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NEWS AND COMMENTARY

Extrafollicular origin of IgM autoantibodies

IgM autoantibodies: Roquin and Bob1ng to a different tune

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Pathogenic autoantibodies directed against ubiquitous self-antigens such as immunoglobulin-G (IgG) anti-double-stranded DNA (anti-dsDNA) antibodies in systemic lupus erythematosus are produced by plasma cells that have undergone immunoglobulin isotype switching and affinity maturation in the germinal centre (GC).[1] These autoantibodies form circulating immune complexes that are often deposited in the skin, kidneys and joints where they activate complement to cause tissue damage. In contrast, IgM (and IgA) natural autoantibodies are produced in the steady-state from birth by plasma cells derived from B1 cells, and are 'hardwired' to be polyreactive, low-affinity antibodies with relatively low pathogenic potential.[2,3] Nevertheless, IgM autoantibodies bound to antigen are still capable of activating the classical complement pathway and causing diseases such as autoimmune haemolytic anaemias due to cold agglutinins. In this issue, Corcoran and coworkers[4] remind us of this by showing that *sanroque* mice harbouring mutations in *Rc3h1/Roquin1* develop a GC-independent IgM-mediated autoimmune disease when crossed with mice deficient for the transcription factor *Obf1/Ocab/Bob1* (Figure 1). These IgM anti-dsDNA antibodies are deposited in the kidneys where they cause glomerulonephritis. This remarkable observation adds to the growing list of insights into the regulation of autoantibody responses in the *sanroque* ENU-mutant mouse model, which is characterized by excessive follicular T helper (T_{fh}) cell activity and spontaneous GC development.[5] Previous studies using this model have focussed on the role of specific genes and cellular interactions involved in the production of GC-dependent autoantibodies, such as the *Bcl6*, *Sh2d1a*, *Cd28* and *Icos*.[6,7] However, the current study neatly turns this on its head by showing that *sanroque* mice develop an even more severe fatal autoimmunity when *Obf1* is also deficient and they are unable to form GCs and secrete IgG autoantibodies. This unexpected finding is all the more intriguing given that *Obf1* deficiency by itself does not cause autoimmunity, and can also prevent the GC-dependent development of lupus-like autoimmune diseases in aged *Ailos*$^{-/-}$[8] and MRL-*lpr* mice.[9]

So what is driving autoimmunity in these double mutant mice? As OBF1-deficient B cells are unable to form GCs, it is likely that the IgM autoantibodies are produced by

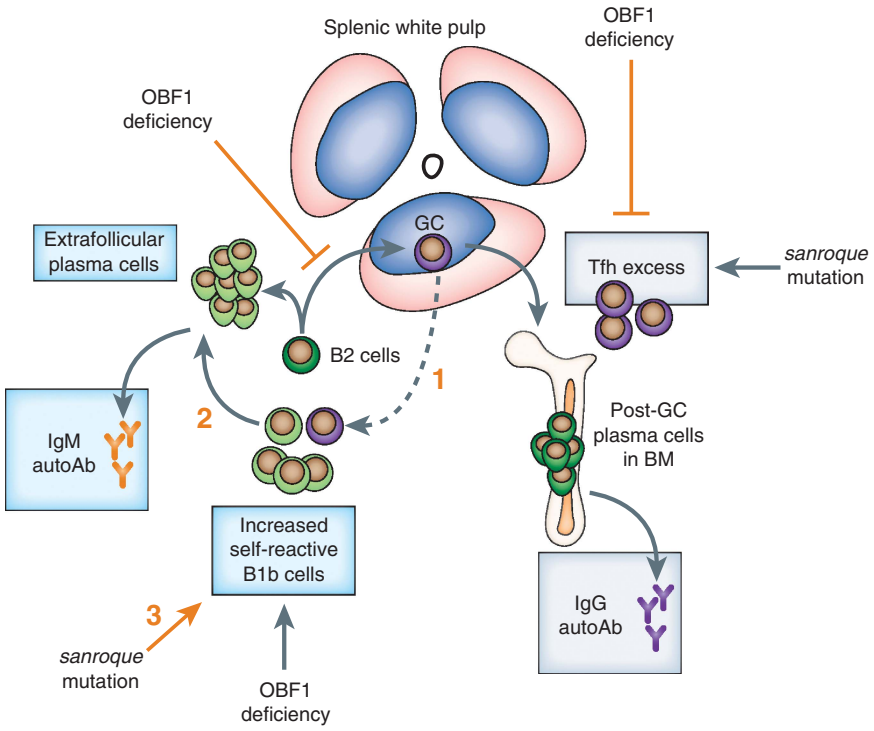

Figure 1 Possible mechanisms for IgM autoantibody production in *sanroque/Obf1*$^{-/-}$ double mutant mice. Double mutant mice are unable to form GCs, and T_{fh} cells are not expanded compared to *sanroque* mice. Thus, IgM autoantibodies are likely to be produced by low-affinity extrafollicular plasma cells derived from the expanded B1b cells rather than affinity-matured post-GC plasma cells. Corcoran and colleagues propose that this may be due to (1) excess soluble cytokines such as IL-5 produced by T_{fh} cells; (2) ectopic interactions between B1b and T_{fh} cells outside the GC; or (3) B-cell intrinsic, T-cell-independent effects of Roquin1 and OBF1 deficiency on the B cells.

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unmutated extrafollicular plasma cells rather than post-GC plasma cells that have undergone somatic hypermutation. These extrafollicular plasma cells may arise from either follicular B2 or peritoneal B1 cells. B1 cells are genetically encoded to express B-cell receptors with low level reactivity against a wide range of self and foreign antigens, including negatively charged phospholipids and nuclear antigens such as single-stranded DNA and dsDNA. Therefore, the types of polyreactive antibodies made by B1 cells are more likely to be detected by anti-dsDNA ELISA kits[10] than those made by monospecific B2 cells. In this regard, it would be useful to determine the affinity and avidity of the IgM anti-dsDNA antibodies by a more specific assay such as the Farr radioimmunoassay.[11] For these reasons, Corcoran and colleagues speculate that the expanded population of $CD5^-$ B1b cells observed in OBF1-deficient mice are the likely source of autoantibodies. Of note, B1b cells are capable of producing long-lived T-independent memory-like IgM responses against some bacteria[12] and it would be useful to see if the double mutant mice develop IgM autoantibodies when housed under germ-free conditions. Thus, it would also be of interest to determine whether the cells responsible for IgM autoantibodies in the current study are long-lived plasma cells or short-lived plasmablasts that are continuously replenished from the self-renewing B1b pool. Consequently, further examination of B-cell development in double mutant *sanroque/Obf1*$^{-/-}$mice with particular emphasis on the B1b cell compartment and the phenotype, localization and lifespan of the IgM autoantibody secreting plasma cells would be quite informative.

So what is the mechanism for the presumed B1b cell hyperactivity in the current study? While OBF1 deficiency may expand a B1b compartment harbouring self-reactive B cells, these B cells are unable to access the GC where the Roquin1 deficiency would enable overactive T_{fh} cells to promote their proliferation and differentiation into plasma cells. Corcoran and colleagues describe several possible scenarios to explain their data: (1) long-range effect of cytokines such as interleukin (IL)-5 secreted by T_{fh} cells into the serum; (2) ectopic interactions between B1b cells and T_{fh} cells outside of the GC, possibly in the circulation; or alternatively (3) compound effects of Roquin1 and OBF1 deficiency on the B1b cells themselves. As noted by the authors, these tantalizing possibilities are all falsifiable. IL-5 supports homeostatic proliferation and antibody secretion by B1 cells[13] and it would be useful to measure serum levels of IL-5 and other cytokines in the double mutant mice. In *sanroque* mice, the expanded T_{fh} compartment spills over into the peripheral blood[5] and it is conceivable that these cells may randomly encounter one of the expanded B1b cells in transit from the peritoneal cavity to the spleen. However, there does not appear to be a T_{fh} cell excess in double mutant mice. Notably, compound heterozygous mice with expanded T_{fh} cells and GCs do make IgM autoantibodies and appear to also develop glomerular IgM deposition. Nevertheless, it would be useful to analyse the peripheral blood, peritoneal cavity and spleen for B1b and T_{fh} cells in double mutant and compound heterozygous mice. Finally, breeding the double mutant mice onto a T-cell-deficient strain would address the possibility that the IgM autoantibodies are B-cell intrinsic and T-cell independent. Regardless, these possibilities will ultimately be resolved by restriction of *sanroque* mutation to the T-cell lineage, *Obf1* deletion to the B-cell lineage and/or both mutations to the T or B lineage for mixed bone marrow chimeras. These eagerly awaited experiments will determine the regulatory mechanisms constraining IgM autoantibody production outside GCs. The outstanding observation by Corcoran and colleagues thus demonstrate that there is indeed life outside the GC—just not as we know it.

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