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Brief Reviews

THE JOURNAL OF IMMUNOLOGY

Pathogenic Long-Lived Plasma Cells and Their Survival Niches in Autoimmunity, Malignancy, and Allergy

Oliver Winter,*,† Christof Dame,† Franziska Jundt,‡ and Falk Hiepe*

Long-lived plasma cells survive in a protected microenvironment for years or even a lifetime and provide humoral memory by establishing persistent Ab titers. Long-lived autoreactive, malignant, and allergen-specific plasma cells are likewise protected in their survival niche and are refractory to immunosuppression, B cell depletion, and irradiation. Their elimination remains an essential therapeutic challenge. Recent data indicate that long-lived plasma cells reside in a multicomponent plasma cell niche with a stable mesenchymal and a dynamic hematopoietic component, both providing essential soluble and membrane-bound survival factors. Alternative niches with different hematopoietic cell components compensate fluctuations of single cell types but may also harbor distinct plasma cell subsets. In this *Brief Review*, we discuss conventional therapies in autoimmunity and multiple myeloma in comparison with novel drugs that target plasma cells and their niches. In the future, such strategies may enable the specific depletion of pathogenic plasma cells while leaving the protective humoral memory intact. ***The Journal of Immunology*****, 2012, 189: 5105–5111.**

Long-lived plasma cells (LLPCs), first identified in the 1990s (1, 2), provide a persisting Ab titer in the blood and form the humoral memory of the immune system, which is independent of permanent Ag presence (3). Therefore, LLPCs are defined as memory PCs (MPCs) (Table I). PCs differ from their direct precursors, the plasma blasts, by proliferation halt, loss of migratory capabilities, downregulation of characteristic B cell markers such as CD19, CD20, CD22, and HLA-DR/MHC class II, and upregulation of CD138 and BLIMP1. Depending on the primary Ag stimulation, the estimated half-life of the humoral memory varies from 11 y (tetanus) to >200 y (measles, mumps) (4). MPCs, however, are not long-lived per se but need antiapoptotic stimuli from their microenvironment, the so-called PC niche (5). If a newly generated PC does not successfully enter a survival niche in a competitive process or, vice versa, if an LLPC is displaced from its niche by an immigrating young PC, it undergoes apoptosis (6) (Fig. 1A). In the past 15 y, several soluble survival factors, for example, the chemokine CXCL12, the BCMA ligands APRIL and BAFF (also known as BLyS), IL-6, TNF-α, and membrane-bound PC survival factors, for example, VCAM-1 and the CD44 ligands hyaluronic acid, fibronectin, and collagen, were discovered both in vitro and in vivo (Table II). These factors can synergistically contribute to PC survival (7), but only BCMA stimulation (8), expression of CD93 (9), and for bone marrow PCs expression of CD28 (10) were demonstrated to be essential for PC longevity. However, the role of CD28 might be controversial, as Njau et al. (11) reported increased Ig titers and PC numbers in $CD28^{-/-}$ chimeras. Whereas the large majority of MPCs are localized in the bone marrow (5, 12), LLPCs are also found in lymphatic organs such as spleen (13), lymph nodes (14), mucosa-associated lymphatic tissues (15), as well as in chronically inflamed tissues such as the synovium in rheumatoid arthritis (16), the CNS in induced multiples sclerosis (17), the kidneys in systemic lupus erythematosus (SLE) (18), the salivary glands in Sjögren's syndrome (19), or the lung during chronic airway inflammation in allergy/asthma (20, 21). In secondary lymphatic tissues, PCs reside in extrafollicular areas such as the lamina propria of mucosa and the red pulp of spleen, and LLPCs are associated with APRIL, BAFF, and IL-6 sources in the vicinity (14, 15, 22, 23). Whereas APRIL is produced by several cell types in the bone marrow (24), only few cells in specific areas (e.g., the subepithelium zone in tonsillar crypts or intestinal villi in the mucosa) secrete this survival factor in other organs (15). Moreover, certain organs have different potential to support PC survival, and induction of angiogenesis seems crucial to maintain PCs in inflamed tissues (25).

In studying the cellular composition of the PC niche, Tokoyoda et al. (26) found that in the bone marrow >95% of all IgG PCs are colocalized with CXCL12-abundant reticular (CAR) cells, a subpopulation of mesenchymal stromal cells. According to cell division studies, only 50–70% of bone

*Department of Rheumatology and Clinical Immunology, Charité–University Medicine Berlin, 10117 Berlin, Germany; †Department of Neonatology, Charité–University Medicine Berlin, 13353 Berlin, Germany; and ‡Department of Hematology and Oncology, Charité–University Medicine Berlin, 13353 Berlin, Germany

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Address correspondence and reprint requests to Dr. Oliver Winter, Charité–University Medicine Berlin, Charitéplatz 1, 10117 Berlin, Germany. E-mail address: oliver.winter@charite.de

Abbreviations used in this article: BCMA, B cell maturation Ag; BLyS, B lymphocyte stimulator; CAR, CXCL12-abundant reticular; HNC, hematopoietic niche component; LLPC, long-lived plasma cell; MCPN, multicomponent plasma cell niche; MM, multiple myeloma; MMC, multiple myeloma cell; MPC, memory plasma cell; PC, plasma cell; SLE, systemic lupus erythematosus; SLPC, short-lived plasma cell.

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Table I. Plasma cell stages

Plasma Cell Stage	Characteristics
Plasma blasts/newly developed PCs	Capable of dividing and migrating, still expressing declining levels of typical B cell markers (e.g., CD19, CD20, CD22, HLA-DR/MHC class II).
SLPCs	Mature PCs that might lack the capability to become long-lived or were not able to enter the survival niche.
LLPCs/MPCs	Survive for extended periods of time and persistently secrete Abs without need of Ag presence, thus providing humoral memory. LLPCs usually arise from T cell–dependent germinal center reactions and secrete affinity-maturated and Ig class-switched Abs. A large majority of LLPCs are generated in secondary immune responses.

marrow PCs appear to be long-lived (27), indicating the existence of another determining factor. Indeed, within the last 3 y, several in vivo studies demonstrated the contribution of hematopoietic cells such as megakaryocytes (27), eosinophils (28), basophils (29, 30), dendritic cells and monocytes/macrophages (14), myeloid progenitors (31), neutrophils (15), and monocytes (22) to the PC niche. In vitro, osteoclasts also stimulate PC survival (32). Of note, in the intestinal mucosa, which contains large numbers of mainly IgA-secreting PCs, induced titers and LLPC numbers were stable for at least 100 d under germ-free conditions but declined under nonsterile conditions, indicating rapid adaptation of the humoral memory to the intestinal microbiota and intense competitive pressure in the mucosal PC niche (33). As such, some cell types may specifically support LLPCs in the bone marrow sustaining stable/long-term humoral memory, whereas others provide PC survival in secondary lymphoid organs or inflamed tissues during chronic inflammation or infection, maintaining temporary/short-term humoral memory. Considering recent findings, we extended the classical stroma/plasma cell model of the survival niche with a hematopoietic niche component (HNC) to the model of a multicomponent PC niche (MCPN) (24) (Fig. 1A). The HNC enriches the concentration of PC survival factors in the niche but may also add specific factors. Thus, different hematopoietic cells form alternative niches that compensate the loss of one particular cell type but may also harbor distinct PC subpopulations, for example, TNF-α and inducible NO synthase producing IgA PCs (34) or nerve growth factor and neurotrophin-3–dependent PCs (20).

Interestingly, all hitherto reported HNCs (Table II) are of myeloid origin and most express CD80/86. Thus, PCs can stimulate IL-6 production in these cells via CD28 (10). The finding that myeloid cells not only cooperate with lymphocytes during early phases of the immune response but sustain humoral memory defines a new hallmark of interaction between the innate and adaptive immune systems.

The understanding of the MCPN should be considered in processes involving long-lived autoreactive, malignant, and allergen-specific PCs. Such an approach may open new avenues to overcome therapy resistance and may be helpful to improve future therapeutic concepts.

Autoreactive PCs

Genetic, hormonal, and environmental factors contribute to the pathogenesis of autoimmune diseases such as chronic immune thrombocytopenia, SLE, rheumatoid arthritis, Sjögren's syndrome, or multiple sclerosis (12). In these disorders, autoreactive MPCs continuously secrete Abs, resulting in chronicity or relapse of autoimmunity (12) (Fig. 1B).

Current therapeutic strategies primarily target the inflammatory processes and activated immune cells (12, 35). Nonsteroidal anti-inflammatory drugs, antimalarials, glucocorticoids, conventional immunosuppressive or cytotoxic drugs, IVIg, as well as cell depletion Abs such as anti-CD20 (rituximab) targeting B lymphocytes can efficiently reduce the acute or chronic inflammation. They can also abrogate temporary PC survival niches in inflamed tissues and thus eliminate LLPCs in these organs, whereas LLPCs in the bone marrow are not affected by them. Patients with severe refractory autoimmune disorders may benefit from splenectomy or immunoablation followed by autologous stem cell transplantation (36). The complete elimination of the autoreactive memory PCs by immune ablation with polyclonal antithymocyte globulin is crucial for the success of the autologous stem cell transplantation (37). Bortezomib, a proteasome inhibitor directly targeting PCs, eliminates both short- and long-lived autoreactive PCs (38, 39). Targeting the survival niche (see Table III) for autoreactive LLPCs may synergize with the primary therapy and thus improve outcome.

Targeting migration (chemokines and their receptors). The CXCR4 antagonist AMD3100 dislocates malignant PCs from their niche and enhances the susceptibility to bortezomib (40). Additionally, CXCR4 inhibitors disturb the migration of newly formed PCs and may prevent $CXCR4^+$ hematopoietic cells from entering the PC survival niche (41). As recently demonstrated, natural (CXCL11) and synthetic (CCX771) ligands for CXCR7 block the CXCR4-mediated transendothelial migration 100-fold more efficiently than does AMD3100 (42) and they interfere with the CXCL12-directed migration (43). Suppressing the migration of $CXCR3^+$ leukocytes toward CXCR3 ligands (CXCL9/10/11), expressed in inflamed tissues, could also serve as a therapeutic target in various autoimmune diseases. Consistent with this hypothesis, $CXCR3^{-/-}$ MRL/lpr mice displayed nephritis with reduced albuminuria and less glomerular tissue damage, which was associated with diminished infiltration of Th1 and Th17 cells into the kidneys (44). In contrast, CXCR3-deficient NZB/W mice had reduced IgG1 titers but did not show clinical improvement (45). This might be explained by the finding that infiltration of CD4, CD8 T cells and IgG, IgM PCs in the kidneys was not disturbed and suggest the presence of CXCR3-dependent and -independent pathways, pointing out the diversity in the pathogenesis of lupus nephritis. Accordingly, some, but not all, SLE patients might benefit from anti-CXCR3 treatment.

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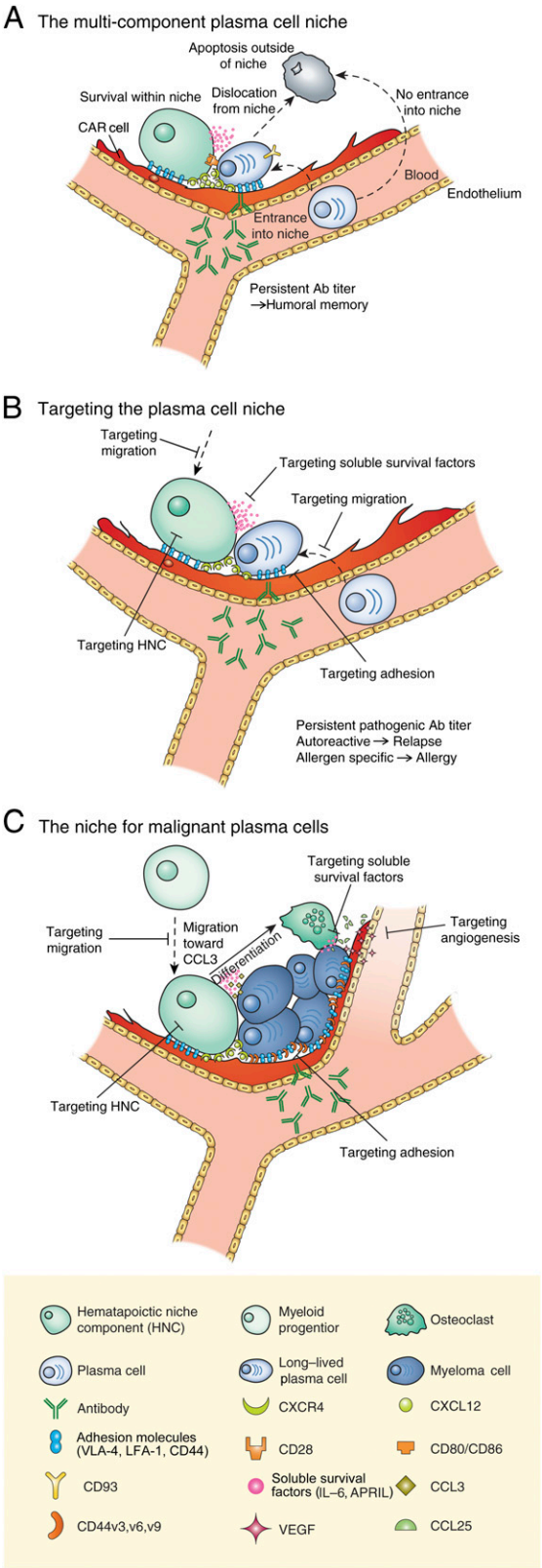

FIGURE 1. The MCPN for protective, autoreactive, and malignant PCs. (**A**) The MCPN model. The newly generated PC enters the bone marrow across the endothelium. Inside the marrow it migrates via CXCR4 (the CXCL12 receptor) toward a CAR cell of mesenchymal origin. The CAR cell provides scaffolding and a meeting point with a dynamic CXCR4$^+$ HNC that releases additional survival factors such as APRIL and IL-6. The PC and the HNC attach to the CAR cell via VLA-4, LFA-1, and CD44, and they can interact with each other via CD28–CD80/86. In its niche, the PC can survive for decades and provides a persistent Ab titer, the humoral memory. When the newly formed PC or respectively the resident LLPC loses the competition for the niche, it undergoes apoptosis. (**B**) Targeting the survival niche for LLPCs. The LLPCs can provide a protective, autoimmune, or allergologic humoral memory. In its niche, with mesenchymal and hematopoietic components, the LLPC is refractory to conventional immunosuppressive therapies. Potential targets within the survival niche for the LLPCs are indicated. (**C**) Targeting the survival niche for malignant PCs. MMCs such as protective PCs depend on stimulatory signals from their survival niche. The MMCs aggressively modify their microenvironment by inducing angiogenesis via VEGF, attracting mesenchymal stem cells via CCL25, and myeloid precursors/immature dendritic cells as hematopoietic niche components via CCL3 and thus generate additional niche space. Targets within the niche for MMCs are indicated.

Targeting soluble survival factors (cytokines and their receptors). Because several inflammatory cytokines also act as PC survival factors, therapeutic Abs directed against such cytokines modulate the milieu within the PC niche (Table III). The anti-BAFF Ab belimumab reduces anti-dsDNA, anti-Smith, anti-cardiolipin, and anti-ribosomal P autoantibodies, normalizes C3/C4 complement levels, and decreases the amount of naive and activated B cells and PCs, but it does not deplete memory B cells (57). As such, the fraction of anti-dsDNA Abs secreted by short-lived PCs (SLPCs) (58), whose numbers correlate with flares (12), is targeted by belimumab whereas the Ab titers against pneumococci, tetanus, and influenza representing LLPCs are not reduced (59). This underscores the necessity to block both compensating BCMA ligands, that is, APRIL and BAFF, to deplete LLPCs (8, 60). Thus, the novel TACI-Ig fusion protein atacicept, which binds APRIL and BAFF, might be a promising therapeutic option (Table III).

Targeting attachment (adhesion molecules). The anti–VLA-4 Ab natalizumab, originally generated to suppress the transmigration of activated leukocytes into inflamed tissues, is approved for the treatment of multiple sclerosis and dislocates PCs from their survival niche, leading to the depletion of autoreactive MPCs. Targeting both adhesion molecules VLA-4 and LFA-1 facilitates the reduction of LLPCs in the bone marrow (48).

Targeting the HNCs. The replacement of pathogenic LLPCs by protective PCs could further improve the therapy. Our data show that in mice the approach of combined vaccination and short-term manipulation of the HNC (stimulation of megakaryopoiesis by recombinant thrombopoietin) decreases the amount of pre-existing LLPCs and enlarges the pool of novel emerged protective MPCs (27). Nevertheless, in individuals with autoimmune disorders a booster immunization with live attenuated vaccines or strong adjuvants may lead to a bystander activation of autoreactive lymphocytes and to an increase of autoreactive cells and an enhancement of the autoimmune memory.

Malignant PCs

Multiple myeloma (MM) is characterized by osteolytic lesions and severe renal failure owing to elevated monoclonal Ig production through malignant PCs, so-called MM cells (MMCs). Furthermore, expansion of MMCs leads to progressive competition and replacement of the hematopoietic compartment in bone marrow (61). Survival of MMCs depends, similar to that of protective PCs, on antiapoptotic stimuli, such as IL-6, IGF-1, APRIL, and BAFF, with osteoclasts being a major source for APRIL and BAFF in MM (62). The receptors for APRIL and/or

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Table II. Plasma cell survival factors

Molecular Niche Components	Cellular Niche Components
Soluble factors	Mesenchymal origin
Chemokines and receptors	CAR cells
CXCL12 (SDF-1)– CXCR4	Hematopoietic origin
CXCL9/10/11–CXCR3	Basophils
Cytokines and receptors	Dendritic cells
APRIL and BAFF (BLyS)–BCMA	Eosinophils
IL-6–IL-6R	Macrophages
TNF-α–TNF-αR	Megakaryocytes
Membrane-bound factors	Monocytes
Adhesion molecules	Myeloid precursors
VCAM-1–VLA-4	Neutrophils
ICAM-1–LFA-1	Osteoclasts
Hyaluronan and fibronectin–CD44	
Miscellaneous	
CD93	
CD80/86–CD28	

BAFF (BCMA, TACI, and BAFF-R) are heterogeneously expressed on MMCs and could not be correlated with disease prognosis (63). Whereas TACI$^+$ MMCs respond to APRIL and BAFF stimulation, BCMA$^+$/TACI$^-$ MMCs only proliferate upon APRIL stimulation (63), reflecting the fact that BAFF has a 1000-fold weaker affinity for BCMA than APRIL. Furthermore, CD138 on PCs is an important costimulatory molecule for APRIL–TACI but not for BAFF–TACI or APRIL–BCMA signaling, as it harvests APRIL from the environment and presents it to TACI (63).

Moreover, gene expression profiles of MMCs (64, 65) and their niche (66) differ from those of protective PCs (e.g., in TRAIL and FAS expression, with both being important mediators of apoptosis).

Transendothelial migration and homing of MMCs is regulated by the CXCL12–CXCR4 axis (43), and VEGFR1$^+$ hematopoietic bone marrow cells initiate a premetastatic niche (67). Experimental removal of these VEGFR1$^+$ cells prevents tumor metastasis. MMCs aggressively modulate their microenvironment by inducing angiogenesis via VEGF-1 and attracting mesenchymal stem cells via CCL25 (Fig. 1C). Latter ones synthesize PC survival factors (IL-6, IGF-1) and counterbalance bortezomib-induced apoptosis (68). Additionally, MMCs attract HNCs such as osteoclast progenitors or immature dendritic cells (69) through secretion of chemokines such as CCL3 (MIP-1α) (70). Moreover, macrophages form a multicomponent niche with stromal cells and extend MMC survival compared with stromal cells alone (71). Via abundant expression of CD28, MMCs promote survival of CD80/86$^+$ myeloid cells in their microenvironment and stimulate IL-6 production in these cells (72). As a result, tight interactions of MMCs with CAR cells, HNC,

Table III. Current therapeutic treatments targeting the survival niche for PCs

Target in the Niche	Drug	Disease/Model	Therapeutic/Mechanistic Effect	Status
Migration				
CXCL12–CXCR4	AMD3100/NOX-A12 or CCX2066	MM, SLE	Increases mobilization into periphery and sensitivity to several antitumor drugs	AMD3100 plus G-CSF is FDA approved for MM (40)
CXCL12–CXCR4/7	CCX771/CXCL11	Tumor metastasis	Inhibits transendothelial migration 100-fold stronger than AMD3100	Exploratory study (42)
CXCL9/10/11–CXCR3	None applied	SLE	Reduces the severity of SLE in (CXCR3$^{-/-}$) MRL, but not in (CXCR3$^{-/-}$) NZB/W mice	Preclinical studies (44, 45)
CCL3–CCR1	CCX721	MM	Decreases tumor burden and osteolytic damage	Exploratory study (46)
Adhesion				
VLA-4	Natalizumab	MS, MM	Delays MS progression; inhibits and resolves attachment of MMCs, sensitizes MMCs to bortezomib; causes rare but fatal viral infections (PML)	FDA approved with restrictions for MS; preclinical study for MM (47)
VLA-4 plus LFA-1	Anti-VLA-4 plus anti-LFA-1 Abs	Healthy mice	Depletes LLPCs from the bone marrow	Preclinical study (48)
Angiogenesis				
VEGF	Bevacizumab	MM	Improves outcome when combined with chemotherapy; rising numbers of bevacizumab-resistant tumors	Phase II trial for MM (49)
Cytokines				
BAFF (BLyS)	Belimumab	SLE	Reduces autoantibodies, naive and activated B cells, and PCs but not memory B cells and LLPCs	FDA approved for SLE
APRIL plus BAFF	Atacicept	RA, MM, SLE	Slows progression of MM; reduces levels of Ig and rheumatoid factor	Phase II trials for RA (50, 51); phase I trial for MM (52); phase II/III trial for SLE (NCT00624338)
IL-6	Siltuximab (CNTO 328); sirukumab (CNTO 136)	MM	Enhances cytotoxic effect of dexamethasone and bortezomib	Preclinical study (53); open trial/healthy induced (54)
IL-6R	Tocilizumab	RA, SLE	Clinical and serological improvement of the disease	FDA approved for RA; phase I trial for SLE (55)
HNC				
Osteoclasts	KRN5500	MM	Induces cell death in MMCs and osteoclasts, reduces bone destruction	Preclinical study (56)

FDA, U.S. Food and Drug Administration; MS, multiple sclerosis; PML, progressive multifocal leukoencephalopathy; RA, rheumatoid arthritis; SS, Sjögren's syndrome.

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endothelial cells, and the surrounding extracellular matrix leads to the so-called cell adhesion–mediated drug resistance.

Current treatment strategies for MM, detailed elsewhere (70, 73), depend on age, secondary diseases, tumor stage, and progression. High-dose chemotherapy and subsequent autologous or allogenic stem cell transplantation is often advised. Additional treatment strategies addressing the interaction between MMCs and their survival niches may improve outcome by enhancing the primary therapy and reducing severe adverse effects (70).

Inducing dislocation and targeting migration. G-CSF mobilizes hematopoietic stem cells (HSCs) and causes evasion of SLPCs and LLPCs from bone marrow (74). Also, AMD3100 dislocates MMCs from their survival niche and renders them more sensitive to therapy (40). Combinatory therapy with G-CSF and AMD3100 results in augmented HSC mobilization compared with G-CSF treatment alone and has been approved by the U.S. Food and Drug Administration for treating MM (75).

Targeting attachment. The adhesion molecule CD44 is synthesized by MMCs in alternative variants (e.g., CD44v3, v6, v9), which differently stimulate IL-6 production in stromal cells. CD44 variants are associated with tumor progression and prognosis (e.g., CD44v6$^+$ frequency: 6% monoclonal gammopathy of unknown significance, 17% MM stadium I, 43% MM stadia II/III) and are promising targets in MM treatment (76). Furthermore, interfering with VLA-4–mediated adhesion inhibits accumulation of MMCs, disrupts binding of MMCs, blocks VEGF-induced angiogenesis, and increases sensitivity of MMCs to bortezomib (47).

Soluble survival factors (cytokines). The anti–IL-6 Ab siltuximab (CNO328) synergizes with dexamethasone and bortezomib, and it improves outcome in MM with only few adverse effects (56). APRIL and BAFF, whose serum levels in MM patients are 5-fold elevated compared with healthy donors, partially prevent MMCs from dexamethasone- and anti–IL-6-induced apoptosis. Deprivation of APRIL and BAFF by TACI-Ig consequently increases the efficiency of dexamethasone and anti–IL-6 treatment, and it eliminates nearly all MMCs in culture (62). Moreover, atacicept reduces the amount of MMCs in the bone marrow and slows disease progression in 82% of patients with relapsed/refractory MM (77).

Hematopoietic niche components. The spicamycin analog KRN5500 causes stress in the endoplasmatic reticulum and induces apoptosis in MMCs and osteoclasts in vitro and in vivo. Reduction of osteoclasts as important HNCs is a valuable feature of KRN5500 treatment (53).

Allergen-specific PCs

Allergen-specific IgE Abs contribute to the pathogenesis of type I hypersensitivity. Independent of allergen presence, IgE Ab titers persist for years, indicating that humoral allergologic memory is formed by LLPCs (78). Additionally, basophils and mast cells, loaded with IgEs on FcεRI, can provide allergologic memory for weeks, even in the absence of PCs and soluble IgE, although for stable memory IgE supply is necessary (79). Recently, it was demonstrated that inhalation of the potent Ag OVA leads to the accumulation of IgG, IgA, and IgE LLPCs in the bone marrow and lung (21). However, the number of IgE LLPCs is lower than those of other Ig classes according to worse migratory capabilities of IgE PCs in the competition for the survival niche (80). Nevertheless, life-threatening anaphylactic reactions in patients with severe forms of allergy are still a tremendous risk. For curative treatment, the elimination of both immediate effectors and allergologic memory would be essential (78). Assuming that IgE LLPCs also depend on survival factors and an intact niche (78), they are susceptible to niche-targeted therapy. However, because few LLPCs are sufficient to load basophils and mast cells with pathogenic IgEs, only partial reduction of LLPCs may not gain improvement.

Conclusions

A supportive microenvironment that supplies soluble and membrane-bound survival factors is essential for the persistence of protective and pathogenic PCs. In autoimmunity, malignancy, and allergy, long-lived memory PCs are protected by their survival niche against most conventional immunosuppressive treatments and maintain a pathogenic Ab titer or in MM a malignant clone that may enable and accelerate the relapse or progression of the disease. Therefore, the survival niche for pathogenic PCs represents an important therapeutic target. The molecular characterization of the PC survival niche and the discovery of a dynamic HNC unveiled potential therapeutic targets for the treatment of PC-associated diseases. Whether alternative niches with different HNCs provide distinct niches for specific PC subpopulations remains an interesting question for future research, especially when considering novel strategies for selective depletion of pathogenic PCs.

Disclosures

The authors have no financial conflicts of interest.

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