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The imperfect control of self-reactive germinal center B cells

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Unlike T cells, B cells diversify their antigen receptor (BCR) binding specificities at two distinct stages of differentiation. Thus, in addition to initial variable region gene rearrangements, B cells recruited into T-dependent immune responses further modify their BCR specificity via iterative rounds of somatic hypermutation (SHM) within germinal centers (GCs). Although critical for providing the high-affinity antibody specificities required for long-term immune protection, SHM can also generate self-reactive B cells capable of differentiating into autoantibody-producing plasma cells. Recent data confirm that self-reactive GC B cells can be effectively removed from the secondary repertoire so as to maintain self-tolerance. However, they can also escape deletion under certain circumstances and so contribute to autoimmune disease via production of somatically mutated, pathogenic autoantibodies.

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Introduction

The ability to direct destructive immune responses against external and internal threats, such as foreign microbes and cancer cells, is one of the key adaptations to have arisen during human evolution [1]. However, the immune system could only evolve this destructive 'yin' if it also possessed the counterbalancing 'yang' of self-tolerance. We now know self-tolerance to be a complex and overlapping system of controls that act collectively to prevent immune attack of the body's own cells and tissues. Nevertheless, the ~5% incidence of autoimmune diseases within the human population indicates that self-tolerance is not absolute and can be subverted in certain circumstances by genetic and/or environmental factors.

Autoantibodies are a hallmark of many autoimmune diseases and result from the differentiation of self-reactive B cells into plasma cells. Whilst there are a number of explanations for how autoantibodies might be produced under various circumstances, the aetiology of pathogenic antibodies in most autoimmune diseases has been difficult to define. A unique challenge to the maintenance of self-tolerance in the B cell compartment is the 'second wave' of BCR diversification within B cells that are recruited into T-dependent immune responses and ultimately enter the germinal center (GC) reaction. Somatic hypermutation (SHM) of the immunoglobulin variable region genes of GC B cells results in the occasional generation of clones with increased affinity for foreign antigen, these cells being specifically perpetuated and subsequently differentiating into the high affinity plasma cells and memory B cells that provide long-term immunity [2]. However, the largely random nature of the SHM process inevitably leads to the generation of self-reactive B cells in the GC that, unless somehow inactivated, have the potential to initiate autoantibody production. The fact that most pathogenic autoantibodies show the hallmarks of SHM and selection strongly suggests that failure to enforce self-tolerance in GCs may contribute to many autoimmune diseases.

This review provides a brief outline of GC structure and cellular dynamics. The reader is referred to recent and excellent overviews both in this volume [3] and elsewhere [2,4] for more details. The major focus here will be on recent insights into how self-tolerance is enforced in the GC how it may break down to generate somatically mutated, pathogenic autoantibodies.

Constituents and function of the germinal center

The GC is classically divided into the light (LZ) and dark zones (DZ). The LZ is characterized by the presence of follicular dendritic cells (FDCs), non-hematopoietic cells that derive from perivascular precursors [5], which hold antigen on their cell surface in the form of immune complexes. Antigen-specific B cells, previously expanded by T-dependent proliferation outside the GC [6], interact with FDC-bound antigen in the LZ and receive cognate stimuli from $CD4^+$ T follicular helper (Tfh) cells also located in the LZ. Delivery of Tfh signals to LZ GC B cells triggers a phenotypic and positional shift whereby they increase surface CXCR4 levels and undergo migration to the DZ [7]. This migration is most likely supported by a newly identified population of stromal cells that reside within the DZ and express the CXCR4 ligand, CXCL12 [8]. GC B cells undergo cell replication in the DZ as well as SHM of their Ig variable region genes. DZ B cells subsequently return to the LZ expressing their revised BCR variable regions and compete

more successfully for antigen and Tfh help if they have acquired increased antigen affinity following SHM. High affinity GC B cells not only survive to undergo further rounds of SHM and selection but selectively differentiate into plasma cells [9] thus guaranteeing the most effective, high affinity antibodies are produced. GCs remain static in size for long periods of the immune response, meaning that the high rate of GC B cell proliferation must be counterbalanced extensive cell death, particularly among B cells that do not acquire high antigen affinity. The final major component cells within the GC are the tangible body macrophages (TBMs) which act as the 'cleaners' of the GC, rapidly ingesting and degrading apoptotic B cells via the MFGE8 molecules that are produced by FDCs and bind to the surface of apoptotic B cells [10].

Some but not all self-reactive B cells are removed from the GC

It has been recognised for over 25 years that pathogenic autoantibodies can be generated by SHM and antigen-driven selection [11], most likely in GCs but also potentially in extrafollicular niches [12]. Whilst the very existence of such autoantibodies indicates that self-tolerance in the GC is not absolute, their absence from most individuals suggests that self-reactive GC B cells are normally kept in check and are only rarely permitted to differentiate into autoantibody-producing plasma cells. Experiments performed nearly 20 years ago in which self-antigen was mimicked by an acutely administered bolus of exogenous (foreign) antigen, suggested that B cells that acquire self-reactivity in the GC are deleted upon contact with self-antigen [13–15]. However, there has been little progress since this time in identifying the fate of self-reactive GC B cells. In particular, the fate of GC B cells that recognise a *bona fide* self-antigen has been difficult to uncover due to the dynamic nature of the GC response and the absence of a suitable model system for identifying and tracking such cells within the GC [16].

A solution to this problem was provided in a recent study by Chan and colleagues [17••] in which B cells expressing a defined BCR against the foreign protein hen egg lysozyme (HEL), obtained from 'SW_{HEL}' mice [18], could undergo affinity maturation when immunized with a HEL variant (HEL^{3X}) [19]. A transgenic mouse line was produced which expressed a related HEL variant (HEL^{4X}) as a self-antigen. Importantly, SW_{HEL} B cells did not bind to HEL^{4X} but acquired cross-reactivity to it when they underwent affinity maturation in response to HEL^{3X} immunization [17••]. In mice ubiquitously expressing HEL^{4X}, GC B cells that bound HEL^{4X} self-antigen were prevented from developing (Figure 1(b)). Strikingly, self-reactive anti-HEL^{4X} GC B cells and anti-HEL^{4X} autoantibodies did develop following HEL^{3X} immunization of transgenic mice that expressed HEL^{4X} self-antigen in a tissue specific manner (e.g. in the liver or kidney) [17••] (Figure 1(c)). In summary, this study indicated first that self-reactive B cells generated in the GC could indeed be removed from the secondary repertoire, but also showed this is not always the case. In particular, if the self-antigen in question is not expressed at sufficient levels in the GC microenvironment, it appears that self-reactive GC B cells remain 'ignorant' of their self-reactivity and can differentiate unimpeded into autoantibody secreting plasma cells [16] (Figure 1).

Selection of self-reactive GC B cells by foreign versus self-antigen

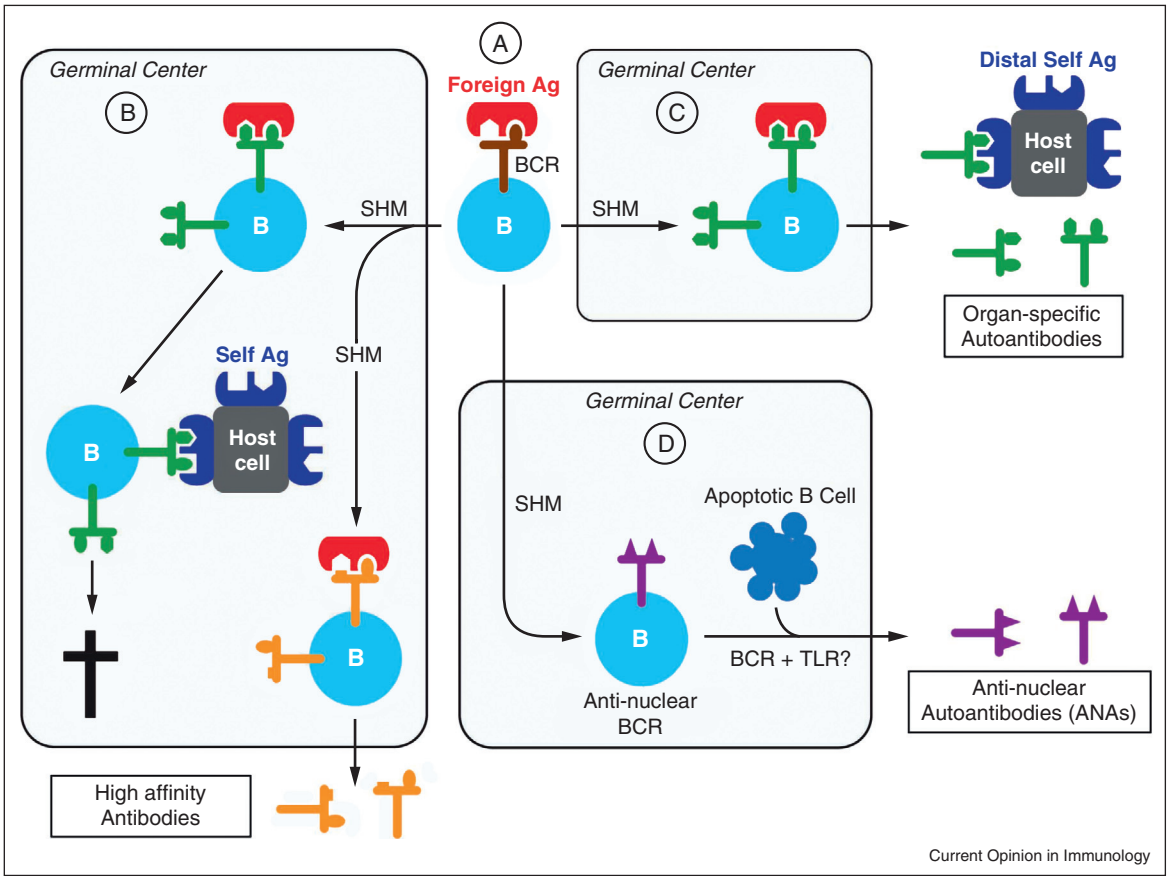
In terms of the potential mechanisms for the production of autoantibodies, the system of Chan and colleagues most accurately models the concept of 'molecular mimicry' — that is, the idea that immune responses generated against foreign antigens (typically infectious pathogens) can give rise to cross-reactive antibodies that bind to a specific self-antigen as well as the foreign antigen. Cross-reactive autoantibodies have been characterized in a number of autoimmune diseases that can occur following particular infections, including hepatitis C-related immune thrombocytopenia, pauci-immune focal necrotizing glomerulonephritis, Chagas disease, Guillain-Barré syndrome and rheumatic carditis (for references see [17••]). A key property of this model of autoantibody production is that it does not require T cell self-tolerance to be compromised, since Tfh cells recognising foreign epitopes can in theory drive the selection of the self-reactive GC B cells since the B cells cross-react with foreign antigen. If self-tolerance has been breached at the T cell level, however, high affinity pathogenic autoantibodies may be selected in the GC based purely on their affinity for self-antigen. It has been reasoned that the nature of the antigen responsible for driving autoantibody production might be clearer if the primary BCR specificity (i.e. that expressed on the original, unmutated B cell clone) from which the autoantibody was derived could be identified.

Deriving the primary specificity of somatically mutated autoantibodies

By the time they are identified, pathogenic autoantibodies are the product of terminally differentiated plasma cells that have long since exited the GC and acquired somatic mutations that obscure the primary specificity encoded in the original naïve B cell clone. A number of recent studies have employed the strategy of 'reverting' the variable region sequences of hypermutated autoantibodies back to putative primary specificity generated by V(D)J recombination.

Autoantibodies associated with the autoimmune skin and mucous membrane disease pehmphigus vulgaris (PV) primarily target the epithelial desmosome protein desmoglein-3 (DSG3). Di Zenzo and colleagues recently reported the results of reverting the variable region sequences of four somatically mutated anti-DSG3 autoantibodies

Figure 1



Potential scenarios for self-reactive B cells generated by SHM in the GC. **(a)** B cells with no initial self-reactivity (brown BCR) can be activated by foreign antigen, enter germinal centers (GCs) and undergo somatic hypermutation (SHM) of their Ig genes. **(b)** SHM can lead to increased affinity for foreign antigen without acquisition of self-reactivity (orange BCR) resulting in the production of high-affinity protective antibodies that are not self-reactive. Alternatively, acquisition of increased affinity for foreign antigen may also result in cross-reactivity with self-antigen (green BCR). If self-antigen is expressed within the GC microenvironment, self-reactive GC B cells can be eliminated. **(c)** However, if the cross-reactive self-antigen is expressed distally, self-reactive GC B cells are not eliminated and may differentiate into plasma cells producing organ-specific autoantibodies. **(d)** BCRs that recognise nuclear self-antigens such as DNA following SHM (purple BCR) may interact with their target self-antigen if clearance of apoptotic GC B cells is compromised. This has the potential to drive the production of anti-nuclear autoantibodies via co-operative signals delivered through the BCR and Toll-like receptors (TLRs) that interact with endogenous nucleic acids or other ligands.

derived from PV patients [20••]. In each case, the primary specificity from which the autoantibody was derived showed no detectable reactivity with DSG3. The authors concluded that the original B cell clones from which these autoantibodies were derived were recruited into the GC by an antigen distinct from DSG3 and that these B cells subsequently acquired high affinity for DSG3 via SHM in the GC [20••]. Whilst molecular mimicry may explain the emergence of these PV autoantibodies, there is no evidence currently that these anti-DSG3 autoantibodies cross-react with a microbial antigen.

In contrast to PV, the autoantibodies that target thyroid-stimulating hormone receptor (TSHR) in Graves' disease have a well-characterized cross-reactivity with antigens expressed by the gram-negative bacterium *Yersinia enterocolitica*. In another recent autoantibody reversion study, Hargreaves and colleagues reverted an anti-TSHR autoantibody derived from a mouse model of Graves' disease and showed that the unmutated version of the antibody reacted strongly with *Yersinia* antigens [21••]. Whilst not definitive, this study does provide strong support for the concept that molecular mimicry could be driving anti-TSHR autoantibody production in Graves' disease. Interestingly, the autoantibodies studied in both the PV and Graves' disease reversion studies are directed against organ specific antigens (DSG3 in skin, TSHR in thyroid). That these autoantibodies may be generated via molecular mimicry is in keeping with the results of Chan and colleagues indicating that this mechanism is most likely

to generate autoantibodies directed against organ-specific rather than systemically expressed self-antigens [17••] (Figure 1).

Although the two investigations discussed above are consistent with molecular mimicry being responsible for the selecting self-reactive B cells in the GC, two other recent studies describe cases where self-antigen itself may have driven autoantibody affinity maturation. In the first of these, Wang and colleagues characterized 19 somatically mutated autoantibodies directed against GM-CSF, isolated from patients with idiopathic pulmonary alveolar proteinosis (IPAP) [22••]. These autoantibodies had diverse variable region usage and reacted with 4 different epitopes on the GM-CSF, strongly suggesting that GM-CSF itself has driven the affinity maturation of the antibodies rather than 4 separate cross-reactive epitopes simultaneously present on a particular pathogen. Similarly, rheumatoid factor (RF, anti-IgG) autoantibodies derived from patients with hepatitis C virus-associated mixed cryoglobulinemia were predominantly found to have reduced but measurable anti-IgG activity following reversion of their somatic mutations [23], again consistent with self-antigen (IgG) initiating the autoantibody response. As both GM-CSF and IgG are systemically available self-antigens, the proposition that autoantibodies directed against these antigens have been generated by a mechanism other than molecular mimicry is also consistent with the general conclusions of Chan and colleagues on the role of self-antigen expression pattern in controlling cross-reactive GC B cells [17••]. It seems likely, therefore, that the production of autoantibodies against broadly expressed self-antigens such as GM-CSF and IgG requires a more fundamental breach of self-tolerance mechanisms than simply cross-reactivity with foreign immunogenic epitopes.

GC cell death and anti-nuclear autoantibody production

A discussion of autoantibodies that recognise ubiquitous self-antigens would not be complete without mention of the anti-nuclear autoantibodies that characterize systemic autoimmune diseases such as SLE. Two recent reviews on these particular autoantibodies [24•,25•] highlight earlier reversion studies on anti-DNA autoantibodies that consistently show a lack of DNA reactivity in the primary BCR [26–28]. Whilst this indicates that anti-DNA autoantibodies acquire their self-reactivity via SHM in the GC, it does not appear that their subsequent positive selection is brought about by molecular mimicry of a cross-reactive foreign antigen. Rather, the combination of the BCR interaction with DNA (or DNA-associated proteins) and the ability of these self-antigens to stimulate B cells via TLR/MyD88-dependent signalling pathways is thought to drive the production of anti-nuclear antibodies by GC-derived B cells [24•,25•] (Figure 1(d)).

The concept that intracellular self-antigens drive the production of anti-nuclear autoantibodies in GCs is consistent with the high rate of B cell death that occurs in these structures. Although dying B cells are removed with great efficiency by the TBMs, it might be expected that circumstances which reduce the rate of corpse removal would increase the chances of anti-nuclear autoantibody production (Figure 1(d)). This has been proposed to explain the high incidence of anti-DNA autoantibodies in mice with absent expression of a number of molecules involved in this process, including FDC-expressed MFGE8 [29] and TBM-expressed members of the TAM tyrosine kinase family such as Mer [30]. Additional support for this concept comes from the recent demonstration that mice lacking the Mer tyrosine kinase preferentially accumulate apoptotic cells in GCs and exhibit prolonged GC and antibody responses [31•]. The role of apoptotic GC cells in driving the production of anti-nuclear autoantibodies as well as autoantibodies more generally will be an important focus for future investigations into the aetiology of autoimmune disease.

Summary

The generation of high affinity autoantibodies almost certainly occurs via a variety of mechanisms. Recent investigations involving a mouse model system of GC self-tolerance and reversion of somatically mutated autoantibodies support the concept that cross-reactive autoantibodies can be generated from responses initially directed against foreign antigens such as infectious pathogens (molecular mimicry). This is most likely to occur in the case of organ-specific autoantibodies that are not expressed in the GC microenvironment and does not necessarily rely on any breach in T cell self-tolerance. Autoantibodies directed against ubiquitously expressed self-antigens are more likely to arise from more fundamental breaches in self-tolerance mechanisms, whilst anti-nuclear autoantibodies are likely to be particularly favoured when apoptotic cells are not efficiently cleared from the GC and provide additional stimuli to self-reactive GC B cells.

References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

1. Olalde I, Allentoft ME, Sanchez-Quinto F, Santpere G, Chiang CW, Degiorgio M, Prado-Martinez J, Rodriguez JA, Rasmussen S, Quilez J *et al.*: **Derived immune and ancestral pigmentation alleles in a 7,000-year-old Mesolithic European**. *Nature* 2014, **507**:225-228.
2. Victora GD, Nussenzweig MC: **Germinal centers**. *Annu Rev Immunol* 2012, **30**:429-457.
3. Victora GD, Mesin L: **Clonal and cellular dynamics in germinal centers**. *Curr Opin Immunol* 2014, **28**:90-96.
4. Gatto D, Brink R: **The germinal center reaction**. *J Allergy Clin Immunol* 2010, **126**:898-907.

5. Krautler NJ, Kana V, Kranich J, Tian Y, Perera D, Lemm D, Schwarz P, Armulik A, Browning JL, Tallquist M *et al.*: **Follicular dendritic cells emerge from ubiquitous perivascular precursors**. *Cell* 2012, **150**:194-206.

6. Schwickert TA, Victora GD, Fooksman DR, Kamphorst AO, Mugnier MR, Gitlin AD, Dustin ML, Nussenzweig MC: **A dynamic T cell-limited checkpoint regulates affinity-dependent B cell entry into the germinal center**. *J Exp Med* 2011, **208**:1243-1252.

7. Victora GD, Schwickert TA, Fooksman DR, Kamphorst AO, Meyer-Hermann M, Dustin ML, Nussenzweig MC: **Germinal center dynamics revealed by multiphoton microscopy with a photoactivatable fluorescent reporter**. *Cell* 2010, **143**:592-605.

8. Bannard O, Horton RM, Allen CD, An J, Nagasawa T, Cyster JG: **Germinal center centroblasts transition to a centrocyte phenotype according to a timed program and depend on the dark zone for effective selection**. *Immunity* 2013, **39**:912-924.

9. Phan TG, Paus D, Chan TD, Turner ML, Nutt SL, Basten A, Brink R: **High affinity germinal center B cells are actively selected into the plasma cell compartment**. *J Exp Med* 2006, **203**:2419-2424.

10. Aguzzi A, Kranich J, Krautler NJ: **Follicular dendritic cells: origin, phenotype, and function in health and disease**. *Trends Immunol* 2014, **35**:105-113.

11. Shlomchik MJ, Marshak-Rothstein A, Wolfowicz CB, Rothstein TL, Weigert MG: **The role of clonal selection and somatic mutation in autoimmunity**. *Nature* 1987, **328**:805-811.

12. William J, Euler C, Christensen S, Shlomchik MJ: **Evolution of autoantibody responses via somatic hypermutation outside of germinal centers**. *Science* 2002, **297**:2066-2070.

13. Shokat KM, Goodnow CC: **Antigen-induced B-cell death and elimination during germinal-centre immune responses**. *Nature* 1995, **375**:334-338.

14. Pulendran B, Kannourakis G, Nouri S, Smith KG, Nossal GJ: **Soluble antigen can cause enhanced apoptosis of germinal-centre B cells**. *Nature* 1995, **375**:331-334.

15. Han S, Zheng B, Dal Porto J, Kelsoe G: **In situ studies of the primary immune response to (4-hydroxy-3-nitrophenyl)acetyl IV. Affinity-dependent, antigen-driven B cell apoptosis in germinal centers as a mechanism for maintaining self-tolerance**. *J Exp Med* 1995, **182**:1635-1644.

16. Chan TD, Brink R: **Affinity-based selection and the germinal center response**. *Immunol Rev* 2012, **247**:11-23.

17. •• Chan TD, Wood K, Hermes JR, Butt D, Jolly CJ, Basten A, Brink R: **Elimination of germinal-center-derived self-reactive B cells is governed by the location and concentration of self-antigen**. *Immunity* 2012, **37**:893-904.
Developed a novel mouse model to identify cross-reactive, anti-self B cells generated in the GC and show that these cells were eliminated only when the self-antigen was expressed within the GC microenvironment.

18. Phan TG, Amesbury M, Gardam S, Crosbie J, Hasbold J, Hodgkin PD, Basten A, Brink R: **B cell receptor-independent stimuli trigger immunoglobulin (Ig) class switch recombination and production of IgG autoantibodies by anergic self-reactive B cells**. *J Exp Med* 2003, **197**:845-860.

19. Paus D, Phan TG, Chan TD, Gardam S, Basten A, Brink R: **Antigen recognition strength regulates the choice between extrafollicular plasma cell and germinal center B cell differentiation**. *J Exp Med* 2006, **203**:1081-1091.

20. •• Di Zenzo G, Di Lullo G, Corti D, Calabresi V, Sinistro A, Vanzetta F, Didona B, Cianchini G, Hertl M, Eming R *et al.*: **Pemphigus autoantibodies generated through somatic mutations target the desmoglein-3 cis-interface**. *J Clin Invest* 2012, **122**:3781-3790.
Isolated a number of anti-DSG3 autoantibodies from patients with pemphigus vulgaris and showed by reversion mutagenesis that their oriiginal (primary) specificity did not bind to this self-antigen, suggesting original B cell activation occurred via a different antigen.

21. •• Hargreaves CE, Grasso M, Hampe CS, Stenkova A, Atkinson S, Joshua GW, Wren BW, Buckle AM, Dunn-Walters D, Banga JP: ***Yersinia enterocolitica* provides the link between thyroid-stimulating antibodies and their germline counterparts in Graves' disease**. *J Immunol* 2013, **190**:5373-5381.
Performed reversion mutagenesis on anti-TSHR autoantibodies isolated froma mouse model of Graves' disease and showed that their oriiginal (primary) specificity reacted with antigens on the bacterium *Yersinia enterocolitica.* Consistent with molecular mimicry driving autoantibody production in this autoimmune disease.

22. •• Wang Y, Thomson CA, Allan LL, Jackson LM, Olson M, Hercus TR, Nero TL, Turner A, Parker MW, Lopez AL *et al.*: **Characterization of pathogenic human monoclonal autoantibodies against GM-CSF**. *Proc Natl Acad Sci U S A* 2013, **110**:7832-7837.
Identified four distinct interaction sites for human autoantibodies directed against GM-CSF from patiens with IPAP. Indicates that molecular mimicry is unlikely to have driven autoantibody production in this case.

23. Charles ED, Orloff MI, Nishiuchi E, Marukian S, Rice CM, Dustin LB: **Somatic hypermutations confer rheumatoid factor activity in hepatitis C virus-associated mixed cryoglobulinemia**. *Arthritis Rheum* 2013, **65**:2430-2440.

24. • Schroeder K, Herrmann M, Winkler TH: **The role of somatic hypermutation in the generation of pathogenic antibodies in SLE**. *Autoimmunity* 2013, **46**:121-127.
One of two recent reviews that focus on the contribution of somatic mutation to the generation of pathogenic anti-nuclear autoantibodies and how signals from apoptotic cells in the GC may drive this process.

25. • Detanico T, St Clair JB, Aviszus K, Kirchenbaum G, Guo W, Wysocki LJ: **Somatic mutagenesis in autoimmunity**. *Autoimmunity* 2013, **46**:102-114.
One of two recent reviews that focus on the contribution of somatic mutation to the generation of pathogenic anti-nuclear autoantibodies and how signals from apoptotic cells in the GC may drive this process.

26. Wellmann U, Letz M, Herrmann M, Angermuller S, Kalden JR, Winkler TH: **The evolution of human anti-double-stranded DNA autoantibodies**. *Proc Natl Acad Sci U S A* 2005, **102**:9258-9263.

27. Mietzner B, Tsuiji M, Scheid J, Velinzon K, Tiller T, Abraham K, Gonzalez JB, Pascual V, Stichweh D, Wardemann H *et al.*: **Autoreactive IgG memory antibodies in patients with systemic lupus erythematosus arise from nonreactive and polyreactive precursors**. *Proc Natl Acad Sci U S A* 2008, **105**:9727-9732.

28. Guo W, Smith D, Aviszus K, Detanico T, Heiser RA, Wysocki LJ: **Somatic hypermutation as a generator of antinuclear antibodies in a murine model of systemic autoimmunity**. *J Exp Med* 2010, **207**:2225-2237.

29. Kranich J, Krautler NJ, Heinen E, Polymenidou M, Bridel C, Schildknecht A, Huber C, Kosco-Vilbois MH, Zinkernagel R, Miele G *et al.*: **Follicular dendritic cells control engulfment of apoptotic bodies by secreting Mfge8**. *J Exp Med* 2008, **205**:1293-1302.

30. Rahman ZS, Shao WH, Khan TN, Zhen Y, Cohen PL: **Impaired apoptotic cell clearance in the germinal center by Mer-deficient tingible body macrophages leads to enhanced antibody-forming cell and germinal center responses**. *J Immunol* 2010, **185**:5859-5868.

31. • Khan TN, Wong EB, Soni C, Rahman ZS: **Prolonged apoptotic cell accumulation in germinal centers of Mer-deficient mice causes elevated B cell and CD4+ Th cell responses leading to autoantibody production**. *J Immunol* 2013, **190**:1433-1446.
Describes the specific accumulation of apoptotic cells in GCs from mice lacking the TBM-expressed tyrosine kinase Mer and the resulting enhancement of GC responses and antibody production.