Which B-cell subset should we target in lupus?

Gianfranco Ferraccioli,1 Frédéric A Houssiau2

The role of B-cells in the pathophysiology of lupus nephritis (LN) is suspected since decades. Amazingly, a report from 1977, aimed at describing the pathological characteristics of human LN described ‘proliferation of plasma cells (PCs) and plasmacytoid mononuclear cells’ in the spleen and the bone marrow (BM), but not in the kidneys.1

In murine lupus, Dixon’s group discovered that polyclonal B-cell activation was the first detectable immunological abnormality in all strains, which could be observed as early as after 2 weeks of age.2 Somewhat later, the same group postulated that murine lupus can be divided into two main types: type 1 murine systemic lupus erythematosus (SLE) (NZB/W and BXSB strains), characterised by primary B-cell hyperresponsiveness to B-cell growth and differentiation factors and type 2 murine SLE (MRL/lpr strain), characterised by T-helper cell hyperactivity and overproduction of B-cell growth factors by proliferating T cells.3 A step forward was the discovery by Talal’s group that besides polyclonal B-cell activation, a more restricted autoantibody response occurred with time, as suggested by a preferential use of some VH genes by certain MRL/lpr mice,4 thereby leading to further work demonstrating the presence of somatic mutations, affinity maturation and isotype switching as critical mechanisms of pathogenic anti-DNA antibody production in murine and human lupus.

PLASMACLASTS AND PCS

The production of autoantibodies depends on the capacity of activated and proliferating autoimmune B-cells to become autoantibody-secreting cells (ASCs). During this process, B-cells progressively lose their proliferating ability but increase their autoantibody production. Two types of ASCs have been described: plasmablasts (PBs) and PCs, the former being the precursor of the latter.5 PBs are CD19+ CD20− CD27+ CD38++ CD138+ highly proliferating IL-6-dependent cells, which have the capacity to migrate. PCs are CD19+ CD20− CD27+ CD38++ CD138+ non-dividing cells, which have lost their migration ability. The transition from B-cells to PBs and PCs is characterised by downregulation of transcription factors Pax-5 and Bcl-6 and upregulation of transcription factor Blimp1. Both PBs and PCs are short-lived but, if PCs find a niche in the BM (under normal conditions) or in inflamed tissues (under pathological conditions), they become long-lived PCs. The others die by apoptosis.

In NZB/W mice, PCs can be found in the BM, the spleen and in the kidneys, where they infiltrate the tubulointerstitial of the cortex and the outer medulla.6 Interestingly, 40% of spleen ASC in NZB/W mice are non-dividing long-lived PCs, which cannot be removed by immunosuppressive treatment and continue to produce autoantibodies.7 In human lupus, the numbers of circulating PBs and PCs are increased, commensurate with disease activity, as assessed by the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI).8 9 Moreover, PC infiltration was detected in the kidney of patients suffering from more severe renal disease, namely, Class III or IV LN (compared with Class II and V).10

KIDNEY STROMAL FACTORS AND PCS FATE

Stromal cells strongly interact with surrounding infiltrating cells (including those from the B lineage), in particular, by production of several growth factors. Thus, in multiple myeloma (MM), vascular endothelial growth factor, fibroblast growth factor-2 (FGF-2), stromal-derived factor-1 (SDF-1) and hepatocyte growth factor (HGF), all produced by stromal cells, promote MM cells migration.11 HGF is of importance in LN not only as a chemotactic molecule for PBs but also as an antagonist of the profibrotic effects of TGFβ1(transforming growth factor β1). Of interest in human SLE nephritis Peterson et al showed that immunoglobulin heavy (IgH)3 and light (IGL) chains transcripts (B cell signature) marked one of the clusters (cluster IV) and Lyn a Src-family kinase activated after B-cell receptor stimulation also had an increased expression. In addition, B cell transcripts expression correlated significantly with cellular crescents, fibrous crescents and chronicity index, yet TGFβ1 expression was decreased compared with controls, while no data were provided on HGF expression.12 In this respect, the balance between the expression of the two major cytokines, HGF and TGFβ1, on LN baseline biopsies, was found to predict short-term renal outcome after treatment with cyclophosphamide.13 The counterpart in NZB/W mice showed an increased expression of CXCR4 (a chemokine receptor, bindind CXCL12, expressed on PCs) and of Lyn, especially in the interstitium, thus mimoring B-cell findings in human nephritis.14 On the whole, these data indicate that the fate and function of PCs in the kidney result from a subtle equilibrium between resident cells, stromal-derived growth factors and the PCs themselves.

TARGETING PCS

Cheng et al15 used a novel model to demonstrate the role of long-lived PCs in murine LN. They adoptively transferred NZB/W spleen-derived ASCs (a 70/30% mixture of short-lived PBs/PCs) into Rag−/− mice (that lack the B-cell lineage) and followed their engraftment in the BM and the kidneys. They demonstrated: (i) that adoptively transferred PBs proliferated in the BM of Rag−/− mice during 2 weeks before becoming non-dividing long-lived PCs; (ii) that these long-lived PCs remained the only surviving transferred cells; (iii) that they continuously produced anti-dsDNA antibodies (more in the BM than in the spleen); (iv) that transferred mice developed immune complex nephritis and had reduced survival; and (v) that treatment with cyclophosphamide (a drug not targeting long-lived non-dividing PCs) was not efficacious in preventing LN. Although some methodological issues can be raised (such as a possible effect of contaminating B1 cells also known for their migratory capacity), the logical conclusion of these experiments is that long-lived PCs should be the target of therapy, a goal currently neither achieved by cytotoxic drugs nor completely by anti-CD20 blockade.

PERSPECTIVES IN HUMAN NEPHRITIS

Some preliminary evidence suggests that our armamentarium against long-lived PCs may well develop in the near future. First, bortezomib (BTZM), an inhibitor of the 26S proteasome, was shown to deplete long-lived PCs in lupus-prone mice by activation of the unfolded protein response and to ameliorate survival of...
Editorial

such strains (NZB/W and MRL/lpr), probably through prevention of podocyte damage and loss. Carfilzomib (another proteasome inhibitor) and BTZM were found to suppress the production of IFNa by TLR-activated plasmacytoid DCs, a purported critical event in the pathogenesis of lupus. Second, in NZB/W and MRL/lpr mice, a selective inhibitor of Janus Kinase 2 (JAK2), CEP-33779, was recently found to deplete ASCs and long-lived PCs defined as CD19−, CD45R/B220, CD138hi, CD38hi positive cells, with concomitant reduction of serum IL-12, IL-17A, IFNa, IL-1b and TNFa (25% and 35% of the patients), even years after treatment, in order not to miss a relapse. Toxicity such as nephrotic syndrome in murine lupus nephritis remains an issue, as targeting of T cells can not be expected to prevent glomerulonephritis.

Type 1–like LN will benefit the most by targeting long-lived PCs, while we have no data on whether targeting T cells can also lead to wipe out PC in kidney tissues. Targeting of long-lived PCs may become a goal in the clinic, in particular, in LN, where relapses are so common (between 25% and 35% of the patients), even years after the first renal insult, likely because of reactivation of a dormant long-lived PC located in the BM, the spleen or other niches, including the kidneys themselves. In this respect, more attention should be paid to the persistence of residual PCs in renal tissue before and after immunosuppressive treatment, in order not to miss a ‘PC window of opportunity’. Toxicity may however be an issue, as targeting of long-lived PCs will likely not be restricted to the autoimmune subset. A strict follow-up of Ig levels in nephritis patients with low immunoglobulin plasma levels will be necessary.

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Notes