Rajewsky 1990). Furthermore, MBC have a lower BCR signaling threshold, enabling more rapid entry into cell cycle compared to pre-immune pools (Gagro et al. 2003; Good et al. 2009; Yefenof et al. 1986). Moreover, the Ig genes of MBCs can be highly mutated or not, and MBCs can express either switched or unswitched BCRs (Gourley et al. 2004; Anderson et al. 2007). Lastly, MBCs are generally derived from GCs; however, evidence also exists for GC-independent MBC generation (Shlomchik and Weisel 2012).

In contrast to the relationship between BLYS and pre-immune B cell homeostasis, survival requisites for memory and plasma cells are not yet resolved. Alternative members of the BLYS ligand and receptor family may play a role, but are likely redundant with other survival promoting mechanisms. For example, B cells stimulated with TLR-4, 7, and 9 ligands upregulate TACI expression, suggesting APRIL or BLYS may be important for the differentiation of short-lived PCs and/or their persistence (Trembl et al. 2007; Groom et al. 2007). Similarly, long-lived PCs express both TACI and BCMA, suggesting APRIL may be an important cytokine for long-lived plasma cell homeostasis. Indeed, reductions—but not complete elimination—of plasma cells were noted when BLYS and APRIL were simultaneously blocked in vivo (Benson et al. 2008). Other cytokines, interleukins, and chemokine receptors are clearly involved in PC survival, suggesting considerable redundancy (Oracki et al. 2010). Whether these can be targeted individually or en masse to achieve therapeutic benefit is not yet clear, but may raise considerable off-target hurdles, inasmuch as eliminating long-lived memory and PC pools could significantly impact preexisting immunity to pathogens or vaccine antigens.

5 Overview of B Cells as Therapeutic Targets

Therapeutics targeting different B cell subsets and activation points are likely to differ in their activity and efficacies both within and between various autoimmune diseases. Indeed, several therapeutic agents that target B lineage cells are in clinical use or development for treating autoimmune diseases (Chugh 2012). The basic strategies involve targeting B cell-specific surface markers, depleting key survival factors, or disrupting critical intercellular or intracellular functions. Key examples of each of these approaches include rituximab (anti-CD20), belimumab (anti-BLyS), CD40 blockade, and bortezomib (proteasome inhibitor), respectively. Here, we briefly consider the effects and implications of each therapy, in order to illustrate how an understanding of B cell biology may provide insight into predicted outcomes, mechanism(s) of action, and potential drawbacks.

Two biologicals that have been applied to humoral autoimmunity are largely targeted towards eliminating members of pre-immune B cell subsets: rituximab and belimumab. Rituximab directly depletes B cells by targeting the CD20 surface molecule. Although effective for treatment of RA, rituximab has yielded perplexing results in off-label use for SLE (Looney et al. 2004; Sanz et al. 2011; Stohl et al. 2011). The basis for such confounding outcomes is unclear, but might reflect unwanted effects on B cell selection, or the lack of activity on relevant subsets in some subjects. For example, since BLyS levels are inversely related to mature B cell numbers, serum BLyS levels increase when B cells are ablated (Cambridge et al. 2006; Kreuzaler et al. 2012). Thus, depletion of mature pre-immune B cells pools without concomitantly limiting BLyS availability could lead to temporarily relaxed TR selection, affording entry of autoreactive clonotypes to mature naïve pool (Cambridge et al. 2006). Alternatively, because long-lived PCs lack CD20 surface expression, rituximab may not target the cells responsible for pathogenic antibody production in some subjects (Pescovitz 2006).

Belimumab—an anti-BLyS monoclonal antibody that neutralizes soluble BLyS—is one of several therapeutic agents designed to target BLyS family members (Cancro et al. 2009; Vincent et al. 2013). This approach ablates pre-immune B cell pools, albeit through survival cytokine blockade rather than direct B cell targeting. Clinical trial results demonstrated reductions in serum BLyS levels following treatment, as expected; along with significant and sustained reductions in mature pre-immune and activated B cells (Wallace et al. 2009; Furie et al. 2011). Nonetheless, the degree of depletion was less than might have been predicted by mouse studies, possibly reflecting the comparatively lower BLyS reliance of human FO B cells (Tangye et al. 2006). Therefore, reducing BLyS levels concomitant with B cell ablation may “normalize” TR selection, although this has not yet been directly assessed.

Other agents have been developed to target activated and antigen experienced B cell subsets. Some impede interactions of activated B cells with elements of T cell help, possibly influencing ongoing or emerging GC reactions, while others are aimed primarily at antibody secreting plasma cells per se. Thus, in SLE patients,

administration of CD40L blocking antibody results in decreased PCs, lowered anti-double-stranded DNA antibody levels, and reduced proteinuria (Grammer et al. 2003). Whether this reflects disruption of ongoing GC responses where negative selection has failed is unclear, but warrants further investigation. Indeed, there is ample evidence that some autoimmune disorders require T cell help (Jiang et al. 2007; Diamond et al. 1992; Shlomchik et al. 1990; Mohan et al. 1995), so blocking T-B interactions may be a highly attractive therapeutic approach. Accordingly, further understanding of B cell selection and tolerance checkpoints in TD responses may suggest future therapies.

How memory or plasma cell subsets are impacted by current ablative approaches remains unclear, probably reflecting heterogeneity and insufficient phenotypic delineation of memory B cell subsets (Anolik et al. 2009). For example, despite results from both mouse studies and clinical trials indicating that MBC and PC pools are not substantially affected by anti-BLyS treatment, initial increases in circulating MBC, followed by a gradual return to baseline levels, were observed in belimumab clinical trials (Wallace et al. 2009; Furie et al. 2011). Nevertheless, there were sustained and significant decreases in a plasma cell subset implicated in SLE pathogenesis, along with IgG anti-dsDNA Ab and ANA titers, while Ab titers to previous immunizations were maintained (Jacobi et al. 2003; Chatham et al. 2012; Furie et al. 2011; Navarra et al. 2011). These results raise the possibility of targeting pathogenic MBCs or PCs while sparing others.

Bortezomib is a proteasome inhibitor originally developed for multiple myeloma. Because PCs synthesize massive amounts of antibody, inhibiting proteasome function induces apoptosis through the unfolded protein response (Obeng et al. 2006). Therefore, inhibiting the proteasome has become an attractive novel therapy. Treatment of lupus prone mice with bortezomib protects from nephritis (Neubert et al. 2008). Similar results were also produced in an experimental model of autoimmune myasthenia gravis (Gomez et al. 2011). Interestingly, bortezomib selectively targets TD generated PCs but spares early TI type 2 responses (Lang et al. 2010). Unfortunately, because molecular inhibitors are global, the therapy lacks the specificity that antibody-based therapeutics provide. A more detailed discussion about bortezomib's role in treating humoral autoimmune disorders can be found elsewhere (Fierabracci 2012).

6 Perspective

Over the past two decades, research in basic B cell biology has cleared the path for the development of therapeutic agents for treating autoimmune disease. With increasing understanding of development, tolerance checkpoints, and function, the coming years promise to yield increasingly targeted agents to allow manipulation of specific B cell types as improved therapies are designed.

References

- Agnes F, Freitas AA (1999) Transfer of small resting B cells into immunodeficient hosts results in the selection of a self-renewing activated B cell population. *J Exp Med* 189:319–330
- Alabyev B, Rahman ZS, Manser T (2007) Quantitatively reduced participation of anti-nuclear antigen B cells that down-regulate B cell receptor during primary development in the germinal center/memory B cell response to foreign antigen. *J Immunol* 178:5623–5634
- Allman D, Jain A, Dent A, Maile RR, Selvaggi T, Kehry MR, Staudt LM (1996) BCL-6 expression during B-cell activation. *Blood* 87:5257–5268
- Allman D, Li J, Hardy RR (1999) Commitment to the B lymphoid lineage occurs before DH-JH recombination. *J Exp Med* 189:735–740
- Allman D, Lindsley RC, Demuth W, Rudd K, Shinton SA, Hardy RR (2001) Resolution of three nonproliferative immature splenic B cell subsets reveals multiple selection points during peripheral B cell maturation. *J Immunol* 167:6834–6840
- Allman D, Pillai S (2008) Peripheral B cell subsets. *Curr Opin Immunol* 20:149–157
- Allman DM, Ferguson SE, Lentz VM, Cancro MP (1993) Peripheral B cell maturation. II. Heat-stable antigen (hi) splenic B cells are an immature developmental intermediate in the production of long-lived marrow-derived B cells. *J Immunol* 151:4431–4444
- Alt FW, Yancopoulos GD, Blackwell TK, Wood C, Thomas E, Boss M, Coffman R, Rosenberg N, Tonegawa S, Baltimore D (1984) Ordered rearrangement of immunoglobulin heavy chain variable region segments. *EMBO J* 3:1209–1219
- Alugupalli KR, Leong JM, Woodland RT, Muramatsu M, Honjo T, Gerstein RM (2004) B1b lymphocytes confer T cell-independent long-lasting immunity. *Immunity* 21:379–390
- Amanna IJ, Carlson NE, Slifka MK (2007) Duration of humoral immunity to common viral and vaccine antigens. *N Engl J Med* 357:1903–1915
- Anderson SM, Tomayko MM, Ahuja A, Haberman AM, Shlomchik MJ (2007) New markers for murine memory B cells that define mutated and unmutated subsets. *J Exp Med* 204:2103–2114
- Angelini-Duclos C, Cattoretti G, Lin KI, Calame K (2000) Commitment of B lymphocytes to a plasma cell fate is associated with Blimp-1 expression in vivo. *J Immunol* 165:5462–5471
- Anolik JH, Friedberg JW, Zheng B, Barnard J, Owen T, Cushing E, Kelly J, Milner EC, Fisher RI, Sanz I (2007) B cell reconstitution after rituximab treatment of lymphoma recapitulates B cell ontogeny. *Clin Immunol* 122:139–145
- Anolik JH, Looney RJ, Lund FE, Randall TD, Sanz I (2009) Insights into the heterogeneity of human B cells: diverse functions, roles in autoimmunity, and use as therapeutic targets. *Immunol Res* 45:144–158
- Avery DT, Kalled SL, Ellyard JI, Ambrose C, Bixler SA, Thien M, Brink R, Mackay F, Hodgkin PD, Tangye SG (2003) BAFF selectively enhances the survival of plasmablasts generated from human memory B cells. *J Clin Invest* 112:286–297
- Baker KP, Edwards BM, Main SH, Choi GH, Wager RE, Halpern WG, Lappin PB, Riccobene T, Abramian D, Sekut L, Sturm B, Poortman C, Minter RR, Dobson CL, Williams E, Carmen S, Smith R, Roschke V, Hilbert DM, Vaughan TJ, Albert VR (2003) Generation and characterization of LymphoStat-B, a human monoclonal antibody that antagonizes the bioactivities of B lymphocyte stimulator. *Arthritis Rheum* 48:3253–3265
- Basso K, Dalla-Favera R (2010) BCL6: master regulator of the germinal center reaction and key oncogene in B cell lymphomagenesis. *Adv Immunol* 105:193–210
- Baumgarth N (2011) The double life of a B-1 cell: self-reactivity selects for protective effector functions. *Nat Rev Immunol* 11:34–46
- Benson MJ, Dillon SR, Castigli E, Geha RS, Xu S, Lam KP, Noelle RJ (2008) Cutting edge: the dependence of plasma cells and independence of memory B cells on BAFF and APRIL. *J Immunol* 180:3655–3659
- BERLAND R, WORTIS HH (2002) Origins and functions of B-1 cells with notes on the role of CD5. *Annu Rev Immunol* 20:253–300

- Billingham RE, Brent L, Medawar PB (1953) Actively acquired tolerance of foreign cells. *Nature* 172:603–606
- Binder CJ, Silverman GJ (2005) Natural antibodies and the autoimmunity of atherosclerosis. *Springer Semin Immunopathol* 26:385–404
- Bortnick A, Chernova I, Quinn WJ 3rd, Mugnier M, Cancro MP, Allman D (2012) Long-lived bone marrow plasma cells are induced early in response to T cell-independent or T cell-dependent antigens. *J Immunol* 188:5389–5396
- Bos NA, Kimura H, Meeuwssen CG, De Visser H, Hazenberg MP, Wostmann BS, Pleasants JR, Benner R, Marcus DM (1989) Serum immunoglobulin levels and naturally occurring antibodies against carbohydrate antigens in germ-free BALB/c mice fed chemically defined ultrafiltered diet. *Eur J Immunol* 19:2335–2339
- Bossen C, Schneider P (2006) BAFF, APRIL and their receptors: structure, function and signaling. *Semin Immunol* 18:263–275
- Bretscher P, Cohn M (1970) A theory of self-nonsel self discrimination. *Science* 169:1042–1049
- Burnet FM (1976) A modification of Jerne's theory of antibody production using the concept of clonal selection. *CA Cancer J Clin* 26:119–121
- Busslinger M (2004) Transcriptional control of early B cell development. *Annu Rev Immunol* 22:55–79
- Calero I, Nieto JA, Sanz I (2010) B cell therapies for rheumatoid arthritis: beyond B cell depletion. *Rheum Dis Clin North Am* 36:325–343
- Cambridge G, Stohl W, Leandro MJ, Migone TS, Hilbert DM, Edwards JC (2006) Circulating levels of B lymphocyte stimulator in patients with rheumatoid arthritis following rituximab treatment: relationships with B cell depletion, circulating antibodies, and clinical relapse. *Arthritis Rheum* 54:723–732
- Cancro MP, D'cruz DP, Khamashta MA (2009) The role of B lymphocyte stimulator (BLyS) in systemic lupus erythematosus. *J Clin Invest* 119:1066–1073
- Cappione A 3rd, Anolik JH, Pugh-Bernard A, Barnard J, Dutcher P, Silverman G, Sanz I (2005) Germinal center exclusion of autoreactive B cells is defective in human systemic lupus erythematosus. *J Clin Invest* 115:3205–3216
- Carsetti R, Kohler G, Lamers MC (1995) Transitional B cells are the target of negative selection in the B cell compartment. *J Exp Med* 181:2129–2140
- Carter RH, Zhao H, Liu X, Pelletier M, Chatham W, Kimberly R, Zhou T (2005) Expression and occupancy of BAFF-R on B cells in systemic lupus erythematosus. *Arthritis Rheum* 52:3943–3954
- Chatham WW, Wallace DJ, Stohl W, Latinis KM, Manzi S, McCune WJ, Tegzova D, McKay JD, Avila-Armengol HE, Utset TO, Zhong ZJ, Hough DR, Freimuth WW, Migone TS (2012) Effect of belimumab on vaccine antigen antibodies to influenza, pneumococcal, and tetanus vaccines in patients with systemic lupus erythematosus in the BLISS-76 trial. *J Rheumatol* 39:1632–1640
- Cheema GS, Roschke V, Hilbert DM, Stohl W (2001) Elevated serum B lymphocyte stimulator levels in patients with systemic immune-based rheumatic diseases. *Arthritis Rheum* 44:1313–1319
- Chugh PK (2012) Lupus: novel therapies in clinical development. *Eur J Intern Med* 23:212–218
- Cobaleda C, Jochum W, Busslinger M (2007) Conversion of mature B cells into T cells by dedifferentiation to uncommitted progenitors. *Nature* 449:473–477
- Cooper MD, Peterson RD, Good RA (1965) Delineation of the thymic and bursal lymphoid systems in the chicken. *Nature* 205:143–146
- Cooper MD, Raymond DA, Peterson RD, South MA, Good RA (1966) The functions of the thymus system and the bursa system in the chicken. *J Exp Med* 123:75–102
- Crotty S, Felgner P, Davies H, Glidewell J, Villarreal L, Ahmed R (2003) Cutting edge: long-term B cell memory in humans after smallpox vaccination. *J Immunol* 171:4969–4973
- Cyster JG, Hartley SB, Goodnow CC (1994) Competition for follicular niches excludes self-reactive cells from the recirculating B-cell repertoire. *Nature* 371:389–395

- Darce JR, Arendt BK, Chang SK, Jelinek DF (2007) Divergent effects of BAFF on human memory B cell differentiation into Ig-secreting cells. *J Immunol* 178:5612–5622
- Day ES, Cachero TG, Qian F, Sun Y, Wen D, Pelletier M, Hsu YM, Whitty A (2005) Selectivity of BAFF/BLyS and APRIL for binding to the TNF family receptors BAFFR/BR3 and BCMA. *Biochemistry* 44:1919–1931
- Dent AL, Shaffer AL, Yu X, Allman D, Staudt LM (1997) Control of inflammation, cytokine expression, and germinal center formation by BCL-6. *Science* 276:589–592
- Diamond B, Katz JB, Paul E, Aranow C, Lustgarten D, Scharff MD (1992) The role of somatic mutation in the pathogenic anti-DNA response. *Annu Rev Immunol* 10:731–757
- Diamond B, Scharff MD (1984) Somatic mutation of the T15 heavy chain gives rise to an antibody with autoantibody specificity. *Proc Natl Acad Sci U S A* 81:5841–5844
- Diehls SA, Schmidlin H, Nagasawa M, Blom B, Spits H (2012) IL-6 triggers IL-21 production by human CD4⁺ T cells to drive STAT3-dependent plasma cell differentiation in B cells. *Immunol Cell Biol* 90:802–811
- Dorshkind K (2002) Multilineage development from adult bone marrow cells. *Nat Immunol* 3:311–313
- Durandy A, Taubenheim N, Peron S, Fischer A (2007) Pathophysiology of B-cell intrinsic immunoglobulin class switch recombination deficiencies. *Adv Immunol* 94:275–306
- Fernando TR, Rodriguez-Malave NI, Rao DS (2012) MicroRNAs in B cell development and malignancy. *J Hematol Oncol* 5:7
- Fierabracci A (2012) Proteasome inhibitors: a new perspective for treating autoimmune diseases. *Curr Drug Targets* 13:1665–1675
- Forster I, Rajewsky K (1990) The bulk of the peripheral B-cell pool in mice is stable and not rapidly renewed from the bone marrow. *Proc Natl Acad Sci U S A* 87:4781–4784
- Fulcher DA, Basten A (1994) Reduced life span of anergic self-reactive B cells in a double-transgenic model. *J Exp Med* 179:125–134
- Furie R, Petri M, Zamani O, Cervera R, Wallace DJ, Tegzova D, Sanchez-Guerrero J, Schwarting A, Merrill JT, Chatham WW, Stohl W, Ginzler EM, Hough DR, Zhong ZJ, Freimuth W, van Vollenhoven RF (2011) A phase III, randomized, placebo-controlled study of belimumab, a monoclonal antibody that inhibits B lymphocyte stimulator, in patients with systemic lupus erythematosus. *Arthritis Rheum* 63:3918–3930
- Gagro A, Toellner KM, Grafton G, Servis D, Branica S, Radojicic V, Kosor E, Hrabak M, Gordon J (2003) Naive and memory B cells respond differentially to T-dependent signaling but display an equal potential for differentiation toward the centroblast-restricted CD77/globotriaosylceramide phenotype. *Eur J Immunol* 33:1889–1898
- Gathings WE, Lawton AR, Cooper MD (1977) Immunofluorescent studies of the development of pre-B cells, B lymphocytes and immunoglobulin isotype diversity in humans. *Eur J Immunol* 7:804–810
- Gay D, Saunders T, Camper S, Weigert M (1993) Receptor editing: an approach by autoreactive B cells to escape tolerance. *J Exp Med* 177:999–1008
- Georgopoulos K (2002) Haematopoietic cell-fate decisions, chromatin regulation and ikaros. *Nat Rev Immunol* 2:162–174
- Ghosh EE, Sadate-Ngatchou P, Yang Y, Herzenberg LA (2007) Distinct progenitors for B-1 and B-2 cells are present in adult mouse spleen. *Proc Natl Acad Sci U S A* 108:2879–2884
- Gomez AM, Vrolix K, Martinez-Martinez P, Molenaar PC, Phernambucq M, van der Esch E, Duimel H, Verheyen F, Voll RE, Manz RA, De Baets MH, Losen M (2011) Proteasome inhibition with bortezomib depletes plasma cells and autoantibodies in experimental autoimmune myasthenia gravis. *J Immunol* 186:2503–2513
- Good KL, Avery DT, Tangye SG (2009) Resting human memory B cells are intrinsically programmed for enhanced survival and responsiveness to diverse stimuli compared to naive B cells. *J Immunol* 182:890–901
- Goodnow CC (2007) Multistep pathogenesis of autoimmune disease. *Cell* 130:25–35

- Goodnow CC, Crosbie J, Adelstein S, Lavoie TB, Smith-Gill SJ, Brink RA, Pritchard-Briscoe H, Wotherspoon JS, Loblay RH, Raphael K et al (1988) Altered immunoglobulin expression and functional silencing of self-reactive B lymphocytes in transgenic mice. *Nature* 334:676–682
- Gourley TS, Wherry EJ, Masopust D, Ahmed R (2004) Generation and maintenance of immunological memory. *Semin Immunol* 16:323–333
- Grammer AC, Slota R, Fischer R, Gur H, Girschick H, Yarboro C, Illei GG, Lipsky PE (2003) Abnormal germinal center reactions in systemic lupus erythematosus demonstrated by blockade of CD154-CD40 interactions. *J Clin Invest* 112:1506–1520
- Gray D, MacLennan IC, Bazin H, Khan M (1982) Migrant mu+ delta+ and static mu+ delta- B lymphocyte subsets. *Eur J Immunol* 12:564–569
- Griffin DO, Holodick NE, Rothstein TL (2011) Human B1 cells in umbilical cord and adult peripheral blood express the novel phenotype CD20+ CD27+ CD43+ CD70. *J Exp Med* 208:67–80
- Groom J, Kalled SL, Cutler AH, Olson C, Woodcock SA, Schneider P, Tschopp J, Cachero TG, Batten M, Wheway J, Mauri D, Cavill D, Gordon TP, Mackay CR, Mackay F (2002) Association of BAFF/BLyS overexpression and altered B cell differentiation with Sjogren's syndrome. *J Clin Invest* 109:59–68
- Groom JR, Fletcher CA, Walters SN, Grey ST, Watt SV, Sweet MJ, Smyth MJ, MACKAY CR, MACKAY F (2007) BAFF and MyD88 signals promote a lupuslike disease independent of T cells. *J Exp Med* 204:1959–1971
- Gu H, Forster I, Rajewsky K (1990) Sequence homologies, N sequence insertion and JH gene utilization in VHDJH joining: implications for the joining mechanism and the ontogenetic timing of Ly1 B cell and B-CLL progenitor generation. *EMBO J* 9:2133–2140
- Haas KM, Poe JC, Steeber DA, Tedder TF (2005) B-1a and B-1b cells exhibit distinct developmental requirements and have unique functional roles in innate and adaptive immunity to *S. pneumoniae*. *Immunity* 23:7–18
- Hahne M, Kataoka T, Schroter M, Hofmann K, Irmeler M, Bodmer JL, Schneider P, Bornand T, Holler N, French LE, Sordat B, Rimoldi D, TSCHOPP J (1998) APRIL, a new ligand of the tumor necrosis factor family, stimulates tumor cell growth. *J Exp Med* 188:1185–1190
- Halpern WG, Lappin P, Zanardi T, Cai W, Corcoran M, Zhong J, Baker KP (2006) Chronic administration of belimumab, a BLyS antagonist, decreases tissue and peripheral blood B-lymphocyte populations in cynomolgus monkeys: pharmacokinetic, pharmacodynamic, and toxicologic effects. *Toxicol Sci* 91:586–599
- Hardy RR (1989) B cell ontogeny and B cell subsets. *Curr Opin Immunol* 2:189–198
- Hardy RR, Li YS, Allman D, Asano M, Gui M, Hayakawa K (2000) B-cell commitment, development and selection. *Immunol Rev* 175:23–32
- Hardy RR (2006) B-1 B cell development. *J Immunol* 177:2749–2754
- Harless SM, Lentz VM, Sah AP, Hsu BL, Clise-Dwyer K, Hilbert DM, Hayes CE, Cancro MP (2001) Competition for BLyS-mediated signaling through Bcnd/BR3 regulates peripheral B lymphocyte numbers. *Curr Biol* 11:1986–1989
- Haughton G, Arnold LW, Whitmore AC, Clarke SH (1993) B-1 cells are made, not born. *Immunol Today* 14:84–87 (discussion 87–91)
- Herlands RA, Christensen SR, Sweet RA, Hershberg U, Shlomchik MJ (2008) T cell-independent and toll-like receptor-dependent antigen-driven activation of autoreactive B cells. *Immunity* 29:249–260
- Herzenberg LA (2000) B-1 cells: the lineage question revisited. *Immunol Rev* 175:9–22
- Hondowicz BD, Alexander ST, Quinn WJ 3rd, Pagan AJ, Metzgar MH, Cancro MP, Erikson J (2007) The role of BLyS/BLyS receptors in anti-chromatin B cell regulation. *Int Immunol* 19:465–475
- Hsu BL, Harless SM, Lindsley RC, Hilbert DM, Cancro MP (2002) Cutting edge: BLyS enables survival of transitional and mature B cells through distinct mediators. *J Immunol* 168:5993–5996

- Jacob J, Kassir R, Kelsoe G (1991) In situ studies of the primary immune response to (4-hydroxy-3-nitrophenyl)acetyl. I. The architecture and dynamics of responding cell populations. *J Exp Med* 173:1165–1175
- Jacobi AM, Odendahl M, Reiter K, Bruns A, Burmester GR, Radbruch A, Valet G, Lipsky PE, Dorner T (2003) Correlation between circulating CD27^{high} plasma cells and disease activity in patients with systemic lupus erythematosus. *Arthritis Rheum* 48:1332–1342
- Jiang C, Foley J, Clayton N, Kissling G, Jokinen M, Herbert R, Diaz M (2007) Abrogation of lupus nephritis in activation-induced deaminase-deficient MRL/lpr mice. *J Immunol* 178:7422–7431
- Johnson K, Reddy KL, Singh H (2009) Molecular pathways and mechanisms regulating the recombination of immunoglobulin genes during B-lymphocyte development. *Adv Exp Med Biol* 650:133–147
- Jung D, Giallourakis C, Mostoslavsky R, Alt FW (2006) Mechanism and control of V(D)J recombination at the immunoglobulin heavy chain locus. *Annu Rev Immunol* 24:541–570
- Kantor AB, Merrill CE, Herzenberg LA, Hillson JL (1997) An unbiased analysis of V(H)-D-J (H) sequences from B-1a, B-1b, and conventional B cells. *J Immunol* 158:1175–1186
- Karasuyama H, Rolink A, Shinkai Y, Young F, Alt FW, Melchers F (1994) The expression of Vpre-B/lambda 5 surrogate light chain in early bone marrow precursor B cells of normal and B cell-deficient mutant mice. *Cell* 77:133–143
- Kelly K, Manos E, Jensen G, nadauld L, Jones DA (2000) APRIL/TRDL-1, a tumor necrosis factor-like ligand, stimulates cell death. *Cancer Res* 60:1021–1027
- Khare SD, Sarosi I, Xia XZ, McCabe S, Miner K, Solovyyev I, Hawkins N, Kelley M, Chang D, Van G, Ross L, Delaney J, Wang L, Lacey D, Boyle WJ, Hsu H (2000) Severe B cell hyperplasia and autoimmune disease in TALL-1 transgenic mice. *Proc Natl Acad Sci U S A* 97:3370–3375
- Kitamura D, Kudo A, Schaal S, Muller W, Melchers F, Rajewsky K (1992) A critical role of lambda 5 protein in B cell development. *Cell* 69:823–831
- Komori T, Okada A, Stewart V, Alt FW (1993) Lack of N regions in antigen receptor variable region genes of TdT-deficient lymphocytes. *Science* 261:1171–1175
- Kreuzaler M, Rauch M, Salzer U, Birmelin J, Rizzi M, Grimbacher B, Plebani A, Lougaris V, Quinti I, Thon V, Litzman J, Schlesier M, Warnatz K, Thiel J, Rolink AG, Eibel H (2012) Soluble BAFF levels inversely correlate with peripheral B cell numbers and the expression of BAFF receptors. *J Immunol* 188:497–503
- Krop I, de Fougères AR, Hardy RR, Allison M, Schlissel MS, Fearon DT (1996) Self-renewal of B-1 lymphocytes is dependent on CD19. *Eur J Immunol* 26:238–242
- Lang VR, Mielenz D, Neubert K, Böhm C, Schett G, Jack HM, Voll RE, Meister S (2010) The early marginal zone B cell-initiated T-independent type 2 response resists the proteasome inhibitor bortezomib. *J Immunol* 185:5637–5647
- Leadbetter EA, Rifkin IR, Hohlbaum AM, Beaudette BC, Shlomchik MJ, Marshak-Rothstein A (2002) Chromatin-IgG complexes activate B cells by dual engagement of IgM and Toll-like receptors. *Nature* 416:603–607
- Leandro MJ, Cambridge G, Ehrenstein MR, Edwards JC (2006) Reconstitution of peripheral blood B cells after depletion with rituximab in patients with rheumatoid arthritis. *Arthritis Rheum* 54:613–620
- Lebien TW (2000) Fates of human B-cell precursors. *Blood* 96:9–23
- Lentz VM, Cancro MP, Nashold FE, Hayes CE (1996) Bcmd governs recruitment of new B cells into the stable peripheral B cell pool in the A/WySnJ mouse. *J Immunol* 157:598–606
- Lentz VM, Hayes CE, Cancro MP (1998) Bcmd decreases the life span of B-2 but not B-1 cells in A/WySnJ mice. *J Immunol* 160:3743–3747
- Li J, Wan Y, Ji Q, Fang Y, Wu Y (2013) The role of microRNAs in B-cell development and function. *Cell Mol Immunol* 10:107–112
- Li YS, Wasserman R, Hayakawa K, Hardy RR (1996) Identification of the earliest B lineage stage in mouse bone marrow. *Immunity* 5:527–535

- Loder F, Mutschler B, Ray RJ, Paige CJ, Sideras P, Torres R, Lamers MC, Carsetti R (1999) B cell development in the spleen takes place in discrete steps and is determined by the quality of B cell receptor-derived signals. *J Exp Med* 190:75–89
- Looney RJ, Anolik JH, Campbell D, Felgar RE, Young F, Arend LJ, Sloand JA, Rosenblatt J, Sanz I (2004) B cell depletion as a novel treatment for systemic lupus erythematosus: a phase I/II dose-escalation trial of rituximab. *Arthritis Rheum* 50:2580–2589
- Lu TT, Cyster JG (2002) Integrin-mediated long-term B cell retention in the splenic marginal zone. *Science* 297:409–412
- Luning Prak ET, Monestier M, Eisenberg RA (2011) B cell receptor editing in tolerance and autoimmunity. *Ann N Y Acad Sci* 1217:96–121
- Mackay F, Woodcock SA, Lawton P, Ambrose C, Baetscher M, Schneider P, Tschopp J, Browning JL (1999) Mice transgenic for BAFF develop lymphocytic disorders along with autoimmune manifestations. *J Exp Med* 190:1697–1710
- MacLennan IC (1994) Germinal centers. *Annu Rev Immunol* 12:117–139
- MacLennan IC, Gray D, Kumararatne DS, Bazin H (1982) The lymphocytes of splenic marginal zones: a distinct B-cell lineage. *Immunol Today* 3
- Madry C, Laabi Y, Callebaut I, Roussel J, Hatzoglou A, Le Coniat M, Mornon JP, Berger R, Tsapis A (1998) The characterization of murine BCMA gene defines it as a new member of the tumor necrosis factor receptor superfamily. *Int Immunol* 10:1693–1702
- Manz RA, Thiel A, Radbruch A (1997) Lifetime of plasma cells in the bone marrow. *Nature* 388:133–134
- Mariette X, Roux S, Zhang J, Bengoufa D, Lavie F, Zhou T, Kimberly R (2003) The level of BLyS (BAFF) correlates with the titre of autoantibodies in human Sjogren's syndrome. *Ann Rheum Dis* 62:168–171
- Martin F, Kearney JF (2002) Marginal-zone B cells. *Nat Rev Immunol* 2:323–335
- Martins G, Calame K (2008) Regulation and functions of Blimp-1 in T and B lymphocytes. *Annu Rev Immunol* 26:133–169
- Maruyama M, Lam KP, Rajewsky K (2000) Memory B-cell persistence is independent of persisting immunizing antigen. *Nature* 407:636–642
- Medvedovic J, Ebert A, Tagoh H, Busslinger M (2011) Pax5: a master regulator of B cell development and leukemogenesis. *Adv Immunol* 111:179–206
- Meffre E, Wardemann H (2008) B-cell tolerance checkpoints in health and autoimmunity. *Curr Opin Immunol* 20:632–638
- Melchers F (1997) Control of the sizes and contents of precursor B cell repertoires in bone marrow. *Ciba Found Symp* 204:172–182 (discussion 182–186)
- Melchers F, Strasser A, Bauer SR, Kudo A, Thalmann P, Rolink A (1989) Cellular stages and molecular steps of murine B-cell development. *Cold Spring Harb Symp Quant Biol* 54(Pt 1): 183–189
- Miller DJ, Hanson KD, Carman JA, Hayes CE (1992) A single autosomal gene defect severely limits IgG but not IgM responses in B lymphocyte-deficient A/WySnJ mice. *Eur J Immunol* 22:373–379
- Miller DJ, Hayes CE (1991) Phenotypic and genetic characterization of a unique B lymphocyte deficiency in strain A/WySnJ mice. *Eur J Immunol* 21:1123–1130
- Mohan C, Shi Y, Laman JD, Datta SK (1995) Interaction between CD40 and its ligand gp39 in the development of murine lupus nephritis. *J Immunol* 154:1470–1480
- Monroe JG (2006) ITAM-mediated tonic signalling through pre-BCR and BCR complexes. *Nat Rev Immunol* 6:283–294
- Montecino-Rodriguez E, Dorshkind K (2012) B-1 B cell development in the fetus and adult. *Immunity* 36:13–21
- Moore PA, Belvedere O, Orr A, Pieri K, Lafleur DW, Feng P, Soppet D, Charters M, Gentz R, Parmelee D, Li Y, Galperina O, Giri J, Roschke V, Nardelli B, Carrell J, Sosnovtseva S, Greenfield W, Ruben SM, Olsen HS, Fikes J, Hilbert DM (1999) BLyS: member of the tumor necrosis factor family and B lymphocyte stimulator. *Science* 285:260–263

- Muramatsu M, Kinoshita K, Fagarasan S, Yamada S, Shinkai Y, Honjo T (2000) Class switch recombination and hypermutation require activation-induced cytidine deaminase (AID), a potential RNA editing enzyme. *Cell* 102:553–563
- Namen AE, Lupton S, Hjerrild K, Wignall J, Mochizuki DY, Schmierer A, Mosley B, March CJ, Urdal D, Gillis S (1988) Stimulation of B-cell progenitors by cloned murine interleukin-7. *Nature* 333:571–573
- Navarra SV, Guzman RM, Gallacher AE, Hall S, Levy RA, Jimenez RE, Li EK, Thomas M, Kim HY, Leon MG, Tanasescu C, Nasonov E, Lan JL, Pineda L, Zhong ZJ, Freimuth W, Petri MA (2011) Efficacy and safety of belimumab in patients with active systemic lupus erythematosus: a randomised, placebo-controlled, phase 3 trial. *Lancet* 377:721–731
- Nemazee D, Weigert M (2000) Revising B cell receptors. *J Exp Med* 191:1813–1817
- Neubert K, Meister S, Moser K, Weisel F, Maseda D, Amann K, Wiethe C, Winkler TH, Kalden JR, Manz RA, Voll RE (2008) The proteasome inhibitor bortezomib depletes plasma cells and protects mice with lupus-like disease from nephritis. *Nat Med* 14:748–755
- Ng LG, Sutherland AP, Newton R, Qian F, Cachero TG, Scott ML, Thompson JS, Wheway J, Chtanova T, Groom J, Sutton IJ, Xin C, Tangye SG, Kalled SL, Mackay F, Mackay CR (2004) B cell-activating factor belonging to the TNF family (BAFF)-R is the principal BAFF receptor facilitating BAFF costimulation of circulating T and B cells. *J Immunol* 173:807–817
- Nieuwenhuis P, Opstelten D (1984) Functional anatomy of germinal centers. *Am J Anat* 170:421–435
- Noguchi M, Yi H, Rosenblatt HM, Filipovich AH, Adelstein S, Modi WS, McBride OW, Leonard WJ (1993) Interleukin-2 receptor gamma chain mutation results in X-linked severe combined immunodeficiency in humans. *Cell* 73:147–157
- Nossal GJ, Pike BL (1975) Evidence for the clonal abortion theory of B-lymphocyte tolerance. *J Exp Med* 141:904–917
- Nunez C, Nishimoto N, Gartland GL, Billips LG, Burrows PD, Kubagawa H, Cooper MD (1996) B cells are generated throughout life in humans. *J Immunol* 156:866–872
- Nutt SL, Kee BL (2007) The transcriptional regulation of B cell lineage commitment. *Immunity* 26:715–725
- Obeng EA, Carlson LM, Gutman DM, Harrington WJ Jr, Lee KP, Boise LH (2006) Proteasome inhibitors induce a terminal unfolded protein response in multiple myeloma cells. *Blood* 107:4907–4916
- Obukhanych TV, Nussenzweig MC (2006) T-independent type II immune responses generate memory B cells. *J Exp Med* 203:305–310
- Oettinger MA, Schatz DG, Gorka C, Baltimore D (1990) RAG-1 and RAG-2, adjacent genes that synergistically activate V(D)J recombination. *Science* 248:1517–1523
- Oliver AM, Martin F, Gartland GL, Carter RH, Kearney JF (1997) Marginal zone B cells exhibit unique activation, proliferative and immunoglobulin secretory responses. *Eur J Immunol* 27:2366–2374
- Oracki SA, Walker JA, Hibbs ML, Corcoran LM, Tarlinton DM (2010) Plasma cell development and survival. *Immunol Rev* 237:140–159
- Osmond DG, Rolink A, Melchers F (1998) Murine B lymphopoiesis: towards a unified model. *Immunol Today* 19:65–68
- Owen RD (1945) Immunogenetic consequences of vascular anastomoses between bovine twins. *Science* 102:400–401
- Palanichamy A, Barnard J, Zheng B, Owen T, Quach T, Wei C, Looney RJ, Sanz I, Anolik JH (2009) Novel human transitional B cell populations revealed by B cell depletion therapy. *J Immunol* 182:5982–5993
- Pavri R, Gazumyan A, Jankovic M, Di Virgilio M, Klein I, Ansarah-Sobrinho C, Resch W, Yamane A, Reina San-Martin B, Barreto V, Nieland TJ, Root DE, Casellas R, Nussenzweig MC (2010) Activation-induced cytidine deaminase targets DNA at sites of RNA polymerase II stalling by interaction with Spt5. *Cell* 143:122–133
- Pavri R, Nussenzweig MC (2011) AID targeting in antibody diversity. *Adv Immunol* 110:1–26

- Pennell CA (1995) Selection for S107-V11 gene expression by peritoneal B cells in adult mice. *J Immunol* 155:1264–1275
- Pennell CA, Mercolino TJ, Grdina TA, Arnold LW, Haughton G, Clarke SH (1989a) Biased immunoglobulin variable region gene expression by Ly-1 B cells due to clonal selection. *Eur J Immunol* 19:1289–1295
- Pennell CA, Sheehan KM, Brodeur PH, Clarke SH (1989b) Organization and expression of VH gene families preferentially expressed by Ly-1+ (CD5) B cells. *Eur J Immunol* 19:2115–2121
- Peron S, Pan-Hammarstrom Q, Imai K, Du L, Taubenheim N, Sanal O, Marodi L, Bergelin-Besancon A, Benkerrou M, de Villartay JP, Fischer A, Revy P, Durandy A (2007) A primary immunodeficiency characterized by defective immunoglobulin class switch recombination and impaired DNA repair. *J Exp Med* 204:1207–1216
- Pescovitz MD (2006) Rituximab, an anti-cd20 monoclonal antibody: history and mechanism of action. *Am J Transplant* 6:859–866
- Pillai S, Baltimore D (1987) Formation of disulphide-linked mu 2 omega 2 tetramers in pre-B cells by the 18K omega-immunoglobulin light chain. *Nature* 329:172–174
- Pillai S, Cariappa A (2009) The follicular versus marginal zone B lymphocyte cell fate decision. *Nat Rev Immunol* 9:767–777
- Pillai S, Cariappa A, Moran ST (2005) Marginal zone B cells. *Annu Rev Immunol* 23:161–196
- Pinna D, Corti D, Jarrossay D, Sallusto F, Lanzavecchia A (2009) Clonal dissection of the human memory B-cell repertoire following infection and vaccination. *Eur J Immunol* 39:1260–1270
- Pisitkun P, Deane JA, Difilippantonio MJ, Tarasenko T, Satterthwaite AB, Bolland S (2006) Autoreactive B cell responses to RNA-related antigens due to TLR7 gene duplication. *Science* 312:1669–1672
- Plotkin SA (2008) Vaccines: correlates of vaccine-induced immunity. *Clin Infect Dis* 47:401–409
- Preud'homme JL, Seligmann M (1972) Surface bound immunoglobulins as a cell marker in human lymphoproliferative diseases. *Blood* 40:777–794
- Prieyl JA, LeBien TW (1996) Interleukin 7 independent development of human B cells. *Proc Natl Acad Sci U S A* 93:10348–10353
- Puel A, Ziegler SF, Buckley RH, Leonard WJ (1998) Defective IL7R expression in T(–)B(+)NK(+) severe combined immunodeficiency. *Nat Genet* 20:394–397
- Reimold AM, Iwakoshi NN, Manis J, Vallabhajosyula P, Szomolanyi-Tsuda E, Gravalles EM, Friend D, Grusby MJ, Alt F, Glimcher LH (2001) Plasma cell differentiation requires the transcription factor XBP-1. *Nature* 412:300–307
- Rolink AG, Andersson J, Melchers F (1998) Characterization of immature B cells by a novel monoclonal antibody, by turnover and by mitogen reactivity. *Eur J Immunol* 28:3738–3748
- Roll P, Palanichamy A, Kneitz C, Dorner T, Tony HP (2006) Regeneration of B cell subsets after transient B cell depletion using anti-CD20 antibodies in rheumatoid arthritis. *Arthritis Rheum* 54:2377–2386
- Rothenberg EV, Pant R (2004) Origins of lymphocyte developmental programs: transcription factor evidence. *Semin Immunol* 16:227–238
- Sanz I, Yasothan U, Kirkpatrick P (2011) Belimumab. *Nat Rev Drug Discov* 10:335–336
- Schatz DG, Oettinger MA, Baltimore D (1989) The V(D)J recombination activating gene, RAG-1. *Cell* 59:1035–1048
- Schiemann B, Gommerman JL, Vora K, Cachero TG, Shulga-Morskaya S, Dobles M, Frew E, Scott ML (2001) An essential role for BAFF in the normal development of B cells through a BCMA-independent pathway. *Science* 293:2111–2114
- Schitteck B, Rajewsky K (1990) Maintenance of B-cell memory by long-lived cells generated from proliferating precursors. *Nature* 346:749–751
- Schmidlin H, Diehl SA, Blom B (2009) New insights into the regulation of human B-cell differentiation. *Trends Immunol* 30:277–285
- Scholz JL, Crowley JE, Tomayko MM, Steinel N, O'Neill PJ, Quinn WJ 3rd, Goenka R, Miller JP, Cho YH, Long V, Ward C, Migone TS, Shlomchik MJ, Cancro MP (2008) BLyS inhibition

- eliminates primary B cells but leaves natural and acquired humoral immunity intact. *Proc Natl Acad Sci U S A* 105:15517–15522
- Scholz JL, Luning Prak ET, Cancro M (2011) Targeting the BLyS family in autoimmunity: a tale of mouse and man. *Clinical Investigation* 1:951–967
- Seidl KJ, Wilshire JA, Mackenzie JD, Kantor AB, Herzenberg LA (1999) Predominant VH genes expressed in innate antibodies are associated with distinctive antigen-binding sites. *Proc Natl Acad Sci U S A* 96:2262–2267
- Shaffer AL, Lin KI, Kuo TC, Yu X, Hurt EM, Rosenwald A, Giltzane JM, Yang L, Zhao H, Calame K, Staudt LM (2002) Blimp-1 orchestrates plasma cell differentiation by extinguishing the mature B cell gene expression program. *Immunity* 17:51–62
- Shaffer AL, Yu X, He Y, Boldrick J, Chan EP, Staudt LM (2000) BCL-6 represses genes that function in lymphocyte differentiation, inflammation, and cell cycle control. *Immunity* 13:199–212
- Shlomchik M, Mascelli M, Shan H, Radic MZ, Pisetsky D, Marshak-Rothstein A, Weigert M (1990) Anti-DNA antibodies from autoimmune mice arise by clonal expansion and somatic mutation. *J Exp Med* 171:265–292
- Shlomchik MJ, Weisel F (2012) Germinal center selection and the development of memory B and plasma cells. *Immunol Rev* 247:52–63
- Sims GP, Ettinger R, Shiota Y, Yarboro CH, Illei GG, Lipsky PE (2005) Identification and characterization of circulating human transitional B cells. *Blood* 105:4390–4398
- Singh H, Pongubala JM, Medina KL (2007) Gene regulatory networks that orchestrate the development of B lymphocyte precursors. *Adv Exp Med Biol* 596:57–62
- Slifka MK, Antia R, Whitmire JK, Ahmed R (1998) Humoral immunity due to long-lived plasma cells. *Immunity* 8:363–372
- Srivastava B, Quinn WJ 3rd, Hazard K, Erikson J, Allman D (2005) Characterization of marginal zone B cell precursors. *J Exp Med* 202:1225–1234
- Stadanlick JE, Kaileh M, Karnell FG, Scholz JL, Miller JP, Quinn WJ 3rd, Brezski RJ, Trembl LS, Jordan KA, Monroe JG, Sen R, Cancro MP (2008) Tonic B cell antigen receptor signals supply an NF-kappaB substrate for prosurvival BLyS signaling. *Nat Immunol* 9:1379–1387
- Stoel M, Jiang HQ, van Diemen CC, Bun JC, Dammers PM, Thurnheer MC, Kroese FG, Cebra JJ, Bos NA (2005) Restricted IgA repertoire in both B-1 and B-2 cell-derived gut plasmablasts. *J Immunol* 174:1046–1054
- Stohl W, Metyas S, Tan SM, Cheema GS, Oamar B, Xu D, Roschke V, Wu Y, Baker KP, Hilbert DM (2003) B lymphocyte stimulator overexpression in patients with systemic lupus erythematosus: longitudinal observations. *Arthritis Rheum* 48:3475–3486
- Stohl W, Scholz JL, Cancro MP (2011) Targeting BLyS in rheumatic disease: the sometimes-bumpy road from bench to bedside. *Curr Opin Rheumatol* 23:305–310
- Suryani S, Fulcher DA, Santner-Nanan B, Nanan R, Wong M, Shaw PJ, Gibson J, Williams A, Tangye SG (2010) Differential expression of CD21 identifies developmentally and functionally distinct subsets of human transitional B cells. *Blood* 115:519–529
- Tangye SG, Bryant VL, Cuss AK, Good KL (2006) BAFF, APRIL and human B cell disorders. *Semin Immunol* 18:305–317
- Tarlinton DM (2008) Evolution in miniature: selection, survival and distribution of antigen reactive cells in the germinal centre. *Immunol Cell Biol* 86:133–138
- Thien M, Phan TG, Gardam S, Amesbury M, Basten A, Mackay F, Brink R (2004) Excess BAFF rescues self-reactive B cells from peripheral deletion and allows them to enter forbidden follicular and marginal zone niches. *Immunity* 20:785–798
- Thompson JS, Bixler SA, Qian F, Vora K, Scott ML, Cachero TG, Hession C, Schneider P, Sizing ID, Mullen C, Strauch K, Zafari M, Benjamin CD, Tschopp J, Browning JL, Ambrose C (2001) BAFF-R, a newly identified TNF receptor that specifically interacts with BAFF. *Science* 293:2108–2111
- Tiegs SL, Russell DM, Nemazee D (1993) Receptor editing in self-reactive bone marrow B cells. *J Exp Med* 177:1009–1020

- Tiller T, Tsuiji M, Yurasov S, Velinzon K, Nussenzweig MC, Wardemann H (2007) Autoreactivity in human IgG+ memory B cells. *Immunity* 26:205–213
- Tomayko MM, Steinel NC, Anderson SM, Shlomchik MJ (2010) Cutting edge: hierarchy of maturity of murine memory B cell subsets. *J Immunol* 185:7146–7150
- Tonegawa S (1983) Somatic generation of antibody diversity. *Nature* 302:575–581
- Treml LS, Carlesso G, Hoek KL, Stadanlick JE, Kambayashi T, Bram RJ, Cancro MP, Khan WN (2007) TLR stimulation modifies BLYS receptor expression in follicular and marginal zone B cells. *J Immunol* 178:7531–7539
- Victoria GD, Dominguez-Sola D, Holmes AB, Deroubaix S, Dalla-Favera R, Nussenzweig MC (2012) Identification of human germinal center light and dark zone cells and their relationship to human B-cell lymphomas. *Blood* 120:2240–2248
- Victoria GD, Nussenzweig MC (2012) Germinal centers. *Annu Rev Immunol* 30:429–457
- Vieira P, Rajewsky K (1990) Persistence of memory B cells in mice deprived of T cell help. *Int Immunol* 2:487–494
- Vincent FB, Saulep-Easton D, Figgett WA, Fairfax KA, Mackay F (2013) The BAFF/APRIL system: Emerging functions beyond B cell biology and autoimmunity. *Cytokine Growth Factor Rev* 24(3):203–215
- Vogler LB, Crist WM, Bockman DE, Pearl ER, Lawton AR, Cooper MD (1978) Pre-B-cell leukemia. A new phenotype of childhood lymphoblastic leukemia. *N Engl J Med* 298:872–878
- von Boehmer H, Melchers F (2010) Checkpoints in lymphocyte development and autoimmune disease. *Nat Immunol* 11:14–20
- von Bulow GU, Bram RJ (1997) NF-AT activation induced by a CAML-interacting member of the tumor necrosis factor receptor superfamily. *Science* 278:138–141
- Vugmeyster Y, Seshasayee D, Chang W, Storn A, Howell K, Sa S, Nelson T, Martin F, Grewal I, Gilkerson E, Wu B, Thompson J, Ehrenfels BN, Ren S, Song A, Gelzleichter TR, Danilenko DM (2006) A soluble BAFF antagonist, BR3-Fc, decreases peripheral blood B cells and lymphoid tissue marginal zone and follicular B cells in cynomolgus monkeys. *Am J Pathol* 168:476–489
- Wallace DJ, Stohl W, Furie RA, Lisse JR, McKay JD, Merrill JT, Petri MA, Ginzler EM, Chatham WW, McCune WJ, Fernandez V, Chevrier MR, Zhong ZJ, Freimuth WW (2009) A phase II, randomized, double-blind, placebo-controlled, dose-ranging study of belimumab in patients with active systemic lupus erythematosus. *Arthritis Rheum* 61:1168–1178
- Wardemann H, Nussenzweig MC (2007) B-cell self-tolerance in humans. *Adv Immunol* 95:83–110
- Wardemann H, Yurasov S, Schaefer A, Young JW, Meffre E, Nussenzweig MC (2003) Predominant autoantibody production by early human B cell precursors. *Science* 301:1374–1377
- Warnatz K, Salzer U, Rizzi M, Fischer B, Gutenberger S, Bohm J, Kienzler AK, Pan-Hammarstrom Q, Hammarstrom L, Rakhmanov M, Schlesier M, Grimbacher B, Peter HH, Eibel H (2009) B-cell activating factor receptor deficiency is associated with an adult-onset antibody deficiency syndrome in humans. *Proc Natl Acad Sci U S A* 106:13945–13950
- Warren LA, Rothenberg EV (2003) Regulatory coding of lymphoid lineage choice by hematopoietic transcription factors. *Curr Opin Immunol* 15:166–175
- Wong EB, Khan TN, Mohan C, Rahman ZS (2012) The lupus-prone NZM2410/NZW strain-derived Sle1b sublocus alters the germinal center checkpoint in female mice in a B cell-intrinsic manner. *J Immunol* 189:5667–5681
- Xiao C, Calado DP, Galler G, Thai TH, Patterson HC, Wang J, Rajewsky N, Bender TP, Rajewsky K (2007) MiR-150 controls B cell differentiation by targeting the transcription factor c-Myb. *Cell* 131:146–159
- Xiao C, Rajewsky K (2009) MicroRNA control in the immune system: basic principles. *Cell* 136:26–36
- Yan M, Wang H, Chan B, Roose-Girma M, Erickson S, Baker T, Tumas D, Grewal IS, Dixit VM (2001) Activation and accumulation of B cells in TACI-deficient mice. *Nat Immunol* 2:638–643

- Yan Y, Wang YH, Diamond B (2012) IL-6 contributes to an immune tolerance checkpoint in post germinal center B cells. *J Autoimmun* 38:1–9
- Yefenof E, Sanders VM, Uhr JW, Vitetta ES (1986) In vitro activation of murine antigen-specific memory B cells by a T-dependent antigen. *J Immunol* 137:85–90
- Yurasov S, Nussenzweig MC (2007) Regulation of autoreactive antibodies. *Curr Opin Rheumatol* 19:421–426
- Yurasov S, Wardemann H, Hammersen J, Tsuiji M, Meffre E, Pascual V, Nussenzweig MC (2005) Defective B cell tolerance checkpoints in systemic lupus erythematosus. *J Exp Med* 201: 703–711
- Zotos D, Tarlinton DM (2012) Determining germinal centre B cell fate. *Trends Immunol* 33: 281–288
- Zou YR, Diamond B (2013) Fate determination of mature autoreactive B cells. *Adv Immunol* 118:1–36

Drugs Targeting B-Cells in Autoimmune Diseases

Bosch, X.; Ramos-Casals, M.; Khamashta, M.A. (Eds.)

2014, XI, 292 p. 3 illus., 2 illus. in color.,

ISBN: 978-3-0348-0706-7