Plasma Cells

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Plasma cells are terminally differentiated B lymphocytes that provide protective immunity through the continuous secretion of antibodies. Antibody-secreting cells develop in secondary lymphoid tissue following antigen stimulation and may enter a short-lived plasma cell population that reside primarily in the nonlymphoid area of the spleen or lymph nodes, or instead may migrate to the bone marrow where the majority enter a long-lived population of plasma cells.

Advanced article

Article Contents

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Introduction

The humoral branch of the immune system is critical for providing protective, circulating antibodies. In humans, antigen-specific antibody has been detected in the serum for decades following antigen encounter. The antibody pool is maintained by plasma cells, which secrete antibodies following antigen exposure.

Since soluble antibody is necessary for providing protective immunity to an individual or animal, it must be able to circulate readily throughout the body as a means of surveillance. Because plasma cells themselves are not known to migrate from tissue to tissue, it is important that plasma cells are situated in tissues such that antibody can easily enter the circulation. In the spleen and lymph nodes, plasma cells are detected among the reticular sinusoidal cells in the red pulp and medullary cords, respectively, which are rich in vasculature facilitating antibody circulation. The exact location of plasma cells in the bone marrow is not known, however, it is hypothesized that plasma cells interact with the reticular stromal cells surrounding the sinusoidal endothelial cells, again facilitating antibody secretion directly into the bloodstream. **See also**: Lymph nodes; Spleen

The plasma cell literature is often confusing as plasma cells are repeatedly misclassified. It is important when interpreting data that one is clear as to precisely what population of cells is being examined. Plasmablasts are precursor cells of short- and long-lived plasma cells and are generally described as a proliferating fraction of antibody-secreting cells, often found in the bloodstream emigrating to organs such as the bone marrow. Plasma cells are simply terminally differentiated noncycling antibody-secreting cells. Plasma cells are not normally found in the circulation, but rather remain residents in their organ of choice for life; any antibody-secreting cells in the blood en route to, for example the bone marrow, are plasmablasts. With this often ambiguous terminology clear, readers can more effectively evaluate scientific literature regarding plasma cells and their precursors.

Plasma cell morphology

Plasma cells are easily distinguished from mature B cells by their morphological appearance. Mature B cells exhibit a high nucleus to cytoplasm ratio, little rough endoplasmic reticulum (RER), and an uncondensed nucleus. In contrast, plasma cells exhibit a small, dense, eccentric nucleus, voluminous cytoplasm containing prominent amounts of RER and enlarged Golgi (**Figure 1**).

Development, Differentiation and Migration

Parallels between B-cell development and plasma cell support in the bone marrow

The majority of long-lived plasma cells are detected in the bone marrow. Notably, B cells, the precursors of plasma cells, also undergo much of their early development in the bone marrow. A critical component of B-cell development in the bone marrow is the reticular stromal cell. It provides

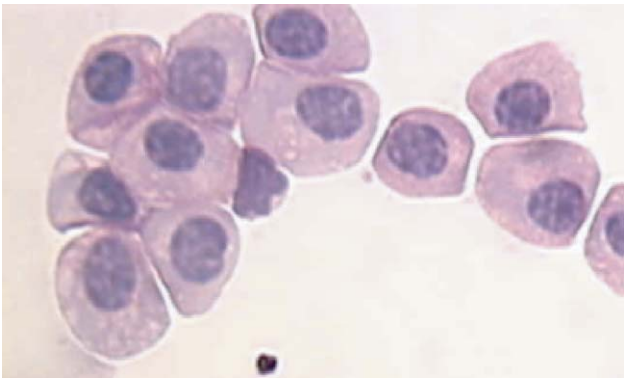

Figure 1 Characteristic plasma cell morphology shown of bone marrow plasma cells stained with haematoxylin and eosin.

both the contact and growth factors B cells need to progress through stages of maturation. Both plasma cells and developing B cells are likely to interact with stromal cells in the bone marrow. Therefore, an important understanding of the components required for B-cell development may elucidate similar requisites for plasma cell survival. Studies have begun to identify such parallels.

As B cells develop within the marrow, the location of the cells change such that maturation proceeds from the outer region of the bone marrow to the inner region where the central sinus is located (Osmond and Park, 1987). The early stages of B-cell development are dependent on interaction with stromal cells via vascular cell adhesion molecule-1 (VCAM-1), as well as the growth factors stromal cells produce, such as interleukin-7 (IL-7), stem cell factor (SCF) and C-X-C chemokine ligand-12,(CXCL12) among others (Dorshkind, 1990). Without these developmental cues, B cells cease maturation. Concurrent with maturation and migration within the marrow, the B-cell precursors lose dependency for stromal cell-derived cytokines as well as the need for stromal cell contact. To ensure emigration from the bone marrow does not occur prematurely, B-cell precursors are retained in the marrow by chemokines, specifically CXCL12 (Ma *et al*., 1999). Immature B cells, the final stage of development in the marrow and located closest to the central sinus, lose expression of CXCR4 (C-X-C chemokine receptor-4), the receptor for CXCL12, and are no longer retained in the marrow. They enter the central sinus and migrate to the spleen (**Figure 2**). **See also**: Bone marrow; Chemokines; Cytokines; Interleukins; Lymphocyte development

Many of the requirements needed for plasma cell survival in the bone marrow are parallel to those needed for B-cell development. First, plasmablasts and plasma cells appear to regain their dependency for stromal cell interaction and stromal cell-derived factors in the bone marrow. Similar to that observed of developing B cells, contact is necessary for plasma cell survival: plasma cell numbers wane quickly *in vitro* if stromal cells are absent (Minges Wols *et al*., 2002). Although the growth factors indispensable for B-cell development are dispensable for plasma cell survival, stromal cell-derived factors are still a necessity. Stromal cells produce IL-6, which is critical for plasma cell survival. Thus, while the players are different, the interactive dependencies of plasma cells and B-cell precursors in terms of stromal cells parallel each other in several aspects (**Figure 2**).

Just as chemokines are responsible for retaining B-cell precursors in the marrow, chemokines appear responsible for plasmablast entry into and plasma cell retention within the bone marrow. CXCL12 is not only produced by stromal cells in the marrow, but also by the sinusoidal endothelial cells in the marrow – the cells plasmablasts are likely to encounter upon exit from the peripheral blood (Cyster, 2003). Plasma cells express CXCR4 on their surface and exhibit migration towards CXCL12, suggesting plasma cells possess factors necessary to localize within the bone marrow (Cyster, 2003). Thus, the same chemokine that retains B-cell precursors in the marrow before they are developmentally ready to enter the periphery also plays a role in retaining terminally differentiated B cells (plasma cells) in the marrow later in the B-cell lifespan (**Figure 2**).

Plasma cell differentiation

Immature B cells leave the circulation and enter the spleen to complete development into a naive mature B cell. Depending on the events that follow, naive B cells may leave the tissue and reenter the bloodstream to continue scavenging for antigen. Alternatively, B cells may encounter antigen within the tissue during which time the progeny of activated B cells will differentiate into memory B cells, plasma cells or plasmablasts that will emigrate to the bone marrow. **See also**: B lymphocytes

Several *in vitro* studies have attempted to identify the key components of plasma cell generation. The addition of IL-3 and IL-10 to B-cell blasts co-cultured with bone marrow stromal cells stimulates immunoglobulin G (IgG) secretion and differentiation into nonproliferating plasma cells (Merville *et al*., 1995). An essential role for tumour necrosis factor-α (TNF-α) in the differentiation of antibody-secreting cells has also been demonstrated (Rodriguez *et al*., 1993). It appears that the cytokine is critical early in differentiation as the presence of TNF-α is required within the first 24 h of culture for subsequent Ig secretion. The necessity of IL-6 in generating antibody-secreting cells is enigmatic and appears to vary depending on the immunogen and the immunization protocol. Further complicating studies is the detection of plasma cells in IL-6 deficient mice suggesting that IL-6 is dispensable and/or that compensation mechanisms exist (Kopf *et al*., 1994). Taken together, these studies only begin to elucidate the plethora of soluble factors that may be necessary for the commitment to an antibody-secreting cell.

Molecular and cellular events of plasma cell differentiation

An intricate molecular programme governs plasma cell transition and commitment. A transcriptional repressor called B lymphocyte-induced maturation protein-1 (Blimp-1) is a master regulator of plasma cell differentiation (Calame *et al*., 2003). Cytokine activation of the B-cell lymphoma line (BCL-1) induces Blimp-1 expression, whereas removing cytokine help results in the halt of differentiation, decreased *Blimp-1* message, and decreased IgM secretion. Blimp-1 is detected in antibody-secreting cells following both T-dependent and -independent antigen challenge, in plasma cells in the bone marrow, as well as in a subset of cells in the germinal centre displaying a

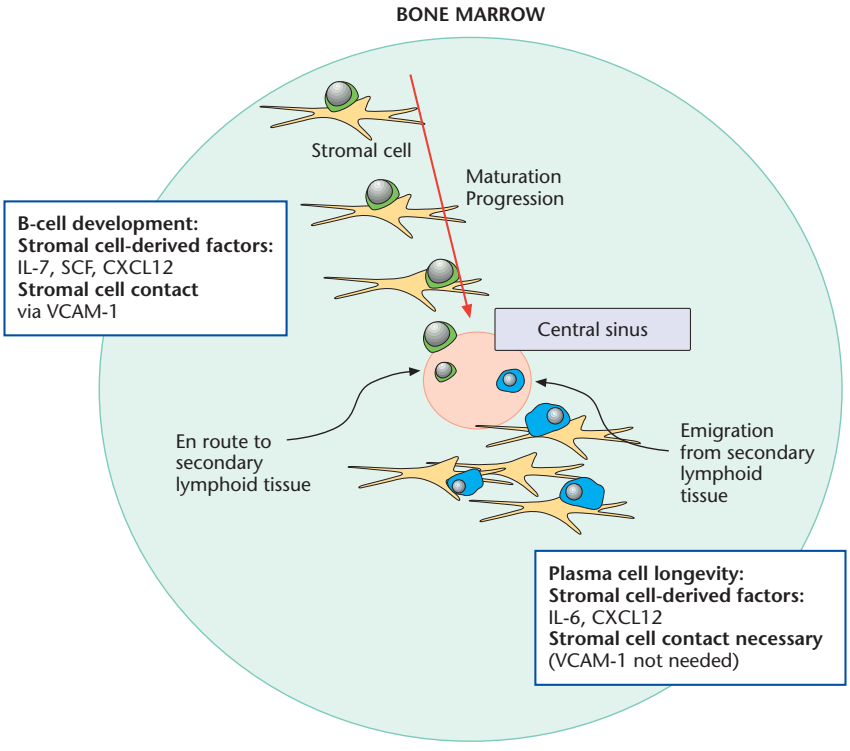

Figure 2 Maturation and migration of developing B cells. B cells develop from haematopoietic stem cells found in the periphery of the bone marrow. Differentiation progresses from the periphery of the marrow towards the central sinus. Development requires specific cytokines produced by and contact provided by stromal cells as indicated. Developing B cells are retained in the bone marrow (and restricted from early release) by chemokines produced primarily by stromal cells, namely CXCL12. Developing B cells express CXCR4, the receptor for CXCL12 on their surface. Once the immature B-cell stage is reached, the cells lose expression of CXCR4 and are released into the central sinus where they migrate to secondary lymphoid tissue. Plasmablasts entering the bone marrow from the secondary lymphoid tissue similarly find stromal cells to support their longevity. Again, stromal cells provide soluble factors necessary for retention and survival in the marrow, such as IL-6 and CXCL12. While contact is needed for plasma cell survival, the adhesion event is unclear; however, VCAM-1 is dispensable.

preplasma phenotype. However, Blimp-1 is not detected in memory B cells (**Figure 3**).

Terminally differentiated plasma cells are noncycling and thus phenotypically different from their predecessors. Expression of Blimp-1 protein results in concomitant repression of the B-cell-specific transcription and survival factors *BCL-6* and *Pax5,* the cell cycle protein *c-myc*, the antigen presentation gene *CIITA* (necessary for MHC Class-II protein synthesis), and the B-cell receptor (BCR) signalling molecules *Spi-B* and *Id3,* among many others (Calame *et al*., 2003). Conversely, Blimp-1 also indirectly upregulates *J-chain* messenger ribonucleic acid (mRNA) expression and Syndecan-1 protein synthesis (Calame *et al*., 2003) (**Figure 4**).

X-box-binding protein-1 (XBP-1) is also a transcription factor essential for plasma cell differentiation (Calame *et al*., 2003). XBP-1 is sufficient to induce the generation of antibody-secreting cells in the BCL-1 cell line. Furthermore, the absence of XBP-1 does not affect Blimp-1 expression suggesting that XBP-1 may promote plasma cell differentiation through an unique pathway or downstream of Blimp-1.

Plasma cells are committed to the synthesis and secretion of antibody. Therefore, their cell surface phenotype differs greatly from memory B cells. The various stages in plasma cell development can also be distinguished based on the expression of cell surface molecules. Because plasmablasts no longer need to bind or present antigen, the expression of the BCR (surface Ig) and MHC Class II are present at decreased levels on the cell surface and are ultimately absent on the surface of plasma cells (Calame *et al*., 2003). Another quintessential B-cell marker is surface expression of B220. The function of this protein is unknown, however its expression is intermediary on plasmablasts and is absent from the surface of plasma cells (**Figure 3**).

Plasma cells are best distinguished from other cell populations based on the membrane expression of Syndecan-1 (Cluster of differentiation, CD138), which is widely used as a means for isolation and detection (Minges Wols *et al*., 2002). Syndecan-1 has been shown to bind fibronectin, collagen and basic fibroblast growth factor; however, the consequence of Syndecan-1 ligation is unknown. In addition to Syndecan-1, plasma cells exhibit surface expression of the adhesion molecules CD44 and very late antigen-4

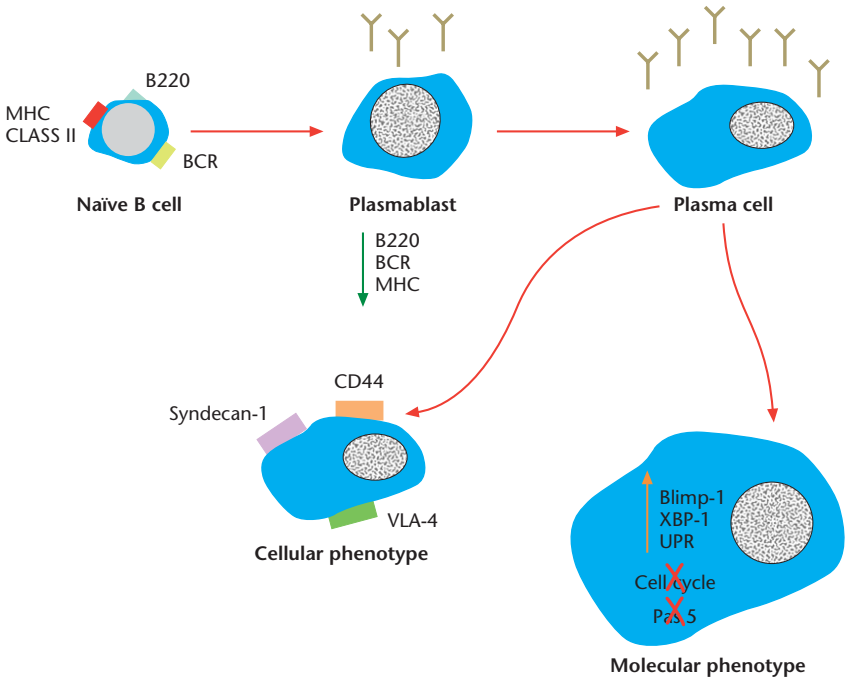

Figure 3 Schematic of plasma cell development and resultant phenotype. Naive B cells stimulated with antigen form antibody-secreting, proliferation-capable plasmablasts. Provided with the appropriate cues, plasmablasts develop into terminally differentiated plasma cells. Plasma cells express Syndecan-1 (CD138), CD44 and VLA-4 on their surface (among others); they downregulate expression of MHC Class II, B220 and the BCR complex. Further, plasma cells express Blimp-1 and XBP-1, which results in the inhibition of proliferation and of *Pax-5* expression, among others (see **Figure 4**).

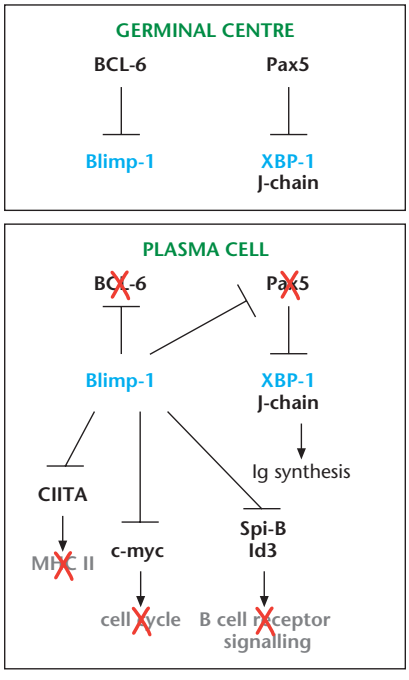

Figure 4 A simplified model of the regulatory cascades initiated during plasma cell differentiation. Targets activated by a particular factor are indicated by arrows; targets repressed are indicated by bars.

(VLA-4) (**Figure 3**) suggesting that there may be various means by which plasma cells can contact stromal elements in the marrow, keeping the antibody-secreting cells in close proximity to stromal cell-derived survival factors. Furthermore, an increase in overall size, as detected by forward light scatter by flow cytometry, is also observed.

The maturation progression of plasma cells

Human antibody-secreting cells isolated from various organs differ in cell surface phenotype. Cell surface molecule expression suggests a maturation progression from tonsil to blood to bone marrow (Medina *et al.*, 2002). For the most part, bone marrow plasma cells exhibit the following phenotypes (in comparison to tonsillar plasma cells): the gain of a Syndecan-1 plasma cell phenotype and the loss of a B-cell phenotype (CD19, CD20, CD22, human leukocyte antigen-DR (HLA-DR), Pax-5, among others), the gain of the survival factor Bcl-2 and the loss of the death receptor CD95, the gain of adhesion molecules such as VLA-4 and the gain of the chemokine receptor CXCR4 (Medina *et al.*, 2002). In addition, antibody-secreting cells from tonsil and blood secrete peak levels of antibody after 3 days of *in vitro* culture whereas bone marrow plasma secrete antibody in a linear fashion for 3 weeks (Brieva *et al.*, 1994). These

studies highlight the differences between tissue-tropic plasma cells and suggest that antibody-secreting cells proceed in maturation from secondary lymphoid tissue to blood to their final destination in the marrow.

Studies performed in mice also support a population of precursor plasma cells found in the marrow. These cells continue to express many B-cell surface markers (such as BCR, MHC Class II and B220, among others) and retain their proliferative capacity (O'Connor *et al*., 2003). These cells do not appear to be memory B cells as they continue to secrete antibody. Further, these cells express VLA-4, CD44 and IL-6 receptor, which likely facilitate their development into terminally differentiated plasma cells when provided with the correct cues in the bone marrow.

Short- and Long-lived Populations of Plasma Cells

Processed antigen is presented to T cells in the secondary lymphoid tissue. Once interactions between antigen-specific B and T cells occur, a tight synapse between the two cells is formed resulting in subsequent B-cell activation and proliferation. Two fates arise for the activated B cells at this juncture: (1) differentiation into short-lived plasma cells or (2) the formation of a germinal centre and generation of long-lived plasma cells. As a generalization, the preponderance of short-lived plasma cells is found in the secondary lymphoid tissue, while the majority of long-lived plasma cells are detected in the bone marrow. However, some long-lived plasma cells remain in secondary lymphoid tissue.

Generation of short-lived plasma cells

Short-lived plasma cells secrete nonmutated IgM or IgG, peak in numbers at days 8–10 postimmunization, and are found primarily at the B/T zone borders of the red pulp in the spleen or in the medullary cords of the lymph nodes. During a primary immune response, the low-affinity antibody secreted by these plasma cells is the early defence against the immunogen, while B cells possessing higher affinity antibodies are generated. Following secondary antigen challenge, the cellular response is several orders of magnitude greater than after a primary immunization. The short-lived plasma cell population contributes largely to the secondary antigen response. Studies suggest that the precursors of the short-lived plasma cells in a secondary response are the antigen-binding B cells located in the marginal zone of the spleen: B cells that have already undergone affinity maturation and selection in the germinal centre during the primary immune response (McHeyzer-Williams, 1997). Thus, the protective antibody from short-lived plasma cells has a greater affinity for the antigen after secondary immunization.

The germinal centre reaction and generation of long-lived plasma cells

A possible fate of B cells following B–T cell interaction in secondary lymphoid tissue is the formation of germinal centres. The details will not be described here, however, as a result of germinal centre formation, B cells displaying high-affinity BCR on their surface are selected to survive. Selected clones may either reenter the germinal centre for further rounds of diversification or contribute to the memory pool as either plasmablasts or memory B cells (McHeyzer-Williams, 1997). **See also**: Germinal centres

One cellular fate of a B cell that has completed the multiple selection checkpoints in a germinal centre is to differentiate into an antibody-secreting plasmablast and ultimately a plasma cell. Currently, it is believed that the plasma cells that do not undergo affinity maturation (non-germinal centre) are short-lived, while the B cells that enter the germinal centre and undergo affinity maturation are long-lived plasma cells (McHeyzer-Williams, 1997). Long-lived plasma cells secrete high-affinity antibody. This is beneficial for the host, because the high-affinity antibody then remains for extended periods of time. **See also**: Antibodies; Antibody classes

Evidence to support the extended longevity of bone marrow plasma cells

The bone marrow becomes a major site of antibody production. It has become apparent that the population of plasma cells that reside in the bone marrow is long-lived. This hypothesis is supported by a study in mice showing that antigen-specific bone marrow plasma cells survive >90 days postimmunization without cell division (Manz *et al*., 1997). This finding suggested that bone marrow plasma cells are not a dynamic, dividing population but instead are long-lived cells constitutively producing antibody. Antigen-specific bone marrow plasma cells are also detected for >300 days after viral infection (Slifka *et al*., 1998). In these same studies, plasma cells transferred to naive mice maintain serum antibody levels for >120 days posttransfer, supporting the idea that plasma cells elicited by a single antigen are long-lived and not a constantly replenishing population. Immunization of naive recipients with the original immunogen does not affect antibody secretion rates from the transferred plasma cells; nor is necessary to maintain plasma cell longevity (Manz *et al*., 1998). However, this view of plasma cell longevity is not universally accepted. Data obtained by Ochsenbein *et al*., (2000) suggest repeated antigen exposure is needed to maintain long-lasting antibody protection.

Effects of ageing

Data indicate that the frequency of plasma cells (regardless of isotype specificity) in the bone marrow is greater in older

Table 1 Changes in the numbers of bone marrow plasma cells with age[a]

Isotype	Age	
	2 months	25 months
IgM	0.1 ± 0.3[b]	16 ± 4
IgG1	0	0.6 ± 0.9
IgG2a	0	10.8 ± 5.1
IgG2b	0	6.8 ± 1.9
IgG3	0	11.8 ± 3.6
IgA	0	8.2 ± 1.3

[a]Bone marrow cells were isolated from mice at the indicated ages. Cells were cytocentrifuged on to slides, fixed, and stained with the indicated isotype-specific antibodies.
[b]The value shown indicates the average number of isotype positive cells/1000 cells counted ± s.d. The value "0" is indicative of detecting <1 isotype positive cell/1000 total bone marrow cells.

animals (25 months) as compared to younger animals (< 9 months) (**Table 1**) suggesting that plasma cells accumulate in the marrow of an aged animal. Freshly isolated bone marrow cells from aged mice secrete Ig (without stimulation) but bone marrow cells from young mice do not. Further, long-term bone marrow cultures that support B-lymphopoiesis initiated from aged mice contain detectable amounts of antibody in their supernatants 'six weeks' after initiation, suggesting that plasma cells are present in the cultures at setup and survive for the duration of the culture period. In contrast, neither plasma cells nor detectable amounts of antibody are found in cultures initiated from young mice. These findings together suggest the plasma cells are long-lived and may be maintained by cells in the bone marrow culture microenvironment. Whether the increased numbers of plasma cells detected in the bone marrow of aged mice is due to an accumulation of plasma cells over the lifetime of the animal or due to an aberrant microenvironment in the aged animal is unclear. **See also**: Ageing and the immune system

While human bone marrow has been found to be a major source of plasma cells and antibody as well, studies that parallel those described above have not been performed, likely due in part to the heterogeneic composition of humans. It is anticipated that similar increases in bone marrow plasma cell numbers occur as humans' age. Indeed multiple myeloma, a malignant plasma cell disorder, tends to afflict primarily older populations.

The role of the bone marrow microenvironment

One critical element of the bone marrow microenvironment is the bone marrow reticular stromal cell. The role of stromal cells in maintaining plasma cell longevity remains largely unexplored. However, recent studies have begun to unravel the interaction between plasma cells and bone marrow stromal cells. Data indicate that plasma cells cultured in the presence of stromal cells survived and continued to secrete antibody *in vitro* for at least 3 weeks, whereas antibody could only be detected for 7 days in the absence of stromal cells, suggesting stromal cell contact and/or secreted factors are necessary components for longevity (Minges Wols *et al*., 2002). Further, the addition of soluble IL-6 enhanced plasma cell survival in the absence of stromal cells, and plasma cells cultured with stromal cells lacking IL-6 resulted in a loss of antibody. The need for IL-6 by plasma cells to maintain longevity was further supported by the observation that IL-6 mRNA message is upregulated in stromal cells following plasma cell co-culture (Minges Wols *et al*., 2002). Further, stromal cells produce CXCL12, which appears to have a role not only in attracting plasmablasts into the marrow, but also in the retention of antibody-secreting cells. CXCL12 may also be necessary for maintaining plasma cell survival within microenvironmental niches (Cassese *et al*., 2003). Finally, VLA-4 must be engaged on plasma cells and may represent one of the mechanisms through which stromal cells and plasma cells interact. Although stromal cells express VCAM-1, one of the ligands for VLA-4, VCAM-1 is not necessary to maintain plasma cell survival. Taken together, the studies provide an initial glimpse of the basic elements necessary for maintaining an extended lifespan of plasma cells in the bone marrow (**Figure 5**). Exactly how IL-6, CXCL12 and VLA-4 interact, if at all, to support plasma cell longevity is presently unknown. **See also**: Immunological adhesion and homing molecules

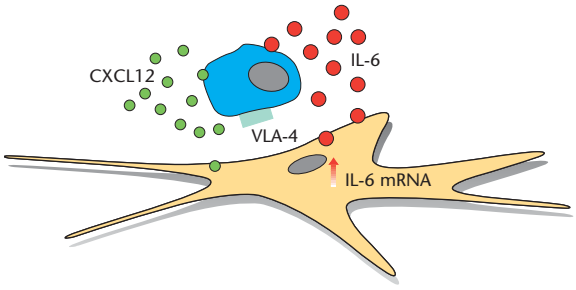

Figure 5 A model of the elements necessary for maintaining plasma cell survival. Plasma cells and stromal cells interact in the bone marrow via VLA-4 on the plasma cell and an unknown ligand on the stromal cell. Contact induces the expression of IL-6 mRNA and consequently IL-6 secretion, which is critical to maintain plasma cell longevity. Further, stromal cells secrete CXCL12, which is important for attracting plasmablasts to the marrow, for retention of plasma cells in the marrow, and possibly for maintaining plasma cell survival.

Antibody Secretion by Plasma Cells

The function of a plasma cell is clear: secrete antibody. In fact, the purpose of a nonsecreting plasma cell is such an

enigma, its rarely considered. Supporting its sole responsibility to secrete antibody, the ratio of secretory Ig heavy chain mRNA to membrane Ig heavy chain mRNA increases greatly in a plasma cell. Further, plasma cells lose expression of membrane Ig and BCR, ablating activation potential. Since the primary role of plasma cells is to secrete antibody, many requirements for plasma cell survival and for antibody secretion appear to be synonymous. Therefore, the survival elements required by murine plasma cells also maintain antibody secretion. Additionally, several studies assessing antibody secretion from human mononuclear cells have found a role for IL-6, TNF-α, IL-1β, VLA-4, and fibronectin in enhancing or maintaining antibody titres *in vitro* (Brieva *et al*., 1994).

Further, several studies have begun to elucidate molecular mechanisms regulating antibody secretion. Transgenic mice possessing a truncated form of Blimp-1 (known to block Blimp-1 functions) exhibit an increased number of IgM-secreting cells and elevated and sustained IgM levels (Calame *et al*., 2003). The increased numbers of antibody-secreting cells appear due to increased proliferation and prolonged survival, suggesting that Blimp-1 has a role in cell cycle arrest and lifespan. Blimp-1 also indirectly regulates 'J-chain' mRNA expression and thus Ig synthesis. Further, XBP-1 expression appears to regulate antibody secretion; it was demonstrated that mice with $XBP\text{-}1^{-/-}$ lymphocytes have extremely low levels of serum Ig, cannot control viral infection or respond properly to T-independent or QJ;T-dependent antigens, and show a general absence of Syndecan-1^{+} cells, despite having normal numbers of B cells and formation of germinal centres (Calame *et al*., 2003).

Cytokine Production by Plasma Cells

Most cytokine production by antibody-secreting cells has been studied in the malignant form of plasma cells: multiple myeloma cells. The literature on multiple myeloma cells is extensive and will not be reviewed here (although interested parties should review Jelinek, 1999 in the Further Reading). Unfortunately, little is known about cytokine production by plasma cells, likely because pure populations are difficult to obtain in adequate quantities to perform such experiments. Further, plasma cells are synthesizing large amounts of Ig and may not exert much energy in secreting cytokines readily available to them in the surrounding microenvironment. However, if plasma cells do secrete cytokines, a likely candidate would be IL-6, based on its necessity for survival and known autocrine production by myeloma cells. Studies found no IL-6 mRNA message in nonmalignant murine plasma cells, suggesting IL-6 is not produced by plasma cells themselves (Minges Wols *et al*., 2002). Thus, although IL-6 is a key element in maintaining plasma cell survival, nonmalignant plasma cells do not produce their own IL-6 but rather induce its production in cells of the surrounding microenvironment. Obviously, this is an area of plasma cell research still unexplored by researchers, and further knowledge is needed to fully appreciate the intricacies of a plasma cell.

See also: Tumours of immune system

References

Brieva JA, Roldan E, Rodriguez C and Navas G (1994) Human tonsil, blood and bone marrow *in vivo*-induced B cells capable of spontaneous and high-rate immunoglobulin secretion *in vitro*: differences in the requirements for factors and for adherent and bone marrow stromal cells, as well as distinctive adhesion molecule expression. *European Journal of Immunology* **24**: 362–366.

Calame KL, Lin K-I and Tunyaplin C (2003) Regulatory mechanisms that determine the development and function of plasma cells. *Annual Review of Immunology* **21**: 205–230.

Cassese G, Arce S, Hauser AE *et al*. (2003) Plasma cell survival is mediated by synergistic effects of cytokines and adhesion-dependent signals. *Journal of Immunology* **171**: 1684–1690.

Cyster JG (2003) Homing of antibody secreting cells. *Immunological Reviews* **194**: 48–60.

Dorshkind K (1990) Regulation of hemopoiesis by bone marrow stromal cells and their products. *Annual Review of Immunology* **8**: 111–137.

Kopf M, Baumann H, Freer G *et al*. (1994) Impaired immune and acute-phase responses in interleukin-6-deficient mice. *Nature* **368**: 339–342.

Ma Q, Jones D and Springer TA (1999) The chemokine receptor CXCR4 is required for the retention of B lineage and granulocytic precursors within the bone marrow microenvironment. *Immunity* **10**: 463–471.

Manz RA, Lohning M, Cassese G, Thiel A and Radbruch A (1998) Survival of long-lived plasma cells is independent of antigen. *International Immunology* **10**: 1703–1711.

Manz RA, Thiel A and Radbruch A (1997) Lifetime of plasma cells in the bone marrow [letter]. *Nature* **388**: 133–134.

McHeyzer-Williams MG (1997) Immune response decisions at the single cell level. *Seminars in Immunology* **9**: 219–227.

Medina F, Segundo C, Campos-Caro A, Gonzalez-Garcia I and Brieva JA (2002) The heterogeneity shown by human plasma cells from tonsil, blood, and bone marrow reveals graded stages of increasing maturity, but local profiles of adhesion molecule expression. *Blood* **99**: 2154–2161.

Merville P, Dechanet J, Grouard G, Durand I and Banchereau J (1995) T cell-induced B cell blasts differentiate into plasma cells when cultured on bone marrow stroma with IL-3 and IL-10. *International Immunology* **7**: 635–643.

Minges Wols HA, Underhill GH, Kansas GS and Witte PL (2002) The role of bone marrow-derived stromal cells in the maintenance of plasma cell longevity. *Journal of Immunology* **169**: 4213–4221.

Ochsenbein AF, Pinschewer DD, Sierro S *et al*. (2000) Protective long-term antibody memory by antigen-driven and T help-dependent differentiation of long-lived memory B cells to short-lived plasma cells independent of secondary lymphoid organs. *Proceedings of the National Academy of Sciences of the USA* **97**: 13263–13268.

O'Connor BP, Gleeson MW, Noelle RJ and Erickson LD (2003) The rise and fall of long-lived humoral immunity: terminal differentiation of plasma cells in health and disease. *Immunological Reviews* **194**: 61–76.

Osmond DG and Park YH (1987) B lymphocyte progenitors in mouse bone marrow. *International Reviews in Immunology* **2**: 241–261.

Rodriguez C, Roldan E, Navas G and Brieva JA (1993) Essential role of tumor necrosis factor-alpha in the differentiation of human tonsil *in vivo* induced B cells capable of spontaneous and high-rate immunoglobulin secretion. *European Journal of Immunology* **23**: 1160–1164.

Slifka MK, Antia R, Whitmire JK and Ahmed R (1998) Humoral immunity due to long-lived plasma cells. *Immunity* **8**: 363–372.

Further Reading

Gass JN, Gunn KE, Sriburi R and Brewer JW (2004) Stressed-out B cells? Plasma-cell differentiation and the unfolded protein response. *Trends in Immunology* **25**: 17–24.

Iwakoshi NN, Lee AH, Vallabhajosyula P *et al*. (2003) Plasma cell differentiation and the unfolded protein response intersect at the transcription factor XBP-1. *Nature Immunology* **4**: 321–329.

Jelinek DF (1999) Mechanisms of myeloma cell growth control. *Hematology/Oncology Clinics of North America* **13**: 1145–1157.

Reimold AM, Etkin A, Clauss I *et al*. (2000) An essential role in liver development for transcription factor XBP-1. *Genes and Development* **14**: 152–157.

Tew JG, DiLosa RM, Burton GF *et al*. (1992) Germinal centers and antibody production in bone marrow. *Immunological Reviews* **126**: 99–112.

Turner CA Jr, Mack DH and Davis MM (1994) Blimp-1, a novel zinc finger-containing protein that can drive the maturation of B lymphocytes into immunoglobulin-secreting cells. *Cell* **77**: 297–306.