

MAINTENANCE OF SERUM ANTIBODY LEVELS

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■ **Abstract** In vertebrates, serum antibodies are an essential component of innate and adaptive immunity and immunological memory. They also can contribute significantly to immunopathology. Their composition is the result of tightly regulated differentiation of B lymphocytes into antibody-secreting plasma blasts and plasma cells. The survival of antibody-secreting cells determines their contribution to the immune response in which they were generated and to long-lasting immunity, as provided by stable serum antibody levels. Short-lived plasma blasts and/or plasma cells secrete antibodies for a reactive immune response. Short-lived plasma blasts can become long-lived plasma cells, probably by competition with preexisting plasma cells for occupation of a limited number of survival niches in the body, in a process not yet fully understood. Limitation of the number of long-lived plasma cells allows the immune system to maintain a stable humoral immunological memory over long periods, to react to new pathogenic challenges, and to adapt the humoral memory in response to these antigens.

INTRODUCTION

More than a century ago, Behring & Kitasato (1) discovered that a component of serum, later termed antibodies, can transfer specific immunity to other animals. Since then, antibodies have been extensively characterized in molecular detail. The genes encoding them and their exclusive use in B lymphocytes have revealed the most astounding mechanisms to generate more than a million different antibodies with different specificities and different functions (classes), to increase the affinity of antibodies by somatic hypermutation, and to ensure that each B lymphocyte expresses only antibodies of one specificity, by exclusion of alleles from expression (2). It has become clear that antibodies are involved in innate and adaptive immunity, contribute to immunopathology, and can be critically involved in the pathogenesis of autoimmune diseases. B lymphocytes use them in their membrane-bound form as antigen receptors, triggering their activation and

enabling them to present the antigen efficiently to T helper lymphocytes. Activation of B lymphocytes can result in their differentiation into antibody-secreting cells (ASCs), plasma blasts and plasma cells. Despite their relevance for the understanding of immunity, little is known about these cells, which have often been regarded as short-lived endstages of B cell differentiation, and of limited relevance. This view has been challenged recently. Here, we review the current concepts on the biology of ASCs with respect to their contribution to the maintenance of serum antibody levels, humoral immunity, and humoral memory.

Serum antibodies are derived from different types of ASCs, reflecting the dual role of B lymphocytes in both innate and adaptive immunity. ASCs of the B1 lineage express antibodies binding with low affinities to multiple antigens, often microbial structures shared by a variety of pathogens. These antibodies are usually of the IgM, IgA, or IgG3 subclass. Prenatal induction of antibody secretion by B1-derived ASCs, producing "natural antibodies," also contributes to this "innate" component of serum antibody levels, which probably is maintained throughout life (3, 4). The production of natural antibodies can be regarded as a first line of defense against pathogens, and it also might be involved in the regulation of the respective immune responses (5, 6). In response to antigen, ASCs also develop from B2 lymphocytes, in a specific humoral immune reaction that peaks at about 1 to 2 weeks after antigenic insult. Secondary encounter with antigen results in the secretion of antibodies of increased affinity to the antigen, an increased peak of specific serum antibody titer, and persistent levels of antibodies in the serum. Following vaccination or infection, persistent levels of specific antibodies are detectable in human serum for decades. They are protective, in that they neutralize or eliminate the pathogen and its toxic products upon reinfection (7, 8). In mice, too, humoral memory for specific pathogens is persistent (9). Owing to transfer of maternal antibodies via milk and placenta (6, 10), protective antibodies of adaptive immune responses of the mother are present already at birth, i.e., before the developing immune system has encountered the respective pathogens.

After the discovery of antibodies, another 60 years passed before the cells secreting the antibodies were identified by A. Fagraeus in rabbit spleen as "plasma cells," long known for their prominent cytoplasm and well-developed endoplasmatic reticulum (as reviewed in 11). In spleen and other secondary lymphoid organs, ASCs develop from B lymphocytes, either from B1 cells of the marginal zones, in immune responses against components of microbial cell membranes, or from follicular B2 cells, which can differentiate either into ASCs or into memory B cells. The development and biology of B memory cells is described in detail in this volume by McHeyzer-Williams (11a). Plasma cell differentiation is accompanied by a switch from expression of the membrane-bound form of the antibodies to expression of the secreted form, and by an enormous increase in production of antibody molecules per cell. Plasma cells can synthesize and secrete several thousand antibody molecules per second (12, 13). Thus, the antibody levels in serum and other body fluids can be maintained by a relatively small population of ASCs, which make up only about 0.1% to 1.0% of the cells of secondary lymphoid organs

and the bone marrow (14–16). In contrast, the half-life of antibody molecules in serum is less than 3 weeks (17, 18). Maintenance of specific serum antibody levels requires continuous secretion of antibodies and thus persistence of ASCs.

ANTIBODY ISOTYPES IN SERUM

Sera of immune competent donors mainly contain antibodies of the IgG, IgA, and IgM classes (19). IgD and IgE are present in serum at only low concentrations, together making up less than 1% of total serum immunoglobulin. Maternal and B1 cell–derived antibodies, generated by various mechanisms, as discussed below, provide high concentrations of immunoglobulins in serum at birth (Figure 1). When maternal antibodies decay, antibody levels provided by ASCs of the newborn rise slowly during infancy and childhood to concentrations which thereafter remain remarkably stable during adulthood (19), with only small variations until old age. Serum antibody levels of individuals older than 95 years can show an increase in IgA, IgG1, and IgG3 (20), leaving it unclear whether this is cause or consequence of reaching old age.

Serum levels vary considerably for antibodies of the different classes (19). Making up about 85% of total serum antibody levels in humans, antibodies of the IgG subclasses are most abundant. This is partly due to their rather long half-life. IgG can shuttle between serum and endothelium surfaces, where it is bound by FcRn, protecting it from degradation (21). IgA is estimated to have the highest rate of biosynthesis, with up to 66 mg/kg of body weight daily, compared with 34 mg of IgG and 7.9 mg of IgM (22, 23). In serum, however, monomeric IgA accounts for 7%–15% of the serum antibody. Most IgA is secreted as a dimer within mucosal fluids (24). Roughly 5% of serum antibody is IgM, mainly pentameric (25, 26).

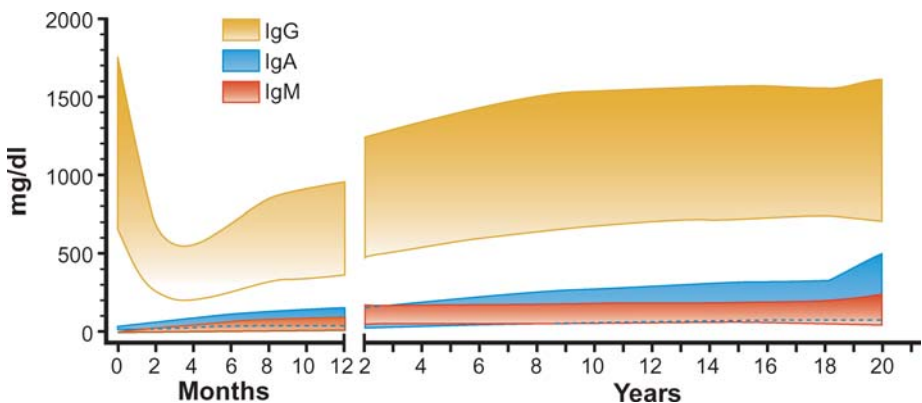


Figure 1 Antibody titers in serum. Levels of IgG, IgA, and IgM increase slowly until adulthood and remain stable thereafter (19).

Owing to its low rate of synthesis of 0.4 mg/kg per day and its high susceptibility to degradation (27), IgD is rare among serum antibodies, contributing only 0.3%. With an average concentration of less than 0.0003 mg/ml in nonatopic adults, the concentration of IgE is the lowest of all serum antibody classes, accounting for 0.02% of total serum antibody. This low level is due to the very low synthesis rate of 0.0016 mg/kg per day, as well as to the short half-life of IgE in serum of 2.5 days (28).

PRENATAL AND NEONATAL SERUM ANTIBODIES

In the serum of newborns, before they have contacted any pathogens, antibodies are already present. IgG levels in fetal serum are comparable to IgG levels of the mother (19). A fraction of these antibodies is produced by ASCs, which developed from B1 lymphocytes (29). The antibodies produced by these cells are often polyreactive and bind with low affinities to multiple antigens (30), including microbial surfaces, thus providing protection against many common environmental pathogens. However, because these “innate” antibodies do not bind with high affinities (30), their protective capacities are limited.

In primates, newborns also have “adaptive” antibodies, transferred to them from their mothers through the placenta. Owing to the structure of this organ in primates, maternal blood makes direct contact with the fetal trophoblast, allowing selective transfer of IgG to the fetus (31). All mammalian newborns are provided with maternal antibodies by transfer of immunoglobulins via milk (32). In humans and primates, the principle antibody class contained within the colostrum is IgA; in most domestic animals it is IgG. The low proteolytic activity in the gastrointestinal tract of newborns and colostrum trypsin inhibitors prevent the degradation of immunoglobulins through the first days of life (33).

For the transfer of antibodies both via milk and via the placenta, the major histocompatibility complex class I-related molecule FcRn (34) plays an important role. FcRn-cDNA and -protein have been isolated from human syncytiotrophoblast (35–37), and FcRn colocalizes with IgG in endosomes of syncytiotrophoblast cells (38). Endothelial cells pinocytose IgG and probably transfer it to the fetal circulation. Carnivores have an endotheliochorial placenta where the fetal chorionic epithelium is in contact with the endothelium of the maternal capillaries. In these species, only 5%–10% of the IgG in the mother's serum is passed to the serum of the offspring through the placenta. The syndesmochorial placenta of ruminants (chorionic epithelium in contact with uterine tissues) and epitheliochorial placenta of horses and pigs (chorionic epithelium in contact with intact uterine epithelium) do not allow the passage of antibodies. Newborns of these animals take up antibodies with colostrum only (39). In rodents as well, the transfer of IgG from milk is quantitatively much more important than that via the placenta (40, 41). Independent of the route of transfer, however, newborns are already equipped with maternal adaptive serum antibodies, representing the humoral memory of the mother, and their own innate serum antibodies, both at concentrations similar to those of adults.

PRODUCTION OF SERUM ANTIBODIES

Histologically, cells with prominent endoplasmic reticulum and large cytoplasm had been termed “plasma cells,” before researchers knew their function. In 1948, A. Fagraeus reported that the presence of “plasma cells” in rabbit spleen was strictly correlated to antibody production following immunization. In 1955, Coons and collaborators demonstrated, by immunofluorescence, the presence of antibodies inside plasma cells. In 1959, G. Nossal finally provided the evidence that these cells were indeed secreting the antibodies they expressed (reviewed in 11). Today, ASCs would be distinguished as “plasma blasts,” the early stages of differentiation from an activated B cell and still proliferating, and “plasma cells,” the endstage of differentiation and no longer proliferating. Plasma cells can be short-lived or long-lived, as discussed below.

SITES OF ANTIBODY SECRETION

Mucosal Immune Responses

After immunization via the gut-associated lymphoid tissue, ASCs are generated in intestinal and nonintestinal mucosal tissue (42). Most of the antibodies secreted here are of the IgA isotype. Most IgA dimerizes because the IgA-secreting cells also express the joining chain protein required for and mediating dimerization. Dimeric IgA is transcytosed by epithelial cells and transported to their extracorporeal surface, where it serves as a component of mucus and an important first line of defense against pathogens of the environment (43). The majority of ASCs induced by immunization with rotavirus, a typical intestinal pathogen, is found in Peyer's patches and intestinal lamina propria, whereas fewer ASCs are located in spleen and bone marrow (44).

A fraction of mucosal IgA plasma cells are descendants of B1 cells, induced to undergo class switch and plasma cell differentiation locally (45). Others are derived from B2 cells, activated with help from T cells in Peyer's patches (46). In response to activation, these ASCs leave the intestine via the draining mesenteric lymph nodes, begin to secrete antibodies while circulating through spleen, and finally relocate to the lamina propria of the gut (47).

Homing of activated B cells and ASCs to the various mucosal sites is a complex process, controlled by chemoattraction, adhesion receptors, and other signaling receptors. CCL28, the ligand of CCR10, is expressed in different mucosal sites and tissues (48). Almost all IgA-secreting cells migrate toward CCL28 (42, 49, 50). This attraction probably allows IgA-secreting cells to spread IgA-mediated protection all over the mucosa. Selective attraction of a fraction of IgA plasma cells to the small intestine is mediated by CCR9 (42). In the mucosa, expression of CCL25, the ligand of CCR9, is restricted to the crypt epithelium (51) and endothelial cells (52) of the small intestine. CCR9-deficient mice have reduced numbers of plasma cells in their small intestine and a low IgA response to oral antigens

(53). The homing of ASCs from mucosal immune responses to mucosal tissue is further mediated by their expression of mucosa-specific adhesion molecules. In contrast to ASCs induced by systemic immunization, those induced by mucosal immunization mainly express $\alpha 4\beta 7$ -integrin (54).

Systemic Immune Responses

Antigen entering the body via skin or blood induces an antibody response in secondary lymphoid tissues such as lymph nodes and spleen (55). Antibody-secreting cells appear after about three days, and are present for a few more days (56). These cells are a mixture of plasma blasts and plasma cells and are located in the vicinity of CD11c^{high} dendritic cells (DCs) in the extrafollicular foci of the spleen and medullary cord of lymph nodes. ASCs not associated with these CD11c^{high} DCs most likely undergo apoptosis (57).

In immune responses that depend on the help of T lymphocytes for the activation and differentiation of the B lymphocytes, ASCs can migrate from lymph nodes and spleen to the bone marrow (58–60). Here, antigen-specific plasma cells can be detected for many years after immunization (9, 61–63). Bone marrow plasma cells are selected for the production of antibodies with high affinity (64). Antibodies secreted by bone marrow plasma cells can be of higher affinity than those expressed by memory B cells binding to the same antigen (65).

ASCs translocate from secondary lymphoid tissue to bone marrow via the bloodstream and lymphatics. In sheep, 60 h after secondary immunization a sharp increase in numbers of lymphoblasts is detectable in the efferent lymph of lymph nodes draining the site of immunization (66). In human blood, the number of antigen-specific ASCs increases transiently after immunization, with a peak at 6 days after immunization (67). In guinea pig, an influx of mononuclear cells from blood into the bone marrow has been observed during the first 3 days after intravascular administration of antigen (68).

Only recently has the molecular basis for migration of ASCs from secondary lymphoid organs to bone marrow begun to emerge. ASCs express several adhesion molecules, which could be involved in homing and selective survival in particular tissues, although so far tissue-specificity has not been demonstrated for any of the adhesion molecules. Among these adhesion molecules are VLA-4, VLA-5, CD9, CD44, and CD138 (syndecan-1) (14, 69, 70). However, chemokine receptors CXCR3 and CXCR4 are involved in the regulation of migration of ASCs from systemic immune responses (60, 71). Unlike B cells, which are attracted by CXCL13, CCL19, and CCL21 (72), ASCs from murine spleen are attracted by CXCL12, the ligand for CXCR4 (73). CXCL12 (SDF-1 α) is expressed in the red pulp of spleen, the medullary cords of lymph nodes, and bone marrow stroma. However, only plasma blasts respond to CXCL12 by migration, whereas plasma cells do not (60). Plasma cells also express CXCR4, and they respond to CXCL12 by improved survival (74). Compared with wild-type cells, CXCR4-deficient ASCs are localized differently in spleen and are about threefold reduced in numbers in bone marrow (73). Thus, CXCR4 is probably one, but not the only, receptor of ASCs controlling

their homing into the bone marrow. IgA-secreting cells from mucosal lymphoid tissues can migrate toward CXCL12, too (42, 49), suggesting that these cells may have the choice of homing to mucosal tissue or bone marrow. Investigators have yet to elucidate whether persistent antibody responses of mucosal immune responses are maintained by ASCs of mucosal tissues or of bone marrow.

Another chemokine receptor expressed by ASCs is CXCR3 (60, 75). CXCL9, CXCL10, and CXCL11, the ligands for CXCR3, are expressed by cells of inflamed tissues and also by a subset of high endothelial venule cells, which surround the B cell follicles in the draining lymph nodes (76). ASCs can readily be detected in chronically inflamed tissue (77, 78). After immunization of NZB/W mice, antigen-specific ASCs migrate not only to the bone marrow, but in similar numbers also to the chronically inflamed kidneys (75, 77). Although the contribution of these plasma cells to the maintenance of serum antibody levels is less clear, they provide high local antibody concentrations in the inflamed tissue. In protective immune responses, this may help to combat the immunizing pathogen at the reactive site. In autoimmunity and allergy, local antibody secretion may contribute to pathogenesis of the inflamed organs.

ANTIBODY-SECRETING CELLS OF THE B1 LINEAGE

A fraction of serum antibodies is usually referred to as “natural” antibodies, mainly IgM, IgA, and IgG3 (3, 79, 80) (Table 1). In mice, these antibodies are secreted by cells of the B1 lineage, distinct from cells of the B2 lineage by their early appearance during fetal development, tissue distribution, phenotype, and capacity of self-renewal (81, 82). The original definition of “natural” antibody invoked the idea that such antibodies are present before the immune system sees the respective antigens. This is a controversial definition because of the antibodies’ polyreactivity, which makes it difficult to determine whether the cells secreting “natural” antibodies are generated in response to antigen, addressing the B cell’s antigen-receptor (surface antibody), or in response to “mitogenic” signals addressing the B cell’s pattern recognition receptors for pathogen-associated molecular patterns (PAMP) (e.g., receptors for lipopolysaccharides, demethylated bacterial DNA, etc.) (83).

TABLE 1 B1 and B2 cell contributions to protective antibody titers

	B1 cells	B2 cells
Stimulation by	Microbial antigens; autoantigens	Antigen (possible contribution of polyclonal activation by microbial agents)
T dependence	Mainly T-independent	T-independent and T-dependent
Dominant antibody classes	IgM; IgA	IgG
ASC	Short-lived	Short-lived and long-lived

In adult mice, cells of the B1 lineage account for only a few percent of all B lymphocytes, but they contribute at least 50% of the serum IgM. The features of natural antibodies and the B1 lineage cells that secrete them, have already been described and reviewed (see 29, 84, 85). In brief, at least two mechanisms are discussed that could drive B1 lymphocytes into differentiation into ASCs, stimulation by microbial antigens and/or mitogens of the gut flora and stimulation by autoantigens. Stimulation of B1 cells in mucosal tissue by microbial antigens of the gut enhances the production of natural antibody titers (83, 86, 87). The comparison of serum antibodies of preimmune mice living in normal versus germ-free environments suggests that cells secreting natural antibodies specific for bacterial antigens are generated in response to stimulation with bacteria (87a). Independent of T cell help, stimulation of B1 lymphocytes by antigens or "mitogens" from the gut flora leads to the production of IgA by B1 lineage ASCs at mucosal sites (88). These antibodies do not contribute significantly to serum antibody, but rather to mucosal antibody levels.

The activation of B1 lymphocytes by autoantigens and their differentiation into ASCs has been demonstrated recently for mice expressing a transgene for hen egg lysozyme (HEL) somatically, and a transgenic HEL-specific antibody in their B cells (89). Intracellular but not membrane-bound or secreted HEL induced the activation and proliferation of B1 cells in the peritoneal cavity. HEL-specific IgM-secreting cells were found in the red pulp cords of the spleen, but not in the bone marrow or lymph nodes. HEL-specific IgM was readily detectable in the sera in amounts matching the fraction of natural antibodies binding to intracellular self-antigens in wild-type mice. Such autoreactive antibodies are present in the sera of most individuals, regardless of whether they suffer from autoimmune disorders. Although definitive evidence is still lacking that the HEL-specific ASCs in their double transgenic mice belong to the B1 lineage, the experiment of Ferry and colleagues (89) shows that natural autoantibodies can be generated by intracellular autoantigens. This is in line with the presence of natural antibodies in human cord blood (86, 90) and in germ-free mice (87) and their polyreactive specificities, including autoantigens, e.g., phosphatidylcholine.

In view of the continuous activation of B1 cells by bacterial antigens, mitogens and autoantigens, and the constant levels of serum antibody levels attributed to this chronic stimulation, it seems that ASCs of the B1 lineage are short-lived and constantly replaced by newly formed plasma blasts and plasma cells, although the lifetime and terminal differentiation of these cells is still poorly characterized.

AQUIRED HUMORAL IMMUNITY

After infection or intentional immunization, antigen-specific antibodies of high affinity can be detected in blood for long periods, up to the lifetime of the individual. The levels of these serum antibodies are maintained even in the apparent absence of

the antigen. This "humoral" memory can effectively protect against reinfection (7). Both mucosal and systemic infections can induce long-lasting humoral immunity, but antibodies induced by systemic infection persist even longer and in human serum are present for several decades after their original induction (91).

The induction phase of an immune response against protein antigens lasts a few days, while large numbers of antigen-specific antibody-secreting plasma blasts are generated in secondary lymphoid tissues (56, 92). After migration to the bone marrow and terminal differentiation into plasma cells, these ASCs maintain the levels of specific serum antibodies, as discussed below. The induction phase can be extended in case of persisting antigen, and specific antibody levels in serum may be maintained by the long-lasting immune response itself, while it lasts (93). Extended formation of specific plasma blasts could result from the continuous activation of memory B cells by antigen, trapped on follicular DCs, or constantly generated *de novo* from proliferating pathogen, as long as it is not eliminated (93, 94). The relative contribution of these mechanisms to the maintenance of serum-antibody levels is not yet entirely clear. In the absence of chronic immune reactions, however, maintenance of humoral memory and most of the serum antibodies not secreted by B1 lineage cells is probably provided by long-lived plasma cells of the bone marrow (95, 96). Researchers have known for some time that bone marrow is the principal site of persistent antibody production in an established humoral memory response (58, 63).

LONG-LIVED PLASMA CELLS

In a secondary immune response of mice to ovalbumin, 60 days after immunization the formation of proliferating plasma blasts and plasma cells stops, as has been shown by labeling proliferating cells with Bromo-deoxy-uridine. Accordingly, in an immune response to phycoerythrin, the specific memory B cells largely cease to proliferate after several weeks (97).

In the immune response to ovalbumin, a population of long-lived, nonproliferating, antigen-specific plasma cells persists in bone marrow and maintains the levels of specific serum antibodies. These plasma cells can be transferred and will continue to secrete antibodies even in antigen-free recipients (92, 96). In this particular study (96), however, after the initial 6 weeks of analysis, the numbers of specific, long-lived plasma cells in the bone marrow did not change detectably until analysis was terminated, i.e., for another 14 weeks, indicating that in an established memory phase, long-lived plasma cells of the bone marrow have a half-life exceeding that of the individual. The half-life of long-lived bone marrow plasma cells formed in response to lymphocytic choriomeningitis virus has been estimated to be around 5 months (95). This may underestimate the true half-life because in those experiments the mice were treated with gamma irradiation or mitomycin C, probably affecting the survival of plasma cells. The survival of plasma cells in the bone marrow is not an intrinsic property of the plasma cell. Rather, plasma cell

survival seems to depend on the ability of the plasma cell to respond to a combination of signals provided by its environment (74, 98). Survival niches providing such signals are apparently scattered throughout the bone marrow (99). Their number seems to be limited because the frequencies of plasma cells in bone marrow are constant at about 0.5% throughout life and in different species (14, 15, 58). This constant frequency implies that newly generated plasma blasts, when migrating to the bone marrow, have to compete with established plasma cells for their survival niches. Competition for the limited number of plasma cell survival niches in the bone marrow offers an intriguing explanation for the regulation of serum antibody levels provided by plasma cells of the B2 lineage (75, 100). The concept would be even more attractive if survival niches for ASCs in bone marrow were shared or overlapped with niches for other lymphocytes (101) and hematopoietic stem cells (102, 103), generating additional levels of regulation.

Although the exact combination of signals making up a plasma cell survival niche in bone marrow is still not known, several signals have been identified that prolong survival of bone marrow plasma cells *ex vivo*. Stromal cells of bone marrow provide such signals (74, 98, 104) and protect plasma cells from apoptosis (105, 106). The signals identified so far include direct adhesive interactions between bone marrow reticular stromal cells and plasma cells, as well as the cytokines IL-6, SDF-1 α (CXCL12), and TNF- α . Although the interruption of CXCR4/CXCL12 signaling in CXCR4-deficient mice leads to a threefold reduction of bone marrow plasma cells (73), an effect hard to attribute to impaired migration of plasma blasts versus impaired survival of plasma cells, IL-6-deficient mice have normal numbers of bone marrow plasma cells, showing that *in vivo* this signal is redundant (74). VLA-4 may be an important molecular link between stromal cells and plasma cells (98).

Another survival signal for plasma cells might be Blys/BAFF. Blys-deficient mice have reduced levels of serum antibodies (107, 108). Plasma cells express B cell maturation antigen (BCMA), a receptor for Blys. Blys and APRIL, another ligand of BCMA, prolong survival of ASCs *in vitro*, in particular in the presence of IL-6 (109). Blocking Blys *in vivo* reduces plasma cell numbers in bone marrow by 65% and increases apoptosis of plasma blasts in spleen about fourfold. Thus, it remains to be demonstrated whether BCMA signaling is required for the establishment of plasma blasts in the bone marrow or for the continued survival of plasma cells there.

PLASMA CELL TURNOVER

For mice, researchers have shown that long-lived plasma cells can maintain specific serum antibody levels for the lifetime of the animals (95, 96). For humans, researchers still debate whether long-lived plasma cells can survive for a lifetime or whether they have a defined half-life, which requires their constant replacement, although at a low rate (Figure 2). Recently it has been proposed that, in the absence of antigen, polyclonal activation of memory B cells in response to cytokine signals

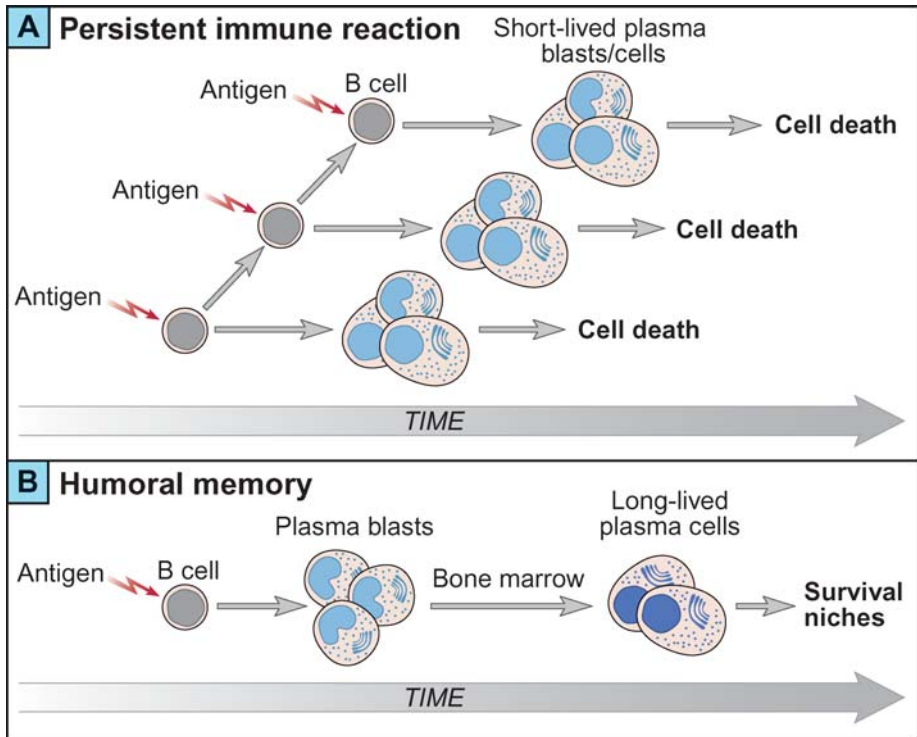


Figure 2 Mechanisms leading to maintenance of specific antibody titers following immunization. Prolonged antigenic stimulation can lead to the continuous activation of B cells and formation of short-lived plasma blasts and plasma cells during persistent immune reactions, e.g., during chronic infections. Long-lived plasma cells maintain specific humoral antibody memory in the absence of persistent antigenic stimulation. It has been proposed that chronic but low-level polyclonal activation of memory B cells generates plasma cells that substitute for old plasma cells within longer periods.

and pathogen-pattern signals in the course of immune reactions generates plasma blasts representing the repertoire of the memory B cells and replaces old plasma cells (110). Indeed, after intentional immunization with one antigen, ASCs specific for recall antigens appeared in the blood at very low frequencies. The actual contribution of this phenomenon to the maintenance of serum antibody levels remains to be demonstrated. An alternative explanation for the appearance of such cells is that they are long-lived plasma cells of the bone marrow, dislocated from their niches by the newly formed plasma blasts specific for the immunizing antigen (75, 100).

The concept of competition between newly generated plasma blasts and old plasma cells for bone marrow survival niches implies that the maintenance of

humoral memory for a specific antigen is regulated by the frequency and strength of subsequent immune responses, i.e., the memory for more recent antigens is established at the expense of the memory for "old" antigens not encountered anymore. Memory for old antigens could be refreshed when such antigens are encountered again and levels of specific antibodies in serum have dropped below protective concentrations. Activation of memory B cells representing the reactive memory would then generate plasma blasts again, which could migrate to the bone marrow and enhance the levels of specific antibodies in serum.

SERUM ANTIBODIES IN IMMUNOPATHOLOGY

The immune system has evolved to provide specific protection to pathogens and, as is evident from immunodeficiencies, is indispensable for the successful survival of vertebrates. If successful, however, immune reactions bear the risk of developing into chronic immunopathology and autoreactivity. Antibodies play a pivotal role in this pathology. Antibodies specific for self-antigens are a common feature of systemic and organ-specific autoimmune diseases (111, 112). Autoantibodies can contribute to the pathogenesis of autoimmune diseases either directly, by classic effector mechanisms, or through extensive formation of immune complexes with autoantigens, creating a deposition problem (5). In chronic autoimmune processes, the levels of serum antibodies increase considerably (hypergammaglobulinemia) as a consequence of chronic activation of autoreactive B cells and their differentiation into ASCs (113–115).

The role of autoantibodies in the pathogenesis of autoimmune diseases can be easily depicted for systemic lupus erythematosus (SLE). Antibodies binding to double-stranded DNA (dsDNA) characterize human and murine forms of SLE, and their levels in serum are an excellent correlate of disease activity. These autoantibodies can cause severe manifestations of disease, such as nephritis and vascular injury (116). During flares of SLE, serum levels of autoantibodies directed against dsDNA, nucleosomes, or SmD1 increase (116–118). In SLE patients with sustained disease activity despite rigorous immunosuppressive treatment, pathogenic anti-dsDNA autoantibodies persist in serum (119, 120). Also, in patients suffering from other autoimmune disorders, autoantibodies to particular autoantigens remain present in serum following immunosuppression (121–125). The persistence of autoantibodies in serum upon immunosuppression is a clear hint that such autoantibodies are secreted by long-lived plasma cells, refractory to immunosuppression and feedback signals from antigen-antibody complexes. The existence of long-lived, nonproliferating autoreactive plasma cells has been demonstrated directly in the murine NZB/W model of SLE (126). In these mice, both long-lived autoreactive plasma cells and short-lived, constantly *de novo* generated plasma blasts and plasma cells contribute to autoantibody levels, with a ratio of 1:3, as evidenced for dsDNA-specific ASCs. Accordingly, immunosuppression of autoimmune patients by selective depletion of B lymphocytes, but not plasma cells,

with anti-CD20 antibodies (Rituximab) does not lead to complete disappearance of autoantibodies (127–129). In sera of rheumatoid arthritis patients improving clinically upon Rituximab treatment, the levels of IgM-, IgA-, and IgG-rheumatoid factor, i.e., autoantibodies to immunoglobulin and autoantibodies to citrullinated peptides, dropped significantly (130). This drop was not observed or was less significant in patients not responding to the treatment with an improved clinical outcome. Interestingly, the serum levels of antibodies to microbial antigens, e.g., pneumococcal capsular polysaccharide, and the levels of tetanus-specific antibodies did not change significantly upon treatment (129, 130). The resistance of protective old serum antibodies to Rituximab demonstrates that these antibody levels are maintained by long-lived plasma cells, which do not express CD20 (70). Autoantibodies, in turn, can be secreted by either long-lived plasma cells or short-lived plasma blasts/plasma cells, which can be visualized in peripheral blood during flares of the disease (131, 132), the generation of which is interrupted by anti-CD20. Whether autoASCs can become long-lived plasma cells may depend on the timing and mode of their generation, as well as whether they belong to the B1 or B2 lineage.

CONCLUDING REMARKS

Blood is an organ of life and defense. Secreted antibodies of blood provide specific protection against pathogens the individual has encountered in the past. The regulation of antibody concentrations in the blood is apparently based on simple principles. Secreted antibodies decay with constant rates independent of their specificity. They are also synthesized at constant rates, by ASCs. The antibody levels in serum can thus be regulated by regulating the numbers of cells synthesizing them. Antibody-secreting plasma blasts are generated in high numbers during immune reactions, but their average lifespan is short. To maintain humoral memory, i.e., stable levels of specific antibodies in serum over long time periods in the apparent absence of antigen, ASCs can be recruited to a pool of long-lived plasma cells. Survival of the plasma cells is dependent on defined signals provided in a limited number of survival niches in the body, most prominently in the bone marrow. Thus, competition between newly generated plasma blasts and old plasma cells for occupancy of survival niches makes humoral memory flexible to add new specificities, allows its regeneration from memory B cells, and keeps the serum antibody levels constant. “Blood is a very special juice,” as the German poet J.W. Goethe has said.

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