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Targeting plasma cells in systemic autoimmune rheumatic diseases – Promises and pitfalls

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ABSTRACT

Plasma cells are the antibody secretors of the immune system. Continuous antibody secretion over years can provide long-term immune protection but could also be held responsible for long-lasting autoimmunity in case of self-reactive plasma cells. Systemic autoimmune rheumatic diseases (ARD) affect multiple organ systems and are associated with a plethora of different autoantibodies. Two prototypic systemic ARDs are systemic lupus erythematosus (SLE) and Sjögren's disease (SjD). Both diseases are characterized by B-cell hyperactivity and the production of autoantibodies against nuclear antigens. Analogues to other immune cells, different subsets of plasma cells have been described. Plasma cell subsets are often defined dependent on their current state of maturation, that also depend on the precursor B-cell subset from which they derived. But, a universal definition of plasma cell subsets is not available so far. Furthermore, the ability for long-term survival and effector functions may differ, potentially in a disease-specific manner. Characterization of plasma cell subsets and their specificity in individual patients can help to choose a suitable targeting approach for either a broad or more selective plasma cell depletion. Targeting plasma cells in systemic ARDs is currently challenging because of side effects or varying depletion efficacies in the tissue. Recent developments, however, like antigen-specific targeting and CAR-T-cell therapy might open up major benefits for patients beyond current treatment options.

1. Introduction

Plasma cells are terminally differentiated B-cells and often described as antibody factories. Their intracellular compartments are specialized on mass protein production and distribution that makes their appearance fundamentally different to that of their B-cell precursors [1]. During plasma cell differentiation B-cells undergo many morphological, transcriptional and metabolic changes to become a functional plasma cell [2–5], that can persist and secrete antibodies for timespans between days and decades [6–8]. This long lifespan presumably also applies to autoreactive plasma cells that secrete potentially pathogenic antibodies targeted against self-antigens [9–11].

A plethora of different autoantibodies can be found in various systemic autoimmune rheumatic diseases (ARD). Systemic lupus erythematosus (SLE), Sjögren's disease (SjD), rheumatoid arthritis (RA) and systemic scleroderma (SSc) are ARDs with systemic manifestations and organ involvement that supposedly share common mechanisms of B-cell alterations with similar outreach into the plasma cell compartment. However, these four diseases typically show differences in the organ that is most affected, namely joints, skin and exocrine glands in RA, SSc and SjD, respectively, while SLE can affect almost every organ. Depending on the organs affected, systemic ARDs can manifest cardiovascular, renal, cerebral, pulmonal, cutaneous, musculoskeletal or glandular complications [12–17]. While clinical phenotypes differ, shared underlying mechanisms for these systemic ARDs include the disturbance of immune tolerance leading to autoimmune reactions against nuclear and/or cytoplasmic self-antigens [18]. Autoreactive immune cells, including B- and T-lymphocytes, contribute to systemic

Abbreviations: APRIL, a proliferation-inducing ligand; BAFF, B-cell activating factor; BCMA, B-cell maturation antigen; BLIMP1, B lymphocyte-induced maturation protein-1; CD, cluster of differentiation; CXCR/L, cysteine-X-cysteine chemokine-receptor/-ligand; HLA, human leukocyte antigen; IL, interleukin; MALT, mucosa-associated lymphoid tissue; MHC, major histocompatibility complex; NFκB, nuclear factor kappa-light-chain-enhancer of activated B-cells; SSA/B, Sjögren's-syndrome-related antigen A (Ro)/B (La); TACI, transmembrane activator and CAML interactor.

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abnormalities and initiate local, inflammatory processes that may lead to tissue destruction [19–21]. B-cell abnormalities are present in many ARDs and are for example reflected by altered distribution of peripheral B-cell subsets [22–24], lowered B-cell activation thresholds and increased risk of B-cell transformation into lymphomas [25]. Increased levels of serum IgG antibodies and various types of self-directed autoantibodies are often considered part of these B-cell abnormalities. Consequently, B-cell-targeted therapies have been widely explored as a treatment option for systemic ARDs. However, most B-cell therapies do not directly affect plasmablasts and plasma cells (often jointly referred to as antibody-secreting cells), the cells which are solely responsible for antibody secretion. For the purpose of simplicity, this review will refer to all antibody-secreting cells as plasma cells.

This review will focus on the special characteristics of plasma cells, their subsets, what is known about their role in systemic ARDs, particularly SLE and SjD, and the promises and pitfalls of plasma cells as target population for treatment.

2. Who? – The origin of plasma cells

2.1. The origin of B-cells

B-cells originate in the bone marrow from hematopoietic stem cells (summarized in [26]). B-cell lymphopoiesis involves rearrangements of *variable, diversity* and *joining* genes that leave every B-cell with a unique B-cell receptor (BCR) out of 100 billion possible different specificities [27]. Given the mostly random nature of these rearrangements, many newly generated B-cells show capabilities to bind self-antigen [28]. To contain this autoreactive potential, central and peripheral tolerance checkpoints exist that remove autoreactive cells from the B-cell pool or induce an anergic state resulting in unresponsive autoreactive B-cells [29–31]. Tolerance mechanisms reduce the frequency of autoreactive B-cells from ~75% in the early stages to 10–20% in mature B-cells in healthy individuals [18,28,32,33].

2.2. Differentiation of B-cells into plasma cells

After their full maturation into naïve B-cells, antigen-specific activation can induce differentiation of B-cells into plasma cells. The nature of the antigen, BCR affinity, co-stimulatory signals during B-cell activation, and the B-cell subtype influence how B-cells differentiate towards plasma cells and might also affect the long-term fate of the resulting plasma cells. This differentiation can either be directly at extrafollicular sites, or indirectly after participation in germinal center reactions (overviewed in [34–40]).

Extrafollicular plasma cell formation occurs after BCR crosslinking and either toll-like receptor (TLR) engagement as additional signal and/or co-stimulation by T-cells. TLR signaling upregulates the TACI receptor, binding the two important B-cell cytokines BAFF and APRIL that induce isotype switching in synergy with BCR and TLR engagement [41]. Consequently, TACI engagement is necessary for adequate IgM and IgG responses against repetitive antigens (e.g., carbohydrate antigens) binding to the BCR, but to which T-cell cannot provide co-stimulation [42]. Elevated BAFF levels might therefore drive especially extrafollicular B-cell responses. In T-cell dependent responses, PD-1^{+}CXCR5^{-} peripheral or PD-1^{+}CXCR5^{+} follicular helper T-cells (T_{PH} or T_{FH}, respectively) can stimulate class switching and plasma cell differentiation outside or inside of follicles [43–45]. Different types of extrafollicular T_{PH} cells have been reported with different mechanisms (IL-21-dependent or -independent) to support plasma cell differentiation [46,47]. Plasma cells derived from extrafollicular responses are often short-lived and mainly secrete IgM or IgG depending on the presence of class switching signals and cellular origin (reviewed in [38]).

Germinal centers are highly organized structures that contain mainly B-cells, T_{FH}-cells and follicular dendritic cells (FDC) (see [48,49] for an overview). Germinal center B-cells rapidly proliferate and express activation-induced deaminase (AID), an enzyme that is responsible for somatic hypermutation in the variable antibody region and isotype switching [50,51]. B-cells compete for antigen presented by FDCs and subsequently present the acquired antigen in the context of MHC class II molecules to obtain stimulatory signals from T_{FH}-cells [52–54]. Several rounds of mutation and selection raises the average B-cell affinity within a germinal center over time [55]. Higher antigen-affinities allow germinal center B-cells to take up more antigen from the FDCs, herewith presenting more antigen to CD4^{+} T-cells, and consequently are able to receive more co-stimulatory signals than low-affinity germinal center B-cells [56,57]. While germinal centers continuously generate memory B-cells [58,59], plasma cell differentiation requires higher antigen-affinities [60]. The germinal center B-cells with higher affinities receive more T-cell help, including stronger CD40 signaling. Only high levels of CD40 signaling induce high levels of interferon-regulatory factor 4 (IRF4) and subsequently Blimp1 [57], two important plasma cell transcription factors. Germinal center reactions frequently give rise to long-lived plasma cells, especially during late phases of immune reactions, that mostly produce IgG antibodies [58].

A classical immune reaction, e.g., towards pathogens or vaccinations, that initiates extrafollicular and germinal center derived plasma cell generation, produces a fast initial peak of antibodies for 2–4 weeks. While antibody levels typically decline to ~10% of the peak antibody response within months [61,62], it can then remain stable over decades [63]. Animal studies showed increased probability of long-lived plasma cell generation at the late stage of an immune reaction around a month after antigen exposure [64] corresponding to stable long-term antibody titers after vaccination in humans [65,66].

2.3. Tolerance during plasma cell differentiation

To protect the body from autoimmunity, autoreactive B-cells participating in germinal center reactions are prone to lose self-binding capacity gradually due to somatic hypermutations [67]. However, somatic hypermutation can also lead to *de novo* autoreactivity during germinal center reactions. Studies with monoclonal autoantibodies from B-cells and plasma cells from SLE or RA patients, respectively, revealed that reversion of the mutated configuration to their respective germline configuration led to reduced or lost binding capacities in at least a proportion of the tested autoantibodies [68,69]. In addition, defects of germinal center exclusion may exist in systemic ARDs [70–72]. In healthy individuals, B-cell autoreactivity is lower in post-germinal center cells, since lower frequencies of anti-nuclear antibody (ANA) reactive cells are observed in IgG memory compared to naïve B-cells in healthy controls [33]. This is likely regulated by T-cells, since T-cell help is required for proper germinal center B-cell responses. T-cell tolerance mediated by negative selection in the thymus during T-cell development is generally considered to be more stringent than for B-cells. Germinal center B-cells are additionally inhibited by follicular regulatory T-cells [73]. This concept of cognate antigen recognition by B- and T-cells serves as additional autoreactivity checkpoint in germinal centers [29].

2.4. Establishing the plasma cell identity

Plasma cells have a unique phenotype largely dedicated to protein production, including enlarged overall cell size, mitochondrial mass, endoplasmic reticulum (ER) and Golgi structures in comparison to their B-cell precursors [74,75] (Fig. 1). This plasma cell identity is induced and maintained by three main transcription factors: IRF4, already up-regulated in plasma cell precursors due to CD40 engagement [76,77], Blimp1, induced by IRF4 and cell division [78,79], and X-box binding protein 1 (XBP1), increased in response to ER protein overload [80,81]. IRF4 and Blimp-1 are both required for plasma cell differentiation. Additionally, IRF4 is required for maintenance of the plasma cell phenotype [82], whereas Blimp-1 and XBP-1 are important for the secretory function [83,84].

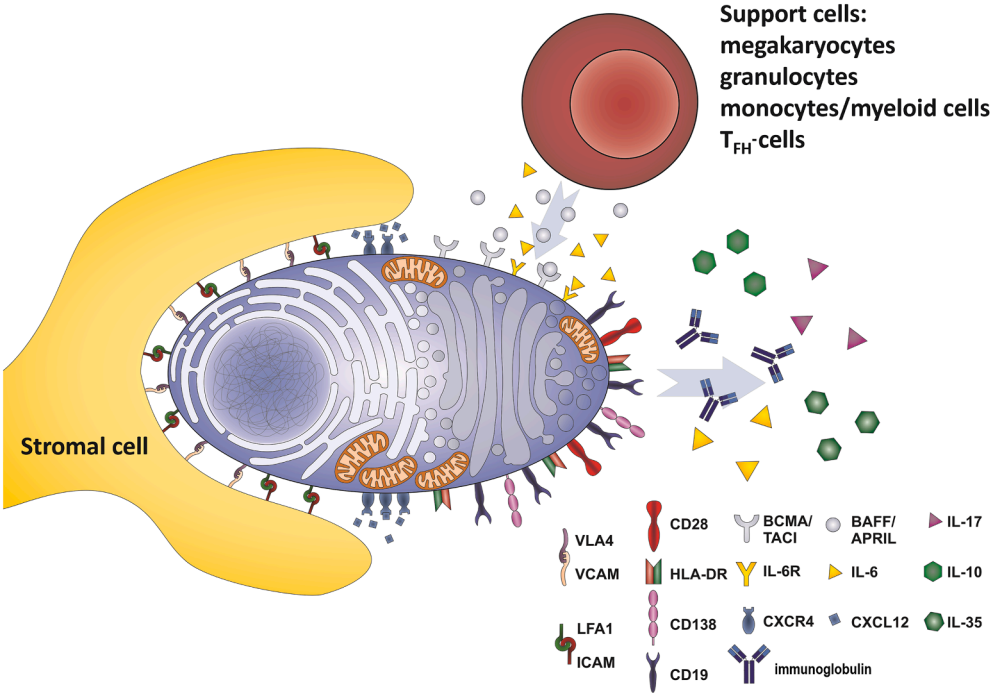

Fig. 1. Steady-state plasma cell niche. Stromal cells in bone marrow, spleen or other secondary lymphoid organs can from a long-term niche for plasma cells by providing integrins like VCAM and ICAM as ankers and cytokines like CXCL12. Additional support cells that may leave and rejoin the niche environment produce pro-survival factors for plasma cells like IL-6, BAFF and APRIL (input arrow). In turn, plasma cells facilitate long-term secretion of antibodies and cytokines (output arrow).

3. How? – Functions of plasma cells

3.1. (Auto)antibody secretion

The most well-known and dominant role of plasma cells is their capacity to produce antibodies. Since every plasma cell can produce up to 10,000 antibody molecules per second [85], the total plasma cell pool produces typically around 3–9 g IgA and 3 g IgG on a daily basis in healthy adults [86]. Some systemic ARDs like SLE and SjD are associated with increased total serum IgG levels (hypergammaglobulinemia), while RA and SSc show no IgG elevation or only in association with disease severity [87–89]). In general, it is thought that bone marrow plasma cells, with typically long-lasting lifespans, are the primary source of circulating antibodies [90], however, a specific location for long-term survival of autoantibody-producing plasma cells is not known yet. Both short- and long-lived autoreactive plasma cells are present in lupus mouse models, and in some mouse models, the spleen seems to represent a major source of autoreactive plasma cells [91]. Persistence of long-lived plasma cells additionally takes place in lymph nodes [92]. Increased numbers of circulating plasmablasts may also mirror autoantibody secretion in systemic ARDs [93–98].

3.2. Secretion of cytokines

Many studies show an important role of cytokine production by B-lineage cells. These cytokines can be pro- or anti-inflammatory, probably depending on the type of immune response or involved B-cell subsets (reviewed in [99]). Since plasma cells have a specialized machinery for protein production and secretion, it is conceivable that they can also produce high amounts of cytokines. Indeed there are plasma cells that produce high amounts of IL-10 and IL-35. These plasma cells are called regulatory plasma cells and are defined by expression of lymphocyte-activating gene 3 (LAG-3) [100]. These plasma cells can produce high amounts of IL-10 and IL-35 early during salmonella infection [101]. Likewise, IL-10 production by murine plasma cells has been shown in the context of experimental autoimmune encephalitis [102]. Studies with human B-cells show that a broad spectrum of B-cells secrete IL-10, including plasmablasts, but these findings mostly rely on *in vitro* B-cell stimulation [103]. Other mouse studies suggested that murine plasma cells could be a major contributor to pro-inflammatory cytokine production, such as GM-CSF and IL-17 [104,105]. These studies should be interpreted with caution, as the plasma cell identity was not always unequivocally established. Nevertheless, it is likely that the type of cytokines produced by plasma cells depends on their stimulatory condition, e.g., due to a pro-inflammatory milieu. Functional studies into the specific role of cytokine production by plasma cells as opposed to total B-cells have not been reported to date. Therefore, it will be of interest to determine the relative contribution of plasma cells to pro- and anti-inflammatory cytokine production in health and disease.

4. When & where? – Maturation of plasma cells and the niche concept

4.1. Current assessment of maturity

The life-span of plasma cells has an enormous range from days to decades [8,106]. But the definition of markers that reflect their maturity and the potential lifetime of a plasma cell has been challenging. By distinguishing newly generated vaccine-specific plasmablasts and previously present plasma cells with non-vaccine specificity, a decrease in CD19, CD45 and MHCII but an increase of B-cell lymphoma protein 2 (Bcl2) and Blimp1 in plasma cells could be observed [107–109]. Additionally, Ki-67 is a common proliferation marker that identifies recently generated plasmablasts [109,110]. CD138 is part of murine plasma cell identification, because CD138 is expressed by all murine plasma cells [111]. However, human plasma cells are usually defined as $CD27^{+}CD38^{high}$ cells, also including plasmablasts, while excluding other immune cell markers like CD3, CD14 and/or CD16 [112]. Expression of CD138 is found on a proportion of circulating human plasma cells and the presence of CD138 is associated with other markers reflecting plasma cell maturity (e.g., lower CD20, CD45 or surface Ig expression), when compared to $CD138^{-}$ plasma cells [110]. In mice, CD138 provides survival advantages for plasma cells by enhancing the utilization of pro-survival cytokines like IL-6 and APRIL [113]. Human CD138 has presumably similar functions, but also participates in cellular adhesion and migration (reviewed in [114]).

CD19 or CD138 alone or in combination are widely used to describe subtypes of plasma cells based on their maturity [7,109,115]. Stratification of bone marrow plasma cells using CD19 and CD138 revealed long-term antibody specificity against tetanus and measles only in $CD19^{-}CD138^{+}$ plasma cells, while $CD19^{+}CD138^{+}$ plasma cells contained influenza-specific cells and tetanus-specific cells just after a recent vaccination [115]. A study on $CD27^{+}CD38^{+}$ plasma cells in the duodenum used CD19 and CD45 to divide plasma cells into early ($CD19^{+}CD45^{+}$), intermediate ($CD19^{-}CD45^{+}$) and late ($CD19^{-}CD45^{-}$) stages. In line with their long lifespan, the frequency of late stage plasma cells increase with age within the duodenum whereas they were barely detectable at those sides in individuals younger than 20 years. Radioactive carbon (^{14}C) dating indicated a median lifespan of late stage plasma cells of 22 years and high expression of CD28, CD56 and Bcl2 in this subset [7].

On the contrary, a study investigating vaccine-specific plasma cells found that $CD19^{+}$ plasma cells contain cells specific for the eradicated vaccinia/smallpox virus [116]. Furthermore, circulating $CD19^{-}$ and $CD19^{+}$ plasma cells survived equally well *in vitro*. Those findings suggest that both subsets may have equal long-lived potential, and that it might be challenging to predict plasma cell survival based on CD19 expression [117,118].

4.2. A novel composite maturity index

Recently, we proposed a new methodology of assessing plasma cell maturity by combining four markers that were previously suggested to be regulated dependent on the maturity of plasma cells: CD19, HLA-DR, CD138 and CD28 [7,9,109,115]. To avoid a strict positive/negative cut-off approach, a continuous expression spectrum of those four markers by plasma cells was mapped by utilizing median fluorescence intensity values obtained by flow cytometry. Maturity ranks were assigned for the four markers individually and for each sample relative to the expression spectrum in the whole test cohort. By calculating the mean of those maturity ranks, a single plasma cell maturity-dependent value termed 'maturity index' was obtained [119]. Applying this novel approach to RNA-sequencing data of *in vitro* differentiating B-cells into plasma cells [120] showed a time-dependent increase of the maturity index. In a second validation attempt using a human blood plasma cell transcriptome dataset [75], a stepwise increase of the maturity index from $CD19^{+}CD138^{-}$ and $CD19^{+}CD138^{+}$ to $CD19^{-}CD138^{+}$ bone marrow plasma cells and a lower maturity index for blood plasma cells was observed [119].

Applying the newly developed maturity index to a cohort of Sjögren's disease patients revealed a correlation of the maturity of circulating plasma cells with pro-inflammatory CXCR3 expression on plasma cells but also with increased salivary gland infiltration and ANA titers [119]. Using this novel maturity index to assess plasma cell maturity in systemic ARDs might identify patient subgroups that can benefit from specific mature or immature plasma cell targeting approaches. However, this proposed method currently uses bulk plasma cell metrics ignoring plasma cell heterogeneity and lacking comparability amongst different data sets. Therefore, a refined approach should take single plasma cell values into account and tackle inter-sample comparability along with further validation in larger study groups.

4.3. Steady-state plasma cell niches

Circulating but also tissue-resident plasma cells quickly die *in vitro* [121,122] despite their ability to achieve decade long lifespans *in vivo* [6,7]. The current lack of reports on plasma cell culturing techniques that keep plasma cells alive over month or years [118,122], suggest a complex mechanism of *in vivo* plasma cell survival that involves both plasma cell-intrinsic (e.g., CD138, CD28, and BCMA) and extrinsic factors. These factors cooperate in so-called plasma cell niches, tissue locations where plasma cells reside and survive for long time periods (Fig. 1). This plasma cell niche usually involves an epithelial-like cell that is in direct contact with the plasma cell via integrins (reviewed in [5,80,123]). In the bone marrow, these niche-providing cells are stromal cells [122,124] that express vascular cell adhesion molecule (VCAM) and intercellular adhesion molecule (ICAM) integrins and CXCL12 to induce pro-survival signals in plasma cells [121,125]. Laminin ß1^{+} stromal cells are important specifically for IgG plasma cell niches in the bone marrow as seen in a *Salmonella* infection model [126].

Another important part of plasma cell niches are additional supporting cells that secrete pro-survival factors for plasma cells like APRIL and IL-6. This function was shown for basophils [127], megakaryocytes [128], dendritic cells, macrophages [129] and myeloid precursor cells [130]. Since those cell types have high turnover rates, their support function is likely transient and highly redundant. Additional redundancy exists between APRIL and BAFF [131], but the receptor with highest affinity for APRIL, BCMA, is fundamental for plasma cell survival while TACI and BAFF-receptor are dispensable [132].

Long-term plasma cell persistence and similar niche structures are described for lymph nodes [92], spleen [91], and mucosal tissues including tonsils and salivary glands [133–137]. Especially IgA plasma cells can persist in the long-term at mucosal sides (reviewed in [136]), thereby relying on mucosal specific markers like CCR9 and integrin α4ß7 to maintain their localization [138]. Healthy murine skin is another example of an alternative plasma cell niche hosting IgM^{+} plasma cells, but with yet unclear lifespan of those cells [139].

Though both intrinsic and extrinsic factors described above are required for survival of plasma cells, it is still unclear whether and how intrinsic factors for long-term survival are imprinted during plasma cell differentiation. Long-term plasma cell survival could also be a stochastic process. In that case, equally generated plasma cells would die at a random timepoint within their potential lifespan, resulting in short- and long-lived plasma cells. Subsets of circulating plasma cells have similar survival potential *in vitro* and share extensive clonal overlap [118] indicating those cells might have comparable survival imprinting. Likewise, it is unclear whether the maturation state of the plasma cells reflected by different markers (see Section 4.1) mirrors solely the kinetic of plasma cell differentiation or also predicts long-lived potential.

4.4. Induced de novo plasma cell niches in inflammation

Besides systemic, long-term secretion of protective antibodies, plasma cells also provide acute local immune protection at sites of inflammation. Local secretion of CXCL12 can attract $CXCR4^{+}$ plasma cells to inflamed tissues to provide on-site antibody production [96,140,141]. Plasma cells can also upregulate CXCR3, presumably in response to interferon γ [142] that enables their homing towards CXCL9–11, chemokines frequently expressed in inflamed tissue [143]. As a consequence, $CXCR3^{+}$ plasma cells are often described in inflammatory and autoimmune settings like infected skin [139], colitis [144], nephrotic kidneys [140] and arthritic synovium [145].

In addition to homing of plasma cells to sites of inflammation, several observations indicate the presence of long-lived plasma cells in inflamed tissues in *de novo* generated plasma cell niches, like clustered plasma cells in kidneys of SLE patients [146]. While salivary glands harbor IgA-specific cells as part of the healthy mucosal immune system [136,147], chronic autoimmune conditions like SjD shift the plasma cell composition towards IgG-specific [137] and autoantigen-specific cells [148]. Upregulation of integrins like αEß7 [149] or laminin ß1 on submandibular duct cells [150] in SjD patients indicate a possible expansion of plasma cell niches in this autoimmune environment. In addition, salivary gland epithelial cells express ICAM, VCAM and CXCL12 similarly to bone marrow stroma cells [151].

Targeting pathogenic long-lived plasma cells gives the potential of a long-lasting disease amelioration, but the lack of definitive maturity-specific markers that reflect the lifespan of plasma cells and the location of plasma cells within tissues are substantial challenges for their

effective depletion. Therefore, a detailed characterization of plasma cells in individual patients might be required, to target the most pathogenic plasma cell populations while sparing as many protective plasma cells as possible.

5. What? - Disease specific properties of plasma cells in systemic ARDs

Systemic ARDs like SLE and SjD share broad alterations of the immune system including B-cell hyperactivity [87,152–155]. A prominent consequence of this B-cell hyperactivity is the general increase in circulating antibody levels (hypergammaglobulinemia) [156–158], serum free light chains [159,160] and high titers of various autoantibodies that may overlap between the diseases. Another feature reflecting systemic inflammation is an interferon signature, which is commonly observed in systemic ARDs in association with B-cell hyperactivity [21,161,162]. Therefore, B-cell targeting therapies have been extensively studied in SLE and SjD.

SLE displays frequent inflammation of the skin and kidneys of patients, but many organs can be involved as well. The spectrum of disease manifestations is heterogeneous and the disease burden can range from mild to severe and switch between remission and flares with lupus nephritis among the most severe complications affecting a large group of patients (overviewed in [163–165]). SjD presents with characteristic inflammation of salivary and lacrimal glands including lymphocytic infiltration and organ damage that result in impaired tear and saliva production and the typical dryness symptoms [87]. Lymphocytic infiltrations in the glandular tissue, resulting in ectopic lymphoid tissues with germinal centers, a plasma cell isotype shift [166], B-cell driven hyperplasia of the epithelium (so-called lymphoepithelial lesions) [167] and an increased risk of B-cell lymphoma development, primarily of the MALT type, are histopathological hallmarks of the affected glands in SjD [168,169].

To date, treatment options for SLE and SjD are limited. In the case of severe organ manifestations, physicians rely on broad immunosuppression with traditional DMARDs (disease-modifying antirheumatic drugs) or rituximab, with variable efficacy. Although recently two targeted DMARDs have been approved for SLE, no DMARDs have been approved for SjD [170,171]. Plasma cell depletion approaches might open up novel treatment paths in both diseases. Hence we focus on plasma cell related similarities and differences in SLE and SjD that could be utilized for targeting.

5.1. Plasma cell related similarities between SLE and SjD

Multiple autoantibodies have been described in SLE and SjD patients with various ANAs, including anti-dsDNA, rheumatoid factor (RF), anti-SSA/Ro and anti-SSB/La antibodies (reviewed in [172,173]). Many of these antibodies can be present years before clinical symptom onset and diagnosis [174–176]. Anti-dsDNA and anti-Smith antibodies are thereby more specific for SLE, while SjD patients are frequently positive for anti-SSA and, to a lower extent, anti-SSB, rheumatoid factor or anti-muscarinic receptor antibodies [172,173]. Anti-dsDNA antibodies are considered pathogenic in SLE, while this is unclearly for other ANAs (reviewed in [177,178]). Animal studies indicate that anti-dsDNA antibodies can bind directly to mouse kidney glomeruli, and that monoclonal anti-dsDNA antibodies cause lupus nephritis [179]. In human disease, increases in anti-dsDNA antibodies frequently precede a disease flare [180–182]. For SjD, animal experiments indicate pathogenic properties of serum IgG from SjD patients by decreasing saliva production when injected into NOD.Igμ^{null} mice [183] and mice immunized with Ro/SSA-antigen show reduced saliva secretion [184]. In SjD patients, anti-Ro/SSA antibodies are indeed associated with impaired glandular functions [173].

SLE and SjD display overlapping B-cell alterations that influence plasma cell generation. B-cells from patients with SLE and SjD have lower activation thresholds and express increased levels of the DNA-sensing receptor TLR9 [185,186], enhancing their potential to form plasma cells, likely by extrafollicular reactions [187]. Since the most common autoantigens (e.g., ribonucleoproteins like SSA/Ro) in SLE and SjD can trigger the B-cell receptor and TLRs simultaneously [177], IgG isotype switching can also take place independent from T-cells [188]. Furthermore, CD27^{-}IgD^{-}CD11c^{+} double negative (DN2) B-cells are frequently involved in extrafollicular reactions and commonly increased in SLE and SjD and show higher TLR7 signaling [23,189,190]. DN2 B-cells are described as direct plasma cell precursor cells in healthy individuals as well as SLE patients [38,191,192]. In addition, ectopic lymphoid structures are also present in inflammatory environments like SLE kidneys and SjD salivary glands with fully organized germinal centers including B- and T_{FH}-cells, FDCs and AID expression (overviewed in [193,194]). T_{FH}-cells are significantly increased in blood and target tissue of patients with SLE and SjD likely supporting elevated germinal center activity and plasma cell output [43,195–197]. However, peripheral helper T_{PH}-cell frequencies (as the extrafollicular counterparts of T_{FH}-cells) and their different subtypes also correlate with plasma cells in SLE and SjD [43,46,47,198].

Taken together, a main question remains if autoantibodies primarily originate from extrafollicular or germinal center responses or both, as this might influence the lifespan of the corresponding plasma cells, and if both responses play different roles in systemic ARDs. An additional open question is whether tissue plasma cells immigrated from blood or differentiate locally either via extrafollicular or germinal center pathways.

5.2. Plasma cell abnormalities in SLE

5.2.1. Circulating plasma cells in SLE

The frequencies of total blood plasma cells (plasmablasts and long-lived plasma cells) in SLE patients correlate with disease activity [93,94,199]. An altered plasma cell transcriptome associates especially with musculoskeletal and renal disease [200]. ANA-reactive plasma cells are also expanded in the blood of many SLE patients, in a relatively stable frequency [201]. The total plasma cell population in SLE blood samples shows an altered phenotype, compared to healthy individuals, that includes increased expression of HLA-DR [202] and CD38 [203]. Abundance of newly generated HLA-DR^{high}CD27^{high} cells, likely representing plasmablasts, correlates to disease activity and anti-dsDNA antibody titers [202], indicating that plasma cell formation is an ongoing process. Treatment of SLE patients with the anti-CD20 antibody rituximab (with or without additional belimumab) decreased anti-dsDNA titers [178]. Since CD20 is expressed on plasmablasts, this argues for plasmablasts as a major population secreting anti-dsDNA autoantibodies. In addition, class-switched plasmablasts show low mutation rates [204] and increased TLR9 expression [205] in active SLE patients suggesting they might originate form extrafollicular activation.

5.2.2. Renal plasma cells in SLE

Renal involvement and nephritis are common and serious conditions in SLE [164]. While circulating autoantibodies can bind to exposed chromatin in kidney glomeruli [179], local infiltration of immune cells including plasma cells are commonly described in SLE patients [146,206]. Numbers of plasma cells in blood and kidney are higher in SLE patients with severe nephritis, compared to patients without nephritis [94]. A tissue transcriptome study in SLE patients reported kidney plasma cells to resemble a phenotype similar to long-lived bone marrow plasma cells after induction of standard treatment while untreated patients showed mainly plasma cells with genes upregulated in short-lived plasma cells [207]. This might suggest an impact of treatment on B-cell to plasma cell maturation that diminishes ongoing generation of plasmablasts while already generated plasma cells might continue to mature. These long-lived renal plasma cells might contribute to relapse of nephritis in some patients. However, an animal study using adoptive

transfer of long-lived plasma cells into lymphocyte deficient mice ($Rag1^{-/-}$) showed preferential homing of those cells to the bone marrow and spleen niches, with onset of nephritis with immune complexes and reduced survival after 20 weeks post transfer [208]. This indicates that the presence of plasma cells is not required for kidney malfunctioning, and that pathogenic plasma cells can be located outside the kidney. This is in line with findings of the accelerating medicines partnership (AMP) study, where no in situ differentiation of plasma cells in the kidneys of lupus nephritis patients was found [209].

5.3. Plasma cell abnormalities in SjD

5.3.1. Circulating plasma cells in SjD

We and others have shown that SjD patients have increased frequencies of plasma cells in peripheral blood, that might be associated with presence of anti-Ro/SSA antibody [210], lymphocytic salivary gland infiltrations (focus score) [95,119,210] or presence of lymphoepithelial lesions [119]. T_{FH}-cell numbers in blood [211] and salivary glands [197] are elevated in SjD patients. This might explain higher plasma cell frequencies, since T-cells from SjD patients also show increased capabilities to induce a plasma cell phenotype when cultured with B-cells [212]. Circulating plasma cells in SjD patients also display a more mature CD19-negative phenotype [95,119] that remains stable even after an immune stimulus like a vaccination [22]. Since rituximab only moderately lowers anti-SSA serum levels [213–215], the majority of those antibodies might either originate from long-lived plasma cells or rituximab-resistant plasmablasts in tissues (see Section 6).

5.3.2. Glandular plasma cells in SjD

SjD is a systemic condition, but the salivary glands are the main inflammatory hotspot. Plasma cells are part of normal mucosal immunity in salivary glands [136], but in SjD patients the isotype composition change from IgA dominance towards a higher frequency of IgG plasma cells [96,137], called plasma cell shift [166,216]. These IgG plasma cells are either the result of infiltration [217], local generation, likely in association with the amount of lymphocytic infiltrates or both [96,217]. Local production of autoantibodies against SSA/Ro and SSB/La antigens was shown for all Ig isotypes [148]. A notion that plasma cells in the salivary gland of SjD patients are located in the vicinity of CXCL12- and IL-6-producing cells might indicate the formation of *de novo* plasma cell niches in SjD [96] either additional to the physiologic IgA plasma cell niche or in competition with it. An animal model of SjD suggests the accumulation of long-lived, none-dividing plasma cells in salivary glands of NOD.B10.H2b mice during the progression of the disease [218], further indicating the potential development of survival niches in salivary glands.

5.3.3. B- and plasma cell derailment in SjD

A prominent result of B-cell hyperactivity in SjD is lymphoma development, especially of the MALT type (reviewed in [168]). High focus scores and rheumatoid factor (reviewed in [162]) but also monoclonal gammopathy of undetermined significance (MGUS) are risk factors for developing lymphoma [169,219]. Although MGUS is rare in SjD with a prevalence of 1.5% [220], SjD elevates the risk for its development [221]. Additionally, MGUS is considered as a potential precursor of multiple myeloma (MM) and SjD patients with MGUS show indeed a higher risk for MM development [219]. In general, SjD patient have a higher risk to develop MM [221,222] that further increases for patients positive for anti-SSA/Ro and anti-SSB/La antibodies [222]. Increased MM development might be an additional indicator of pathogenic, plasma cell-intrinsic abnormalities in SjD.

6. What to do? - Options for plasma cell targeting

Multiple therapeutic strategies directed at B-cells have been approved or are currently under evaluation for the treatment of systemic ARDs. B-cell-targeted therapies can also affect the plasma cell compartment (particularly plasmablasts), by depletion of plasma cell precursors (e.g., rituximab – anti-CD20), inhibition of plasma cell differentiation (e.g., belimumab - anti-BAFF, atacicept - anti-BAFF/APRIL), or both (e.g., ianalumab - anti-BAFF-receptor). These therapies generally do not affect long-lived plasma cells, as shown for rituximab [223,224], which could partially explain the low rates of efficacy for most of the B-cell-targeted therapies in SLE and SjD. Direct inhibition of (autoreactive) plasma cells might be an alternative therapeutic approach to attenuate disease (Fig. 2), in particular in patients with refractory disease after B-cell-targeting treatment. However, the design of plasma cell-targeted therapies has been challenging. Here, we outline different promises and pitfalls of possible approaches.

6.1. Proteasome inhibition

Newly produced proteins in plasma cells need to be folded correctly in the ER and misfolded proteins are degraded by the ubiquitin-proteasome pathway. Regulatory proteins, including cell cycle regulators, are also degraded via this pathway and proteasome inhibition consequently leads to the accumulation of cell cycle regulatory proteins causing higher sensitivity to apoptosis. Proteasome inhibition also blocks NFκB signaling (reviewed in [225]), but NFκB activation is an important pathway for long-term plasma cell survival [121].

The first generation proteasome inhibitor bortezomib shows profound reduction of anti-dsDNA antibodies and total plasma cells by half in SLE patients. At the same time, protective vaccine-specific and total immunoglobulin levels in the serum were reduced by 25–30% [226,227]. Additionally, proteasome inhibition lacks plasma cell specificity, resulting in side effects. Bortezomib treatment, for example, increases the risk of neuropathy and cardiovascular events [228]. Although there are a couple of case reports on successful use of bortezomib in SLE and SjD patients [226,229], its safety profile seems unfavorable for wide application in patients with systemic ARDs.

6.2. Therapeutic antibodies

While conventional B-cell markers, such as CD19 and CD20, are downregulated at different stages of plasma cell maturation, other surface markers are upregulated [7,109]. These upregulated cell surface markers can be used for plasma cell depletion using therapeutic monoclonal antibodies. Examples of such therapeutic antibodies that have been used to target plasma cells, mostly in the context of multiple myeloma, are anti-CD38 (e.g., daratumumab [230]), anti-SlamF7 (elotuzmumab [231]) and anti-BCMA (e.g., belantamab [232]). Especially CD38 and SlamF7 are not selectively expressed by plasma cells, which could result in both advantages and disadvantages for the treatment of systemic ARDs. SlamF7 is also expressed by activated, naïve B-cells and DN2 B-cells as shown in SLE patients [23], and targeting these cells along with plasma cells may be beneficial. However, simultaneous targeting of other CD38- or SlamF7-positive immune cells may be less desirable (e.g., regulatory B- and T-cells in the case of anti-CD38 [230] and natural killer cells in the case of anti-SlamF7 [233,234]). BCMA expression is more specific to plasma cells than CD38 or SlamF7 and has been applied in the field of MM as antibody-drug conjugate, together with a cytotoxic agent (monomethyl auristatin F) [232], or as part of an anti-BCMA/CD3 bispecific antibody that directly engages T-cells to stimulate killing of neoplastic plasma cells [235]. Since BCMA targeting focuses more on long-lived plasma cells due to its expression pattern, it has to be clarified whether pathogenic plasma cells originating from sources like extrafollicular responses, with potentially shorter lifespans, are sufficiently addressed by this approach in different systemic ARDs.

So far, clinical response on daratumumab treatment has been shown in cases of SLE patients mostly with refractory, life-threatening disease and treatment was well-tolerated [203,236], although anti-tetanus and total IgG antibodies were additionally reduced [203]. Daratumumab

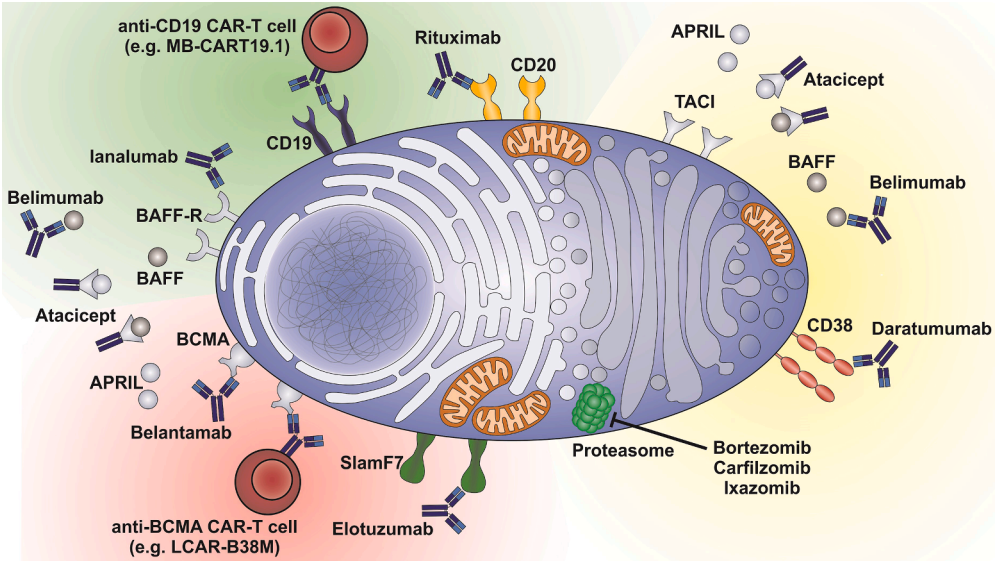

Fig. 2. Approved drugs with plasma cell-targeting potential. Overview of targetable proteins with decreasing (CD19, CD20, BAFF-receptor; green background) or increasing expression (BCMA, SlamF7; red background) during plasma cell maturation or present on all plasma cells (CD38, TACI, Proteasome; yellow background). Corresponding treatment options with clinically-approved therapeutics that have potential for targeting of plasma cells in systemic autoimmune rheumatic diseases are indicated. Monoclonal antibodies mediate antibody-dependent or complement-dependent cytotoxicity, CAR-T-cells directly deplete target cells, while proteasome inhibitors and APRIL/BAFF blockade interfere with survival signals.

efficiently depletes none-neoplastic plasma cells below detectable frequencies in MM patients [237]. Broad depletion implicates potential risks for patients with systemic ARDs, due to higher susceptibility to infections if also protective plasma cells are depleted.

6.3. CAR-T-cell therapy

Chimeric antigen receptor T-cell (CAR-T) therapy has shown great potential for the treatment of various malignancies. The working mechanism of CAR-T therapy include genetic modification of a patient's $CD8^+$ T-cells to express a modified antibody molecule as surface receptor (hence chimeric antigen receptor), which enables attachment to and killing of the target cell. An example of a plasma cell-specific antigen that has been used in CAR-T therapy for MM is BCMA [238], yielding almost complete depletion of plasma cells [239] and herewith a severe reduction of serum immunoglobulins in case reports [240]. In addition to the field of oncology, CAR-T therapy is also increasingly used in other diseases, including systemic ARDs. Anti-CD19 CAR-T-cell treatment of patients with refractory SLE resulted in drug-free remission with disappearance of B-cells from peripheral blood, improvement of clinical symptoms and normalization of serological parameters including conversion of anti-dsDNA and anti-Smith antibodies levels below detection limits [241]. The safety profile also seems favorable with only a mild cytokine-release syndrome in some of the treated patients. Another study using anti-CD19 CAR-T-cells reported efficient depletion of bone marrow plasma cells in children but not in adults [242]. Provided that plasma cells in children might not have had enough time to fully mature yet, this CD19 CAR-T-cell study would imply that mature plasma cells are spared from deletion. Therefore, anti-CD19 CAR-T-cell therapy might be a promising and effective approach for systemic ARDs with a dominant plasmablast and extrafollicular plasma cell component, but might have limited effects on diseases with higher contribution from long-lived (bone marrow) plasma cells. Also, high costs might restrain broad application of CAR-T therapy in patients with systemic ARDs.

6.4. Antigen specific targeting

To prevent depletion of protective plasma cells, an ideal strategy for autoimmune diseases would be a selective depletion of plasma cells based on their antigen specificity. Although such therapies have not yet been tested in humans, plasma cell depletion in an ovalbumin (OVA)-vaccinated mouse model using OVA-conjugated anti-CD138 antibodies resulted in a specific depletion of the majority of OVA-specific bone marrow plasma cells [243]. In principle, this anti-CD138/OVA conjugate binds to all plasma cells that express the respective CD138 marker, but only plasma cells that secrete OVA-specific antibodies opsonize their own cell surface. Following this, OVA-specific plasma cells are depleted by mechanisms similar to the use of therapeutic antibodies [244]. Whether antigen-specific plasma cell targeting can be applied in humans remains to be shown.

7. Perspectives

Plasma cells have been receiving increased attention over the last years as potential contributors to systemic ARDs with more reports covering plasma cell specific research questions. However, plasma cells can differ in lifespan and surface marker expression. Their decade-long survival potential and specialized tissue environments are beneficial traits for protective plasma cells but also raise the bar for efficient plasma cell depletion. Varying plasma cell lifespans and associated marker expression might require adapted targeting strategies potentially differing among systemic ARDs. Advances in oncology, especially in the treatment of multiple myeloma, have generated a broad toolbox of potential plasma cell treatments that are starting to be utilized in the field of systemic ARDs. Future studies on disease- and patient-specific plasma cell characteristics could open up additional and effective treatment options for patients that do not benefit from current treatment schemes.

Declaration of Competing Interest

G. M. Verstappen and F.G.M. Kroese are consultants for ArgenX. T.D. Steinmetz and J. Suurmond have no conflict of interest to declare.

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