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New insights into the mechanisms regulating plasma cell survival and longevity

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Plasma cells correspond to the last stage of B cell differentiation and are professional antibody-secreting cells. While most persist for only few days, some may survive for weeks to years in dedicated survival niches. The determination of plasma cell survival rate seems to rely both on intrinsic and extrinsic factors. Although often opposed, the deterministic and environmental models for plasma cell longevity are certainly overlapping. Understanding the contribution and the regulation of these different factors is paramount to develop better vaccines but also to target malignant plasma cells. Here, we review recent literature highlighting new findings pertaining to plasma cell survival rate, intrinsic regulation of plasma cell persistence and function, as well as the plasma cell/niche dialogue. Moreover, the now well-recognised heterogeneity observed among plasma cells is also discussed.

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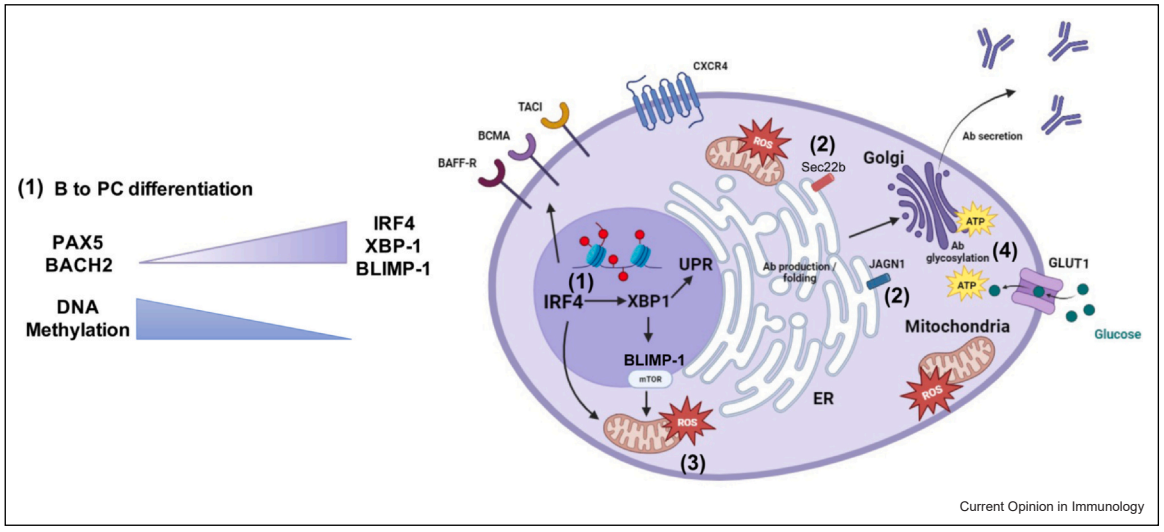
Intrinsic regulatory mechanisms supporting plasma cell maintenance and function

As professional secreting cells responsible for long-term protection against reinfection, plasma cells (PC) need to produce and secrete large amounts of antibodies while surviving for extended periods of time. Understanding how PC survival is regulated is paramount to develop better vaccines as the longevity of the vaccinal antibody response varies greatly from several years [1] to less than a year for influenza (flu), for example [2]. Several intrinsic cellular machineries are thus at play to perform such a deed. The initiation of PC differentiation necessitates a complete rewiring of the B cell transcriptional machinery with increasing evidence that the transcriptome of PC also contributes to their specific function and survival (Figure 1 (1)). As reviewed in depth in the recent literature [3], the mutually exclusive expression of the B cell transcription factors Paired box 5 (PAX5) and BTB domain and CNC homologue 2 (BACH2) and of the PC transcription factors, Interferon regulatory factor 4 (IRF4), X-box-binding protein 1 (XBP-1), and B lymphocyte-induced maturation protein 1 (BLIMP-1) are pivotal not only for PC generation but also for their function. Indeed, XBP-1 has long been known to regulate the unfolded protein response (UPR), thus supporting the secretory capacity of PC [4]. More recently, BLIMP-1 was shown to control the size and fitness of PC through the regulation of mammalian target of rapamycin complex 1 (mTORC1) [5], while IRF4 regulates the endoplasmic reticulum (ER) organisation and mitochondrial activity in these cells [6]. This PC transcriptional program is itself under the control of epigenetic regulations. Several studies have shown a progressive modification of the DNA methylation landscape during PC differentiation in correlation with their gene expression program [7–10]. Accordingly, PC display increased accessibility of the genes encoding IRF4, XBP-1, and BLIMP-1 and regulators of prosurvival proteins, while they display progressive decreased accessibility to genes encoding B cell lineage markers (*IRF8*, *H2-Aa*) [11]. Defective epigenetic mechanisms induce dysfunctional PC, with cells failing to perform oxidative phosphorylation (OXPHOS) and glucose metabolization and to express genes involved in the UPR pathway [12]. PC are also characterised by the expression of some receptors at their surface, such as Transmembrane activator and CAML interactor (TACI), B cell maturation antigen (BCMA), B cell-activating factor receptor (BAFF-R), and C-X-C motif chemokine receptor 4 (CXCR4), which are necessary for their survival, as we will see later.

As mentioned previously, the terminal differentiation of PC also involves important morphological changes to accommodate the ER expansion required for enhanced productive and secretory function. Antibody production

Figure 1



Intrinsic regulatory mechanisms supporting PC maintenance and function. PC development and survival rely on progressive transcriptomic and epigenetic rewiring (1). In parallel, ER expansion mediated by Jagn1 and Sec22b is pivotal for PC survival and for antibody production, folding, and secretion (2). Sec22b is also necessary for mitochondrial fitness, probably through the control of ER/mitochondria contact sites. Together with the PC-specific transcriptional profile, these changes lead to the reprogramming of PC metabolism (3). Finally, the PC-specific metabolic activity is critical for proper antibody glycosylation in the Golgi apparatus (4). Figure generated with BioRender.

was recently shown to rely on biased codon usage [13]. Moreover, in the last two years, several proteins have been shown to regulate the ER in PC (Figure 1 (2)). This is the case of Jagunal1, which is a transmembrane protein involved in the conformation of the ER [14]. Inactivation of *Jagn1* is responsible for an altered ER structure associated with decreased antibody production and secretion by PC. Moreover, the Soluble N-ethylmaleimide-sensitive factor attachment protein receptor (SNARE) Sec22b is pivotal for controlling the UPR, the ER structure, as well as mitochondrial morphology and function [15]. A defect in Sec22b leads to a dilated ER network, reduced ER/mitochondria membrane contact sites, and hyperfused mitochondria, leading to a lack of fitness and dramatic loss of PC. Accordingly, sec22b deficiency in the B lineage translates into a severely reduced humoral immune response after both vaccination and infection. How the expression of these ER and mitochondrial regulators is maintained during PC maturation and long-term survival to support antibody production is still to be determined.

The transition between B cells and PC is also associated with a profound metabolic rewiring (Figure 1 (3)). Naïve B cells are metabolically quiescent with low mitochondrial mass and Reactive oxygen species (ROS) levels. Their differentiation thus requires enhanced energy production to account for the proliferation phase necessary before differentiation into PC. Moreover, PC require high levels of ATP for antibody synthesis and secretion, and accordingly, they have an increased mitochondrial mass and aerobic metabolic activity compared to B cells [16]. Further metabolic changes were also reported as PC matured with splenic short-lived PC and bone marrow (BM) PC (BM-PC) relying on specific metabolic pathways. BM PC seem to use glucose uptake via GLUT1 to generate pyruvate to glycosylate antibodies (Figure 1 (4)). Moreover, they have higher maximal aerobic metabolism compared to splenic PC, which also display low levels of glucose uptake [17,18]. Interestingly, full metabolic activity of PC seems to be under the control of the Blimp-1 transcriptional program since mice lacking Blimp-1 have a defect in OXPHOS upregulation [16]. How these metabolic modulations are coordinated with PC morphological changes remains to be fully established, but considering the close relationship between the ER and mitochondria [15,19], some cross-regulations might be expected.

The last two years have also seen a plethora of papers describing PC subsets thanks to single-cell RNA sequencing (scRNA-seq) and fate-mapping mouse models. These different studies highlight that PC heterogeneity is multifactorial, being linked to their maturation state, ancestral antigenic experience, tissue of residence, and isotype [20–22]. Indeed, these datasets have re-enforced the notion that PC maturation and longevity are associated with transcriptional and metabolic changes [18]. Moreover, most scRNA-seq datasets have confirmed that PC expressing distinct isotypes have different transcriptional profiles [7,20,23–26]. This striking observation may be due to the B cell of origin and its activation history [20,24,25], specific

transcriptional factor requirements [6], and/or the maintained surface expression of the IgA and IgM B cell receptor (BCR) at the surface of PC. While it is difficult to untangle causes, it is interesting to note that IgM-positive long-lived mature PC with few to no somatic hypermutation and expressing public clonotypes were identified in the BM in mouse and human, supporting an extrafollicular origin for these cells [20,24]. Moreover, both pre- and post-germinal centre PC were observed in the long-lived PC (LL-PC) compartment questioning the initial idea that all LL-PC were generated within the germinal centre [27,28]. Additionally, three recent papers reported using germinal centre fate-mapping that germinal centre–derived PC and germinal centre B cell repertoires were largely convergent [29–31]. Focusing on flu-specific PC, Sprumont et al. argue that PC can emerge from different maturation stages during the germinal centre reaction and are not specifically selected from the high-affinity clones [29]. In parallel, El Tanbouly et al. reported identical findings during the early stage of the germinal centre but propose that over time, PC are less diverse than germinal centre B cells, thus leading to an apparent increase in their affinity at the population level [30]. The differences observed between these two studies might be explained by the methodologies used, with one focusing on antigen-specific cells and one analysing all cells irrelevant of their specificity. Altogether, these studies suggest that antigen affinity might not be the main driving force for the selection of PC within the germinal centre. However, they do not address the persistence of these germinal centre–derived PC, and it is thus still possible that PC with the highest affinity may have an intrinsic advantage in terms of longevity in dedicated niches, as suggested by previous works [32,33]. In addition, these studies indicate that germinal centre–derived PC are not the only ones able to persist in the long term and that the activation history of the B cell of origin (i.e. Germinal centre vs extrafollicular) might translate into specific subsets of PC.

Finally, key outputs of the recently published fate-mapping approaches were the re-evaluation of PC lifespan, generation, and turnover rates at the single-cell resolution level. Different models led to similar findings and reported an average half-life of 2–3 weeks with a constant intrinsic turnover of PC and only a few cells able to persist for very long periods of time [21,28,34]. Again, half-life seems to depend not only on the tissue of residence, with BM PC displaying a longer half-life than splenic ones, but also on the isotype with IgM PC in a study and IgA PC in another, having the longest averaged half-life [22,28].

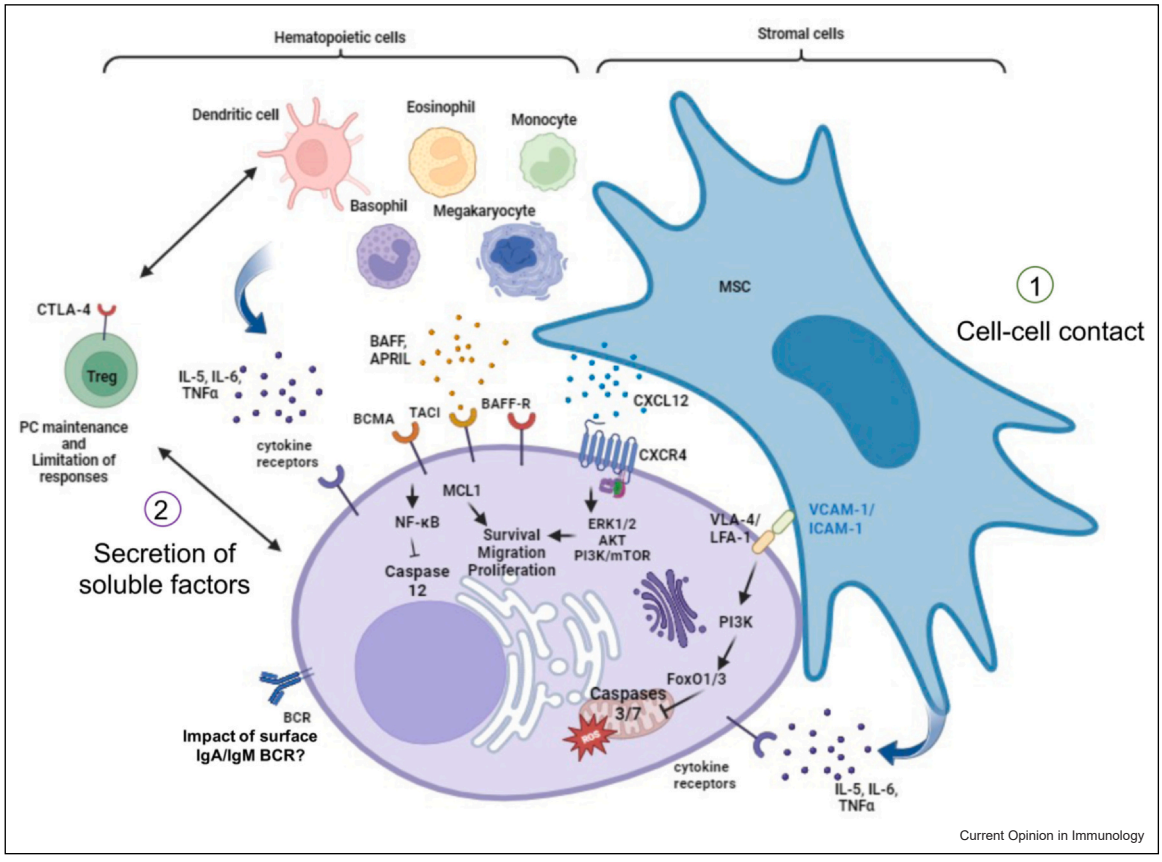
While intrinsic transcriptional and metabolic factors as well as changes at the organelle level are key to establish the PC pool and may depend on the type of stimulation the B cell has received, several recent works have also pushed forward our understanding of the environment-derived extrinsic factors supporting PC maturation and longevity.

Critical extrinsic factors for plasma cell maintenance

The current dogma is that newly generated PC can migrate into specialised niches in which they terminate their maturation, become quiescent, and persist for long periods of time thanks to factors provided by a dedicated survival niche [35]. Tissues that have been described as possibly containing niches have in common the provision of secreted factors and adhesion molecules promoting PC longevity, as well as the expression of chemokines to attract them. They are lymphoid tissues such as the BM, the spleen, the thymus, or the Peyer patches, as well as nonlymphoid tissues such as the salivary and mammary glands [22]. The BM constitutes the most prominent sanctuary site for PC [36]. The prevailing model is that PC persist in a multicomponent niche composed of Cxcl12-expressing stromal cells [37,38] acting as docking sites and of hematopoietic cells providing survival factors. Among hematopoietic cells, granulocytes (especially basophils and eosinophils) [39,40], monocytes [41], dendritic cells [42], and megakaryocytes [43] were proposed to promote PC survival within the BM. T cells, especially regulatory T cells, were also reported to limit PC survival via Cytotoxic T-lymphocyte-associated protein 4 (CTLA-4). Although the mechanisms at play are still unclear, cell–cell contacts may be involved, as well as the secretion of soluble factors affecting both PC and dendritic cells [44] (Figure 2).

Over the last few years, important findings have been made regarding which PC can reach these survival niches, how they mature once in the BM, and which cells and factors contribute to their survival. As mentioned previously, it was initially thought based on somatic hypermutation analyses that LL-PC were generated from the germinal centre [45]. However, this view was first challenged by the identification of BM LL-PC raised from T-independent immunisation [46] and more recently by the tracking of fate-mapped PC and scRNA-seq analyses supporting that high affinity may not be a strict prerequisite for BM PC longevity [20,21]. Considering the turnover rate reported for BM PC by several groups [28,34,47], while most BM PC may receive signals from their environment supporting their survival for a couple of weeks, only a few may access survival niches supporting very long-term persistence. Moreover, the establishment of new LL-PC within the BM may not rely on competition with pre-existing ones as initially proposed. Supporting this, Robinson et al. reported that PC turnover rate was not affected by a block in PC generation nor by a large increase in PC number [34]. In parallel, Koike et al. argued that as the number of LL-PC progressively increases with age, competition for survival niches might not be a key selective force within the BM. Further work will be required to fully understand how PC fate is determined in the BM ecosystem.

Figure 2



Critical extrinsic factors for plasma cell maintenance. PC survival is supported by extrinsic factors produced by stromal and hematopoietic cells of the environment through (1) cell–cell contacts, which allow the activation of pathways promoting PC survival and (2) secretion of factors that attract PC in the niches and contribute to their maintenance. The nature of the stromal component of the PC niche is still not fully established, although LepR+ mesenchymal cells are likely to be an important partner for PC through the production of Cxcl12 and the expression of several integrin ligands and soluble factors. Several hematopoietic cell types were reported to secrete soluble factors in particular BAFF and APRIL that will bind to BCMA, TACI, and BAFF-R expressed at the surface of PC. More recently, Tregs were proposed to limit PC maintenance through direct and indirect CTLA-4–dependent regulation. Whether surface IgA/M BCR expression contributes to PC long-term survival is unclear. Figure generated with BioRender.

Moreover, whether these findings also apply to humans that are constantly exposed to pathogens remains to be determined. While we cannot totally exclude that LL-PC niche occupancy is a random process, some molecular mechanisms are likely at play. For example, a gain of function of the chemokine receptor Cxcr4 was shown to promote extrafollicular PC maturation and long-term persistence within BM [46], suggesting that the Cxcl12–Cxcr4 axis by strengthening interactions between stromal cells and PC might contribute to the determination of which PC persist on the long-term in this tissue.

Once in the BM, PC are thought to terminate their differentiation. The identification of shared clones between newly generated and 'old' PC in humans [24] and the follow-up of time-stamped PC in mouse models [28,34] confirmed that, indeed, PC progressively mature as they reach the BM. Early PC seem to be characterised by high expression of B220, major histocompatibility complex II (MHC-II), and Slam family member 6 (Slamf6), while 'old' PC lack these markers [24,28,34]. Positive markers for fully differentiated LL-PC were also identified and include Epithelial cell adhesion molecule (EpCAM) for IgM+ and IgG+ PC and Ly6a for IgA+ PC [20,26]. Of note, all these markers seem to delineate a continuum of maturation associated with longevity but might not be absolute readouts for the age of the PC. Additional work is required to fully understand which PC are destined to become 'persister' and what are the mechanisms, intrinsic or extrinsic, at play. Moreover, while BM PC were initially described as mostly sessile cells [48,49], this view was challenged recently, and PC were proposed to be a rather motile population capable of leaving the BM to recirculate in the bloodstream [47]. These two opposite views might be reconciled by the observation that newly generated BM PC were indeed motile, while older ones were mainly sessile [28].

Within the niche, cell–cell contacts mediated by integrins and chemokine receptors between PC and stromal cells are essential for the localisation and the retention of PC in the BM. On top of the Cxcl12–Cxcr4 axis, Very late antigen-4 (VLA-4) and Lymphocyte function associated antigen-1 (LFA-1), as well as their respective ligands Vascular cell adhesion protein-1 (VCAM-1) and Intercellular adhesion molecule-1 (ICAM-1), were shown to have an antiapoptotic effect through the phosphatidylinositol 3-kinase (PI3K) pathway that inhibits the FoxO1/3 pathway and activation of caspases 3 and 7 [50]. In addition, a recent transinteractome analysis reported that among stromal cells, leptin receptor–positive mesenchymal stromal cells (MSC) were the most likely partners for PC based on the number and the type of identified interactions. Moreover, this study highlighted that IgG+ PC may form more varied interactions with the BM stromal cells than IgA+ PC, suggesting that some subsets of PC may rely on distinct interacting partners and might be differently retained within the BM niches [26] (Figure 2).

Hematopoietic cells contribute to the PC niche through the production of prosurvival factors, including interleukin (IL-) 5, IL-6, members of the Tumor necrosis factor (TNF) family (TNFα, BAFF and APRIL), and signals through the CD44 and CD28 axes [51]. While BAFF was shown to support PC survival at least *ex vivo* and in the spleen in a B cell depletion context [52,53], APRIL was proposed as key for the extrinsic regulation of PC maintenance in the BM. Indeed, APRIL supports the maturation of immature PC into LL-PC and ensures their survival in the BM by activating Extracellula signal-regulated kinase (ERK), p38, c-Jun N-terminal kinase (JNK), and the classical Nuclear factor-κ B (NF-κB) pathway [54]. The latter leads to the inhibition of caspase 12 in the ER, which inhibits PC apoptosis [50] (Figure 2). A recent work also showed that BM PC express the purinergic ion channel P2RX4 that senses extracellular ATP released by their environment and is required for their persistence [55]. Studies using co-culture experiments confirm that intrinsic regulation of the metabolism and transcriptome is also needed, as well as the natural specific setting of hypoxia in the BM with an O_2 tension that is inferior to 10 mmHg [56]. Hypoxia also promotes the differentiation of B cells into PC by increasing the expression of genes involved in metabolism [57]. However, how hypoxia regulates the local persistence of PC within the BM niches is not clear.

Interestingly, malignant PC in the context of multiple myeloma (MM) were shown to hijack BM niches to promote tumour growth. This incurable haematologic disorder is characterised by the abnormal accumulation of malignant over-proliferative PC associated with altered BM microenvironment composition leading to lytic bone lesions [58]. MM cells rely on the CXCR4/CXCL12 axis and on the integrin VLA4 for their homing to the BM and their interaction with mesenchymal stem/stromal cells, conferring cell adhesion–mediated drug resistance. Moreover, MM cell survival and proliferation are also dependent on IL6, BAFF, and APRIL, like their normal counterpart. MM cells can also shape their environment to promote their survival and escape the immune system. For example, they were shown to alter stromal cell transcriptome [59], cytokine secretion (IL-6, IL-10) [60] and function, leading to impaired osteogenesis and T cell inhibition [59]. MM cells also 'educate' immune cells with a direct impact on myeloid cells by promoting M2 macrophage polarisation and osteoclast differentiation, thus contributing to bone lesions. These pathological niches were reviewed in depth recently [61,62].

Altogether, these findings suggest that upon their arrival within the BM, PC can still be motile with an intrinsically determined half-life, allowing, as they die, the arrival and maintenance of new PC. Moreover, only few PC, upon anchoring within a dedicated niche, may become sessile and long-lived through the coupled action of extrinsic factors and intrinsic modulation of their transcriptome and metabolism. How the few PC that become fully long-lived are selected is not totally clear but may not depend on their origin or affinity. Lastly, understanding whether PC secretory function varies through BM PC maturation and long-term persistence will require further investigations.

Conclusion and open questions

Generation, survival, and function of PC are supported by a network of epigenetic, transcriptional, metabolic, and organelle-related factors that are interlinked. As we learn more and more about PC heterogeneity, it becomes essential to re-interrogate these findings to understand whether distinct PC subsets rely on similar cellular programs for their survival and function. Over the last 2 years, we have gained further insights into the intrinsic regulation of PC survival, and, in particular, the pivotal regulatory role of the ER in PC biology has been re-evaluated well beyond antibody secretion. Moreover, the niche competition model for PC long-term survival has been largely questioned. While total PC number does not seem to influence PC survival, whether PC may compete with other cell types in the frame of dynamic niches likely to evolve during infections and environmental changes (e.g. diet, circadian rhythm, and other possible pathways) still needs to be addressed. How PC may in turn control or affect their environment is also a fascinating and understudied field. Indeed, recent works suggested that BM PC may promote myeloid differentiation of hematopoietic stem and progenitor cells [63,64]. Finally, improving our understanding of the extrinsic and intrinsic factors regulating PC longevity is obviously of paramount importance for not only designing more effective vaccines but also to find new ways of targeting malignant PC in the frame of MM, for example.

Data Availability

No data were used for the research described in the article.

Declaration of Competing Interest

None.

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