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Metabolic Links between Plasma Cell Survival, Secretion, and Stress

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Summary

Humoral immunity is generated and maintained by antigen-specific antibodies that counter infectious pathogens. Plasma cells are the major producers of antibodies during and after infections, with each plasma cell producing some thousands of antibody molecules per second. This magnitude of secretion requires enormous quantities of amino acids and glycosylation sugars to properly build and fold antibodies, biosynthetic substrates to fuel endoplasmic reticulum (ER) biogenesis, and additional carbon sources to generate energy. Many of these processes are likely to be linked, thereby affording possibilities to improve vaccine design and to develop new therapies for autoimmunity. Here, we review aspects of plasma cell biology with an emphasis on recent studies and the relationships between intermediary metabolism, antibody production, and lifespan.

Plasma cell formation and subset heterogeneity

The quality, quantity, and duration of antibody production by plasma cells are the major determinants of immunological protection against many infections and for almost all clinically used vaccines [1]. Plasma cells represent a unique lineage within the immune system, single-mindedly producing enormous quantities of antibodies for as long as they live. Recent studies have begun to uncover the intrinsic diversity of plasma cells, and with this information has come mechanistic details that help explain the range of antibody secretion rates and lifespans within this crucial lineage.

In many aspects of lymphocyte development and activation, B and T cells mimic one another. The general processes of antigen receptor gene rearrangement, negative selection, clonal expansion after engagement of antigen, and memory lymphocyte formation from proliferating precursors are performed similarly by both types of lymphocytes, even in the evolutionarily convergent adaptive immune system of sea lampreys [2]. These commonalities synergistically promote the acquisition of knowledge in both B and T cell biology: when a discovery is made in one field, a parallel finding in the other is likely to

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follow. Immunometabolism is no exception. Just as in T cells, B cell activation and differentiation are accompanied by enhanced nutrient acquisition, glycolysis, and mitochondrial reprogramming [3]. Yet the plasma cell lineage represents one arm of B cell differentiation that lacks even a distant relative in T cells. Because of this dissimilarity, T cell immunometabolism studies are unable to provide much guidance on how best to approach plasma cell metabolism. To begin to understand this unique lineage, we will first define the cellular steps that lead to plasma cell formation.

During a canonical T cell-dependent antibody response, a naïve follicular B cell becomes activated by foreign antigen, begins to proliferate, and then differentiates into either the germinal center or extrafollicular plasma cell lineage in secondary lymphoid organs. Along the plasma cell route, B cells first pass through an immature and proliferative plasmablast stage. These plasmablasts express relatively low levels of canonical factors such as *Prdm1* (PR/SET domain 1, also known as Blimp-1), but eventually mature by increasing the expression of the mature plasma cell transcriptional program to promote antibody secretion [4]. This program is characterized by the devotion of the majority of the transcriptome to immunoglobulin synthesis and the expression of the transcription factors *Xbp1* and *Atf6a*, which mediate stress responses to misfolded antibodies [5–7]. As a general rule, plasma cells that are formed early in the immune response tend to be short-lived, persisting for only several days [8]. Meanwhile, plasma cells are produced continuously from germinal centers with a progressive increase in both lifespan and antibody affinity [9]. Plasma cells formed toward the end of the germinal center reaction generally migrate to the bone marrow where they access pro-survival cytokines such as APRIL and BAFF [10–13]. Depending on the specific infection or vaccination, these plasma cells can persist from a few months ranging up to several decades while constitutively secreting enormous quantities of affinity-matured antibodies [14–17]. The specific bases for these differences remain unknown. Because these circulating antibodies pre-exist subsequent infections, plasma cells can prevent an infection from ever occurring. This stands in contrast to memory B cells, which respond only after an infection has already occurred. For pathogens that rapidly replicate or establish latency, this distinction is critical [1]. The maintenance of high-quality antibodies produced by plasma cells is thus the major determinant of protective humoral immunity. Reciprocally, the transience of humoral immunity is the major basis of vaccine failure against infectious diseases such as malaria and pertussis [18, 19]. Thus, defining the basic mechanisms of plasma cell survival has clear clinical relevance.

One potential way to assign a mechanistic basis of plasma cell lifespan is simply to perform comparisons between short- and long-lived plasma cells and identify functionally important molecular differences. Yet this is more challenging than it may seem. Exceptions are the rule when it comes to plasma cell ontogeny and lifespan. For example, T-independent responses can yield long-lived plasma cells, demonstrating that germinal center reactions are not required per se for longevity [20, 21]. As another example, some plasma cells in the bone marrow are relatively short-lived, while other subsets in the spleen are quite long-lived [22, 23]. Thus, plasma cell survival niches are not restricted per se to specific macroanatomical locations. Clearly, a major barrier to a deep understanding of plasma cell regulation is the intrinsic and extrinsic heterogeneity of this lineage and its associated microenvironments. Moreover, whether this heterogeneity is intrinsically imprinted during plasma cell formation

or imposed by the microenvironment remains unclear [24, 25]. For example, APRIL, a critical plasma cell survival cytokine, induces anti-apoptotic Mcl1 expression [11, 12, 26]. Is APRIL thus instructive to promote plasma cell longevity? Or is the critical survival program imposed during activation in plasma cell precursors? Given these uncertainties, how can one prospectively define a short- vs. a long-lived plasma cell to perform comparisons? Fortunately, some progress has been made in recent years to purify plasma cell subsets and partially define this heterogeneity. For example, mouse CD138⁺ plasma cells with distinct lifespans, kinetics of formation, and T-dependence can be separated by the markers B220 and CD93 [20, 23, 27]. In humans, plasma cell subsets with distinct antigen specificities and lifespans can be separated by expression of CD19, both in the bone marrow and in the intestine [28–30]. Yet despite these prospective isolation strategies and clear functional differences, remarkable transcriptional similarity is observed between short- and long-lived plasma cell subsets [5, 28, 31]. The relatively few and modest transcriptional changes between short- and long-lived plasma cells are not obviously conserved between mice and humans [5, 28, 31], raising further questions as to how or whether plasma cell lifespan and the duration of immunity is controlled at the transcriptional level. Several members of the BTB-POZ family of transcription factors influence infection- or vaccine-specific outcomes on plasma cell lifespan, but these may act on upstream precursors rather than in plasma cells directly [32–34]. Moreover, though numerous pathways have been demonstrated as essential for long-term plasma cell survival [25], many of these factors are not obviously differentially expressed transcriptionally between short- and long-lived plasma cells [5, 28]. It is entirely possible that subtle transcriptional changes mediate large differences in plasma cell lifespan. Yet it may also be that transcriptional control is a relatively minor part of the equation that intrinsically defines plasma cell lifespan. Instead, recent evidence has strongly implicated metabolic pathways in plasma cell formation, function, and maintenance.

Intermediary metabolism in plasma cell formation and maintenance

Much of the research done on B cell metabolism during development and activation prior to plasma cell formation has been recently reviewed [3]. Thus, in this article we will focus on some key findings specifically related to intermediary metabolism, the process by which nutrients are converted into ATP and other cellular biosynthetic products. Naïve resting B cells have scant cytoplasm and ER, appear to have relatively few energy or biosynthetic requirements, and as such are recalcitrant to genetic abrogation of mitochondrial function and glucose uptake (Figure 1) [35, 36]. In fact, B lineage-defining transcription factors such as Pax5 actively suppress glucose uptake, and mutation of such genes plays a key role in lymphoid malignancies through the promotion of **aerobic glycolysis** (see Glossary) [37]. However, activation of naïve B cells *in vitro* with mitogens such as bacterial lipopolysaccharide (LPS) leads to increased glucose transporter expression, glucose uptake, glycolysis, and oxidative phosphorylation (Figure 1) [35, 38]. Germinal center B cells *in vivo* also rely on glycolysis, though the precise metabolic basis for this requirement needs further exploration given that these cells import relatively little glucose [39, 40]. After activation, glucose-derived carbons can be found not only in glycolytic and **tricarboxylic acid cycle** intermediates, but also in **cataplerotic biosynthetic pathways** to generate fatty acids including phosphatidylethanolamine, phosphatidylcholine, ceramide, and cholesterol

[41]. These *de novo* synthesized fatty acids are crucial for the initial expansion of the endoplasmic reticulum that occurs during plasma cell differentiation as well as for the expression of hallmark transcription factors such as Prdm1 [41]. Fatty acids also undergo β -oxidation to generate ATP [42]. The marked ER expansion is coupled with increased translation of ER-associated proteins and production of copious amounts of antibodies, with nearly 70% of the transcriptome devoted to immunoglobulin synthesis [5, 43].

Once plasma cells are formed, the metabolic requirements switch to support antibody production and organelle maintenance rather than biogenesis (Figure 1). Some of these changes are mediated by the aforementioned transcription factor Prdm1, which promotes expression of amino acid transporters [6]. Amino acids such as leucine and arginine activate the mechanistic target of rapamycin complex 1 (**mTORC1**) in plasma cells, which then enhances protein synthesis [6]. B cell-intrinsic genetic manipulation of the mTORC1 pathway suggests that this pathway is essential for the optimal formation of plasma cells from activated precursors [44–47]. Interestingly, systemic inhibition with rapamycin ablates germinal center reactions following influenza infection, leaving behind a broad pool of low affinity plasma cells that cross-protect against heterologous strains [48]. Once plasma cells are fully differentiated, mTORC1 is predominantly used to enhance antibody production [45]. Within intestinal B cells, diet-derived vitamin B1 is essential for promoting oxidative phosphorylation and plasma cell formation, but is dispensable once plasma cells are already formed [49]. Intestinal IgA+ plasma cells instead utilize diet- and gut microbiota-derived short chain fatty acids as at least a small portion of the required carbon sources for the electron transport chain and to maintain cellular fatty acid content [50]. Similarly, dietary palmitic acid increases IgA production and IgA+ plasma cells via the production of S1P and cellular proliferation [49]. Stable isotope tracing studies have also implicated glutamine uptake and oxidation in plasma cell function [51]. In myeloma cells, glutamine is essential for suppressing the expression of the pro-apoptotic molecule Bim [52]. Presumably some portion of this glutamine is also used for the synthesis of other amino acids and antibodies as well. Thus, a theme that will recur in this review is that the very nutrients required for synthesizing antibodies, such as amino acids, are also utilized for plasma cell energy and survival.

Glucose continues to be utilized by plasma cells once they are fully mature, but is preferentially shunted into distinct metabolic pathways than those during B cell activation (Figure 1). Moreover, glucose is potentially imported by unique cell surface transporters in mature plasma cells. Elevated levels of surface Glut1 expression likely promote a major portion of glucose uptake in mouse activated B lymphocytes and plasma cells [35]. Yet given that genetic ablation of Glut1 still allows for plasma cell survival and antibody production [35], it seems likely that other transporters are also involved. In human cells, the essential glucose transporter(s) is even less clear, as the transcriptional levels of Glut1 are nearly undetectable in mature plasma cells [31]. Several studies in human myeloma cells have instead implicated alternative hexose transporters such as Glut8, Glut11, and Glut4, the latter of which is usually controlled post-translationally by insulin signaling in non-malignant cells [53]. During initial B cell activation and differentiation, glucose is used primarily for glycolysis, oxidative phosphorylation, lipid synthesis, and the pentose phosphate pathway,

whereas glucose taken up by mature plasma cells is primarily diverted into the **hexosamine pathway** to glycosylate antibodies [31, 38]. Yet upon depletion of energy reserves, glucose can be diverted from the hexosamine pathway back to glycolysis and the resultant pyruvate used for respiration [31]. This glucose, when catabolized, also stabilizes expression of anti-apoptotic Mcl1 [53], a factor that is essential for plasma cell survival [26]. Glucose thereby maintains energy reserves and survival pathways that promote long-term maintenance of antibody-secreting cells. This is another example of how a nutrient (glucose) that is involved in antibody assembly (glycosylation sugars) is also used to promote plasma cell survival.

Antibodies have a single **N-linked glycan** attached at Asn297 of the constant region of each heavy chain and 20% of antibodies have a second N-linked glycosylation site in the variable region of the heavy chain [54]. Antibody glycosylation at Asn297 improves dynamic motion of immunoglobulin Fc, influences the folding of the protein, and, depending on the specific glycosylation sugars incorporated, changes its interaction with Fc receptors [54]. In this way, antibody glycosylation diversifies the functional repertoire of antibodies. Depending on the antigenic experiences and inflammatory conditions, plasma cell subsets can produce antibodies with distinct glycosylation patterns [54]. It is tempting to speculate that differential nutrient uptake by plasma cell subsets may impact these glycosylation patterns. Although mutation of the Asn297 residue to Gln to prevent glycosylation minimally impacts recombinant antibody production [55], inhibition of glycosylation using pharmacological agents such as **tunicamycin** sharply reduces antibody secretion by hybridomas by promoting misfolding [56]. This in turn leads to endoplasmic reticulum (ER) stress responses and eventually apoptosis. Of interest, short-lived plasma cells secrete far fewer antibodies and import substantially less glucose than do their long-lived counterparts [31]. This presumably leaves short-lived plasma cells with relatively few glycosylation sugars as a result. To what extent does reduced glycosylation sugar availability trigger an ER stress response *in vivo*, and does this help explain the observed differences in lifespan and secretion across plasma cell subsets [31, 57]?

Antibody secretion and ER stress responses in plasma cells

Though there are few unequivocal answers, to begin to address this question some background is required regarding how plasma cells metabolically acquire their secretory capacity and mount ER stress responses. Plasma cells are estimated to secrete several thousand antibody molecules per second [58]. To place this observation into a physiological context, only 1 μ l of passively transferred immune serum is sufficient to protect an immunodeficient mouse from an otherwise lethal West Nile virus infection [59]. This corresponds to antibodies derived from only ~3 antigen-specific long-lived plasma cells [59]! These findings highlight both the protective and secretory capacity of plasma cells and the metabolic burden required to sustain this production. To achieve this secretory capacity, plasma cells must greatly expand the ER and Golgi networks as described above. This expansion, coupled with exceptionally high rates of antibody synthesis in plasma cells, necessitate regulatory steps to ensure that production is commensurate with biosynthetic supplies, immunoglobulin folding, and the capacity of the secretory organelles.

Both ER remodeling and the accumulation of ER proteins that accompany secretory processes trigger unfolded protein, or stress responses [60] (Figure 2). ER stress can activate three parallel pathways: PKR-like endoplasmic reticulum kinase (Perk), activating transcription factor 6 α (Atf6 α), and inositol-requiring enzyme 1 α (Ire1 α) [61]. Of these three ER stress responses, the best-studied in plasma cells is the Ire1 α pathway. Ire1 α acts as a ribonuclease and splicing factor, removing 26 internal nucleotides from the X-box protein 1 (Xbp1) transcript [62]. This leads to a new reading frame and the generation of Xbp1s, a more stable and active transcription factor than the one generated by the unspliced transcript. Xbp1s promotes the expression of genes involved in mitochondrial and ER biogenesis, such as choline cytidyltransferase, the rate limiting enzyme involved in the production of the ER lipid components [63, 64]. The genetic deletion of Xbp1 thus impairs ER expansion and antibody secretion by plasma cells (Table 1) [65, 66]. Yet of note, plasma cells can still be found in normal numbers despite the absence of Xbp1 [67]. Similarly, inhibition of the mTORC1 complex in mature plasma cells sharply reduces antibody secretion, but does not impact survival [45]. These data demonstrate that there is no formal requirement for plasma cells to secrete antibodies in order to survive. On the other hand, additional lines of evidence suggest that antibody secretion and plasma cell survival are linked. Long-lived plasma cell subsets that import high amounts of glucose secrete more antibodies than do short-lived subsets that import less glucose [31]. This glucose is used both for antibody glycosylation and for spare respiratory capacity and survival, thereby linking lifespan and secretion. Conversely, plasma cells that lack Tsc1, a negative regulator of mTORC1, enhance antibody secretion and ER stress but display shortened lifespans [68]. Similarly, plasma cells lacking Atg5, a gene critical for **autophagy**, display enhanced antibody secretion, elevated ER stress responses, and shortened lifespans [69]. These data suggest that multiple mechanisms regulate antibody secretion, some of which may also relate to survival, such as ER stress responses.

To what extent are ER stress responses responsible for limiting the lifespan of plasma cells? Alternatively, is it possible that the inability to mount proper stress responses shortens plasma cell lifespan? As mentioned above, Xbp1 is essential for proper antibody secretion, but is dispensable for plasma cell survival [67]. In another stress response pathway, ATF6 α is an ER-resident protein that becomes cleaved, allowing it to translocate to the nucleus and activate transcription of genes such as heat shock proteins. ATF6 α -deficient plasma cells have no apparent defect in antibody secretion or survival, both *in vitro* and *in vivo* (Table 1) [70]. However, analysis of other ER stress pathways has yielded more equivocal conclusions. First, mouse plasma cells formed in LPS cultures or by LPS administration *in vivo* display significant activation of Caspase 12, an ER-resident and stress-sensitive effector caspase [71]. Interestingly, the activation of Caspase 12 is accompanied by the inhibition of Caspase 3 and 9, which are the canonical initiating and terminal effectors of the intrinsic pathway of apoptosis. Specific inhibition of caspase 12 activation in turn reduces nuclear apoptotic events *in vitro*. However, the necessity of Caspase 12 in promoting ER stress-dependent plasma cell death *in vivo* remains unclear, as most humans lack a functional version of this gene product [72]. Moreover, there is no information as to whether Caspase 12 is preferentially active in short- vs. long-lived plasma cells. As another example, the role of PERK in plasma cell secretion and survival can be considered. PERK phosphorylates

Ser51 of eukaryotic initiation factor 2 α (eif2 α), leading to an overall suppression of protein translation while paradoxically enhancing the translation of activating transcription factor 4 (Atf4) [73, 74]. Atf4 then promotes expression of amino acid biosynthesis genes and, upon prolonged stress, pro-apoptotic effectors such as Ddit3/Chop. *In vitro* studies have found very limited activation of Perk in plasma cells [68, 75]. Consistent with these findings, genetic ablation of Perk or Chop led to no obvious defects in plasma cell survival *in vitro* (Table 1) [76, 77]. On the other hand, mice carrying a phosphorylation-resistant S51A mutation in eif2 α display modest to severe defects in plasma cell formation and function *in vivo*, depending on the bone marrow reconstitution system used (Table 1) [78, 79]. It is unclear how to reconcile these results. It is theoretically possible that another integrated stress response kinase can also phosphorylate eif2 α in plasma cells, thereby rendering Perk dispensable. Possible candidates include heme-regulated inhibitor kinase, which is activated by low levels of heme, and general control non-derepressible 2 kinase, which is activated by low free amino acid levels [61]. Both of these other enzymes are highly expressed transcriptionally by plasma cells [31]. Or perhaps the S51A mutation in eif2 α negatively impacts B cell development and/or activation, thereby precluding downstream analysis of plasma cell-intrinsic functions. Alternatively, these apparently conflicting data might potentially be attributed to differences in ER stress responses between plasma cells formed *in vitro* vs. those generated *in vivo*. Additional studies will be required to quantify ER stress pathways such as Perk in primary short- vs. long-lived plasma cells, and more genetic studies will be required to demonstrate their importance or lack thereof *in vivo*. Yet based on the evidence to date, it seems that each arm of the ER stress response pathway is not uniformly activated or utilized in plasma cells. Rather, the response is tuned to regulate antibody production and possibly plasma cell survival.

Concluding Remarks

Despite the uncertainties listed above, some compelling evidence links specific ER stress, nutrient uptake, and antibody secretion pathways. Prdm1 not only promotes amino acid uptake in plasma cells, but also promotes the expression of Xbp1 [6, 7]. Xbp1s then directs the diversion of glucose into the hexosamine pathway by enhancing expression of rate-limiting enzymes [80], which may in turn promote antibody secretion [31, 56]. Finally, the very uptake of amino acids and glucose is linked to plasma cell survival through its effects on anti-apoptotic pathways and the generation of ATP [31, 52, 53]. Much of this, of course, remains speculative, so we pose some specific remaining issues that can potentially be addressed in the near-term to shed further light on plasma cell metabolism (see Outstanding Questions).

Outstanding Questions

1. How is plasma cell metabolic programming initiated and maintained in long-lived cells? Do signals received during activation initiate a metabolic positive feedback loop that is maintained throughout life? Or do unique survival 'niches' provide signals that promote distinct plasma cell metabolic properties?

2. Are antibody secretion and plasma cell lifespan functionally and causally linked by glucose import, or is glucose uptake simply a marker and correlate of other more directly relevant pathways that enhance secretion?
3. Do ER stress responses such as Perk control plasma cell lifespan or antibody secretion *in vivo*? Or are bioenergetic supplies the primary determinants of plasma cell lifespan and secretion?
4. How do other intermediary metabolic pathways such as amino acid catabolism and fatty acid oxidation integrate to control plasma cell function?
5. Which metabolic pathways are good targets for plasma cell diseases such as multiple myeloma and autoimmunity?

Several technical advancements and points of emphasis will continue to allow the field of plasma cell metabolism to move forward. First, as described above, defining the heterogeneity of plasma cells is critical to continue to identify functionally important pathways. When heterogeneous groups of cells are pooled together for comparison, differences in truly important factors and pathways can potentially be diluted and overlooked. Fortunately, advances in single-cell transcriptomics and in methods to assess certain metabolic properties in single cells or small numbers of cells will undoubtedly help to uncover this heterogeneity. Second, novel genetic models, facilitated by new gene editing tools and mutant mouse repositories, will allow for careful dissections of *in vivo* metabolic requirements of plasma cells. Historically, much of the work on plasma cells has been performed through *in vitro* cultures and differentiations, largely because of the ease and scale of such assays. Yet for *in vitro* metabolism experiments, it is difficult to precisely mimic variables such as nutrient conditions and oxygen tension as they would normally exist *in vivo*. Moreover, substantial functional and transcriptional differences exist between *in vitro*-differentiated plasma cells and primary plasma cells [5]. Instead, when large numbers of cells are needed for the assay, discarded human tissues such as bone marrow from hip replacement surgeries and tonsils from tonsillectomies are excellent sources of primary plasma cells. By performing functional genetic experiments *in vivo* and assessing metabolic properties of primary mouse and human plasma cells directly *ex vivo*, confidence can be gained regarding the physiological significance of conclusions as the field moves forward. Though the field of plasma cell immunometabolism is very much at its beginning, studies performed thus far point to an exciting future, both for basic and translational purposes.

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Glossary

Aerobic glycolysis

Metabolic pathway that converts glucose into pyruvate and then into lactate despite the presence of oxygen. Normally, when oxygen is present, pyruvate is carried into the

mitochondria for oxidative phosphorylation, a highly efficient method for generating ATP. When pyruvate is instead converted into lactate in oxygen-replete conditions, this process is often referred to as Warburg metabolism, named after its discoverer Otto Warburg. Aerobic glycolysis is preferentially utilized by malignant cells as a means of generating biomass and regenerating the coenzyme nicotinamide adenine dinucleotide (NAD⁺)

Autophagy

A cellular process by which cellular proteins and organelles are degraded in double-membraned vesicular structures called autophagosomes. Once degraded, the component pieces of the cargo can be recycled and re-used by the cell. Autophagy can be triggered by nutrient shortage, among other stimuli

Cataplerotic biosynthetic pathways

In addition to generating ATP, the tricarboxylic acid cycle generates biosynthetic precursors for fatty acids and several amino acids. This process of substrate exit from the tricarboxylic acid cycle to generate biosynthetic products is known as cataplerosis. Cataplerosis must be balanced by anaplerotic reactions, which restore tricarboxylic acid intermediates

Hexosamine pathway

This metabolic pathway shunts the glucose catabolite fructose-6-phosphate away from glycolysis to produce N-acetyl glucosamine, and then into various glycosylation sugars. Through a complex set of subsequent enzymatic reactions, various glycosylation sugars such as mannose, galactose, fucose, and sialic acids are added to proteins

mTORC1

mammalian target of rapamycin complex 1 is a complex made up of five proteins. mTORC1 positively regulates biosynthesis cell growth and proliferation by phosphorylating specific enzymatic substrates, which then promote biosynthesis of proteins, lipids, and organelles and limit autophagy

N-linked glycan

Protein modification where sugar molecules or glycans are attached to the nitrogen atom of asparagine residues. In contrast, O-linked glycans are covalently added to serine or threonine residues

Tricarboxylic acid cycle

Also known as the citric acid cycle or Krebs cycle. This cyclical metabolic cascade occurs within the inner matrix of the mitochondria, and oxidizes carbon sources in a process known as oxidative phosphorylation. The process of oxidative phosphorylation generates electrons for the electron transport chain. The electron transport chain in turn couples the reduction of oxygen to the synthesis of ATP

Tunicamycin

Antibiotic mixture that blocks N-linked glycosylation and causes cell cycle arrest in G1 phase. A commonly used reagent used to induce the unfolded protein response

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Trends

- Plasma cells secrete enormous quantities of antibodies and play critical roles in humoral immunity and autoimmunity. This secretory activity underlies very specific metabolic requirements in this cell type.
- As B cells differentiate into plasma cells, marked changes in nutrient uptake and intermediary metabolism promote antibody synthesis and expansion of the endoplasmic reticulum (ER).
- Some of the same substrates used for antibody synthesis and ER biogenesis are also used to generate energy and prevent plasma cell apoptosis. Differences in nutrient uptake thus correlate with plasma cell lifespan and antibody secretion rates.
- Expansion of the secretory apparatus in plasma cells triggers compensatory stress responses. Potential links between intermediary metabolism, ER stress, and plasma cell lifespan are starting to emerge.

Figure 1.

Major metabolic fates of nutrients during B cell differentiation to plasma cells. The known metabolic fates of glucose (green), amino acids (blue), and fatty acids (red) are shown as B cells (left) differentiate into plasma cells (right). Arrows passing through mitochondria indicate a metabolic process that takes place in that organelle, while the endoplasmic reticulum (ER) and nucleus indicate sites where the end products of nutrients are used.

Figure 2.

Endoplasmic reticulum stress and unfolded protein responses in plasma cells The major pathways involved in responses to endoplasmic reticulum (ER) stress and unfolded protein responses (UPR) and their outcomes are depicted. Question marks indicate speculative links. Abbreviations used: Casp: caspase, ATF6α: Activating transcription factor 6α, PERK: protein kinase R-like endoplasmic reticulum kinase; IRE1: Inositol-requiring enzyme 1, Xbp1(s): X-box binding protein 1 (spliced), eIF2α: eukaryotic translation initiation factor 2α

Table 1

Phenotypes of plasma cells with deficiencies in ER stress response genes

	Xbp1 ^{-/-} [65-67]	Atf6a ^{-/-} [70]	Perk ^{-/-} [76]	Chop ^{-/-} [77]	eif2a-S51A [78,79]
Survival	No effect <i>in vivo</i>	No effect <i>in vivo</i>	No effect <i>in vitro</i>	No effect <i>in vitro</i>	Decreased mature and plasma B cell formation <i>in vivo</i>
Secretion	Impaired antibody production and ER expansion <i>in vivo</i>	No effect <i>in vivo</i>	No effect <i>in vitro</i>	Modest decrease in IgM production <i>in vitro</i> Normal serum IgM levels <i>in vivo</i>	Decreased serum IgG and IgM antibody titers <i>in vivo</i>