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Pathogenic memory plasma cells in autoimmunity

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Plasma cells represent a final stage of the B cell differentiation when activated B lymphocytes switch from antigen sensing to antibody secretion. As long-lived memory plasma cells, in particular those maintained in the bone marrow, they constitute an independent component of immunological memory [1] Plasma cells can persist long-term and constitutively secrete their antibodies, providing 'humoral' memory and protection against pathogens repeatedly encountered [2••,3•]. At secretion rates of up to 10.000 antibodies per cell per second [4] even few specific memory plasma cells are sufficient to confer protection against a given pathogen. It is widely accepted that these most efficient weapons of the adaptive immune system are highly detrimental when they secrete pathogenic antibodies against self-antigens. It is difficult to understand, why plasma cells in the past had received so little attention in research on autoimmunity and chronic inflammation. Probably because they had not been recognized as an independent component of immune memory, refractory to conventional immunosuppression and able to drive the disease on their own. Therapeutic targeting of memory plasma cells secreting pathogenic antibodies, as selectively as possible, is increasingly recognized as a challenge and necessity to break refractoriness, regenerate immunological tolerance and induce therapy-free remission in these diseases.

Rational approaches to target (pathogenic) plasma cells should be based on a molecular understanding of their lifestyle, spotting their 'Achilles' heel', at best an exclusive one. However, selective targeting of autoreactive plasma cells remains a challenge as no unique or druggable markers have been identified so far. What do we know about the generation and persistence of plasma cells? *In vitro*, plasmablasts can develop from any type of activated B cell including naive, marginal zone, follicular, germinal center and memory B cells. In the process of becoming a plasma cell, the activated B cell undergoes considerable differentiation, transcriptionally and morphologically, in order to enable the massive production and secretion of antibodies [5]. While for a long time plasma cells had been regarded as short-lived end products of B cell differentiation, arguing that the B cell would be the decisive target in antibody-mediated diseases, we now distinguish between short-lived plasmablasts/plasma cells with a lifetime of only a few days and long-lived memory plasma cells which can persist for many years [1]. The molecular competence of a plasmablast to become a memory plasma cell is still not well defined. T cell signaling via CD40L seems to be pivotal, since genetic ablation of the CD40/CD40L axis leads to severe impairment of humoral memory [6], and (T cell-derived) cytokines like IL-10 and IL-21 promote plasma cell development [7,8]. However, it has also been demonstrated that memory B cells can develop into memory plasma cells independently of T cell help, but in this case the generation of memory B cells is T cell-dependent [9,10].

Plasma cells are tissue-resident

We and others have shown that in secondary T cell-dependent immune responses approximately 10% of the plasmablasts generated differentiate into long-lived memory plasma cells [11]. In the memory phase of the immune response, most of these memory plasma cells persist in the bone marrow, while some are maintained in the spleen, resting in terms of proliferation [12]. They persist independently of B cell precursors and residual antigen [13–15]. Plasmablasts are attracted to the bone marrow by CXCL12. They express the CXCL12-sensing chemokine receptor CXCR4, and blockade or deficiency of CXCR4 prevents their translocation to the bone marrow [16,17]. Interestingly, and of physiological relevance, plasmablasts are migratory, while plasma cells are not, implying that they are not circulating [18]. When

generated in the presence of interferons, plasmablasts also express the chemokine receptor CXCR3 [19] which senses the proinflammatory, interferon-induced chemokines CXCL9, 10 and 11. Indeed, in the 'never-ending' immune reactions of autoimmune diseases, long-lived plasma cells are also attracted to and persist in inflamed tissue, as has been shown for the inflamed kidneys of patients with systemic lupus erythematosus (SLE) [20], the inflamed central nervous system of patients with multiple sclerosis [21], the spleens of patients with autoimmune thrombocytopenia [22], the inflamed synovia of rheumatoid arthritis patients [23] or the thymus of myasthenia gravis patients [24]. In acute, that is, successful immune reactions, plasma cells of inflamed tissues would provide local protection, but obviously in chronic (auto) immune reactions plasma cells of inflamed tissues, secreting pathogenic antibodies, will enhance local immunopathology.

Plasma cells require survival signals from their niche

Memory plasma cells are not intrinsically long-lived. When isolated from the bone marrow, they rapidly die. In the bone marrow, they colocalize to and contact mesenchymal stromal cells expressing CXCL12 and VCAM1 (Vascular cell adhesion molecule 1, CD106) [25]. The composition of the synapse between memory plasma cells and stromal cells is not entirely clear so far. CXCL12/CXCR4, VLA4/VCAM1, LFA1/ICAM1 and CD44/hyaluronic acid have been shown to play a role [16,26,27] (reviewed in Ref. [1]). Concomitant inhibition of VLA4 and LFA1 ablated plasma cells in mice [26]. However, targeting of CD49d, the integrin α4-subunit of VLA4, with natalizumab did not affect plasma cell numbers or antibody titers [28,29]. The apparently divergent results from mouse and human studies suggest that other integrins mediate plasma cell-stroma contact or can compensate for the blockade of VLA4 in humans. Recently, laminin β1 has been identified as a crucial and selective component of the niche for IgG-secreting plasma cells in the bone marrow [30]. BAFF (B cell-activating factor, also known as BlyS, B-lymphocyte stimulator) or APRIL (a proliferation-inducing ligand), addressing the plasma cell receptor B cell maturation antigen (BCMA) are crucial for the survival of memory plasma cells in the bone marrow as well [31,32]. Whether or not the BCMA ligands are provided by eosinophilic granulocytes is a matter of debate [33–35]. We recently could show that a distinct subpopulation of bone marrow stromal cells expresses BAFF [36]. Also regulatory T cells (Tregs) have been shown to be in close interaction with plasma cells in the bone marrow. Depletion of Tregs resulted in the concomitant reduction of plasma cells in the bone marrow suggesting a supportive role of Tregs for plasma cell survival [37]. Which signals Tregs could provide to plasma cells is still unclear. However, considering the important role of Tregs in immune homeostasis and maintenance of tolerance, targeting Treg-plasma cell interaction to target plasma cells has to be carefully considered.

Which cells and signals sustain persistence of plasma cells in inflamed tissue is not clear, but several cytokines abundant in inflamed tissue, such as IL-6, IL-12, TNF and type 1 IFN, support survival of plasma cells *ex vivo* [27,38].

Pathogenic plasma cells are refractory to immunosuppression

Upon adoptive transfer, memory plasma cells secreting pathogenic antibodies suffice to transfer chronic immunopathology. This has been demonstrated by transfer of plasmablasts and plasma cells, excluding B cells, from the spleen of lupus-prone (New Zealand Black × New Zealand White)F1 (NZB/W) mice into RAG-deficient mice lacking an adaptive immune system of their own. In NZB/W mice, these antibody-secreting cells include cells secreting autoantibodies against double-stranded DNA, antibodies causing immune-complex mediated nephritis. In the RAG-deficient hosts, the transferred cells developed into long-lived plasma cells secreting autoantibodies and the mice developed immune complex-mediated nephritis [39]. This observation identifies pathogenic memory plasma cells as a key target for therapy of chronic antibody-mediated diseases, which requires new therapeutic strategies, since memory plasma cells are refractory to conventional immunosuppression, including irradiation [25,40,41]. In NZB/W mice, but also in SLE patients and patients with rheumatoid arthritis, memory plasma cells secreting (pathogenic) autoantibodies develop early in disease, even before clinical onset of the disease [42,43]. Thus, rituximab, an antibody targeting cells expressing CD20, does not effectively reduce autoantibody titers [44] as memory plasma cells do not express CD20 and have already been established. Likewise, abatacept, a CTLA4-Ig fusion protein which targets T-dependent plasma cell generation, does not abolish autoantibody production, suggesting that these are secreted by refractory memory plasma cells, and not by constantly *de novo* generated short-lived plasma cells [45]. Indeed, refractoriness of titers of pathogenic (auto)antibodies to conventional therapies is probably the best available marker suggesting that pathogenic memory plasma cells are involved, and should be targeted in these patients. But how?

Therapeutic targeting of plasma cells in refractory autoimmune diseases

Probably the most drastic option is immunoablation with anti-thymocyte globulin (ATG), which contains plasma cell-ablative antibodies [46,47] followed by regeneration of the patient's immune system from autologous stem cells. In about 70% of patients with refractory chronic inflammatory diseases, this treatment induces therapy-free

remission for extended time periods [48]. Memory plasma cells disappear, as well as protective and pathogenic antibodies, and pathogenic memory plasma cells are not regenerated, due to the apparently efficient ablation of the cells involved in their generation [49]. The patients undergo an extended period of immunodeficiency, thus require supplementation with protective intravenous immunoglobulins (IVIG), and lose their acquired immunity. This will not be a therapy for everybody.

Can we target memory plasma cells more selectively? A number of strategies have been or are currently under investigation, developed for the therapy of multiple myeloma, a plasma cell malignancy, or building on the phenotype and lifestyle of plasma cells as such, but not discriminating between protective and pathogenic plasma cells. This includes atacicept (TACI-Ig), preventing BCMA activation [50,51], AMD3100, targeting CXCR4 [16], daratumumab, targeting CD38, an ectoenzyme expressed on long-lived plasma cells [52,53], and etoluzumab targeting CD319 [54]. Initial trials with atacicept in SLE patients showed drastic reduction of antibody titers indicating a very efficient depletion of plasma cells [51] and further trials are ongoing. It will be exciting to see whether and how blockade of BCMA ligands by atacicept find their way into other antibody-mediated diseases.

Daratumumab is approved for the treatment of multiple myeloma and has been shown to deplete plasma cells of SLE and RA patients *ex vivo* [53]. Also etoluzumab displayed binding to human plasmablasts and plasma cells and was able to reduce autoantibody titers and histopathology in a pre-clinical test in a collagen-induced arthritis model in rhesus monkeys [54]. For both antibodies clinical trials aiming at plasma cell depletion in non-malignant diseases are still pending.

The proteasome inhibitor Bortezomib approved for the treatment of multiple myeloma, efficiently depletes murine memory plasma cells and saves NZB/W mice from immune-complex mediated nephritis [55]. In patients with SLE, and highly refractory to conventional immunosuppression, off-label use of Bortezomib led to a significant drop in disease activity and autoantibody titers [56••]. Bortezomib has also been efficient in patients with refractory Sjögren syndrome [57], refractory thrombotic thrombocytopenia purpura [58], refractory anti-NMDA receptor encephalitis [59] and refractory myasthenia gravis [60]. Second-generation proteasome inhibitors and inhibitors targeting selectively the immunoproteasome with more favourable safety profiles including lower frequency of polyneuropathy are currently being tested [61].

Eventually, the targeting of memory plasma cells will reveal which immunopathology of which diseases is caused by pathogenic memory plasma cells. Nevertheless, all these therapeutic strategies aim at the generic ablation of pathogenic as well as protective plasma cells and none include a strategy to prevent regeneration of pathogenic plasma cells from their precursors. Indeed, the SLE patients treated with Bortezomib eventually regenerated their pathogenic plasma cells [56••]. However, this regeneration could be stopped with conventional therapy, that is, treatment with Bortezomib had broken the refractoriness of the patients, suggesting that the pathogenic memory plasma cells indeed had been a refractory, diseased-driving element.

An important caveat of an untargeted plasma cell depletion to consider is the potential loss of regulatory plasma cells, which have been described by several groups [reviewed in Ref. [62]]. Regulatory plasma cells expressing IL-10, IL-35 and the inhibitory receptor LAG-3 may have an important role in maintaining immune homeostasis [63•] but have also been shown to prevent or resolve autoimmune reactions [64]. A more targeted approach sparing potentially beneficial, immunoregulatory plasma cells by comparing the phenotype and lifestyle of regulatory plasma cells versus 'pathogenic plasma cells' could lead to additional benefit.

Selective targeting of pathogenic plasma cells

Beyond generic ablation of plasma cells, strategies are scarce for the selective ablation of pathogenic versus protective plasma cells, or plasma cells according to the specificity of the pathogenic (auto)antibodies they secrete. Manne *et al.* have recently identified laminin β1 as an exclusive component of the bone marrow niche of IgG-secreting memory plasma cells, required for their persistence [30]. As most pathogenic memory plasma cells are secreting IgG, blocking laminin β1 appears to be an option to ablate IgG-secreting memory plasma cells selectively. Interestingly, this strategy has been discovered as an evasion mechanism of *Salmonella typhimurium*. Finally, a strategy emerges for the ablation of plasma cells according to the specificity of the antibodies they secrete. Since memory plasma cells do not display their antibodies on the cell surface, conjugates of anti-CD138 antibodies or any other antibody binding to the plasma cell surface and the antigen-of-interest are used to label all plasma cells with that antigen [65•]. Those plasma cells secreting antibodies specific for that antigen, and binding to the affinity-matrix on their surface, will be targeted for antibody-mediated effector mechanisms, such as complement-mediated lysis or antibody-dependent cellular cytotoxicity (ADCC), and eliminated. Antigen-specific approaches have also been shown for B cells using T cells with chimeric antigen receptors (CAR) consisting of the autoantigen [66•] which would bind the specific surface B cell receptor (BCR). As plasma cells expressing IgG lose their surface BCR expression, combining the affinity-matrix approach with CAR T cells

may prove to be a feasible option which could lead to the depletion of both auto-antibody secreting plasma cells as well as their B cell precursors in an antigen-specific manner.

Conclusion and outlook

Memory plasma cells secreting pathogenic antibodies, and generated early in pathogenesis, are a long-neglected target of therapy in immune-mediated diseases, of prime relevance, since they are refractory to conventional therapies. They are easy to identify, according to refractory titers of their pathogenic antibodies as surrogates in the blood. Strategies for the generic targeting of memory plasma cells, based on their phenotype and lifestyle, are currently in preclinical and clinical trials, and confirm pathogenic memory plasma cells as a refractory 'roadblock' to response to conventional therapy and tolerance induction. Therapeutic targeting of (memory) plasma cells will also eventually identify diseases with significant contribution of pathogenic memory plasma cells, that is, 'plasma cell' diseases. Strategies for the selective targeting of pathogenic memory plasma cells are scarce and still represent a challenge to biomedical research. An important component of strategies targeting memory plasma cells, and aiming at the regeneration of immunological tolerance, will be the prevention of their regeneration.

Conflict of interest statement

Nothing declared.

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