PERSPECTIVES: IMMUNOLOGY

Long Live the Mature B Cell—a BAFFling Mystery Resolved

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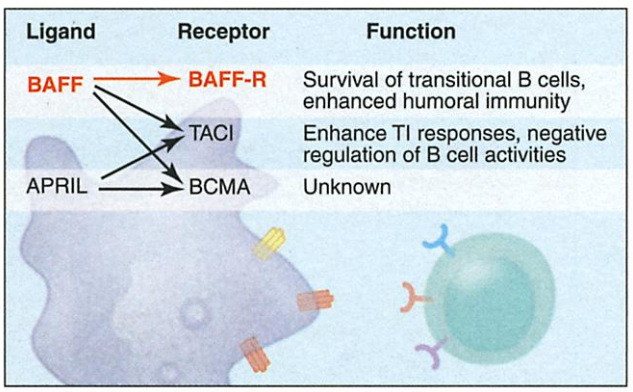
The diversity and longevity of the mature B lymphocyte pool determines our capacity to mount protective immune responses, and also influences the development of autoimmune disease. The antigen receptor diversity of the long-lived B cell pool is governed largely by positive and negative selection of maturing B cells in the bone marrow. Once in the periphery, numerous signals control the final selection and survival of the newly formed B cells. After differentiation and selection in the bone marrow, newly emerging B lymphocytes (termed transitional B cells) migrate to the spleen. Their peripheral migration and positioning is a complex process regulated by chemokines and interactions with nonhematopoietic elements (*1*). In addition, signaling through membrane immunoglobulin appears to be important for facilitating selection of transitional B cells into the mature B cell pool (*2*). A major challenge facing immunologists is the identity of the factors that support differentiation of selected transitional B cells into mature long-lived lymphocytes. Two papers on pages 2111 (*3*) and 2108 (*4*) of this week's issue define the ligand BAFF (also called BLyS, TALL-1, THANK, zTNF4, TNFS13B) (*3*) and its newly identified receptor (BAFF-R) (*4*) as principal regulators of peripheral B cell fate. These and previous studies make it clear that BAFF and BAFF-R are essential for optimal antibody-based (humoral) immunity, and that dysregulation of this receptor-ligand pair may give rise to either immune deficiency or autoimmunity.

Although a number of investigators have characterized BAFF as an enhancer of B cell survival (*5*), identification of the receptor responsible for this activity has been problematic. BAFF—B cell activation factor from the tumor necrosis factor (TNF) family—is expressed on cells of the myeloid lineage and binds to the TNF family receptors BCMA (B cell maturation antigen) and TACI (transmembrane activator, calcium modulator and cyclophilin ligand interactor), which are expressed on B cells (*5*). In addition to binding BAFF, BCMA and TACI are also receptors for APRIL (a proliferating inducing ligand), another member of the TNF family. To define the importance of these receptors in B cell survival, several groups have produced mice deficient in either BCMA or TACI (*3*, *6*–*8*). However, the phenotypes of these two knockout mouse strains are perplexing: BCMA-deficient mice have no B cell deficiency (*8*), and TACI-deficient mice have increased numbers of peripheral B cells coupled with reduced responses to carbohydrate (T cell–independent) antigens (*6*, *7*). The phenotype of the TACI-deficient mice suggests that TACI is a negative regulator of B cell survival on the one hand, and a positive regulator of T cell–independent responses on the other. Taken together, these studies indicate that neither BCMA nor TACI mediates the survival activity of BAFF, pointing to the existence of a third receptor.



A new receptor for BAFF. BAFF and APRIL are ligands belonging to the TNF family. BAFF is predominantly expressed on myeloid cells, whereas APRIL is expressed on hematopoietic cells and some tumor cells. BAFF binds to the receptors BAFF-R, TACI, and BCMA; APRIL binds only to TACI and BCMA. TACI is expressed on a subset of B cells and activated T cells, whereas BCMA is restricted to B cells. BAFF-R is also selectively expressed on B cells. The binding of BAFF to BAFF-R is primarily responsible for supporting transitional B cell maturation and enhancing the survival of mature B cells. TACI is a negative regulator of B cell activity and may be important for the development of T cell–independent humoral responses.

Thompson and co-workers (*4*) confirm the prediction of a third receptor for BAFF. Unlike BCMA or TACI, the BAFF-R that they identify binds only to BAFF and shows no specificity for APRIL or other TNF ligand family members (*4*). Of particular interest, these authors demonstrate that the immunodeficient A/WySnJ mouse strain harbors a natural mutation in the third exon of the BAFF-R gene (*4*). Complementing this finding is the description by Schiemann and colleagues (*3*) and Gross *et al.* (*9*) of BAFF-deficient mice. Both mouse strains exhibit a number of strong parallels, unequivocally defining BAFF and BAFF-R as central regulators of peripheral B cell survival. Both the A/WySnJ BAFF-R mutant mouse and the BAFF-deficient mice display normal B cell development in the bone marrow and the presence of early transitional (T1) B cells in the spleen (*3*, *10*). With the exception of B1 cells, all other peripheral B cell subsets—including follicular, marginal zone, and late-transitional (T2) B cells—are markedly reduced (*3*, *10*). The few B cells that do attain mature status, however, are unable to survive long-term as measured by bromodeoxyuridine incorporation (*10*). As expected, immunization of A/WySnJ and BAFF-deficient mice with both T cell–independent and T cell–dependent antigens results in compromised antibody responses (*3*, *11*). Although both mutant strains have remarkably similar characteristics, the B cell defects in BAFF-deficient mice appear to be more severe. In particular, BAFF-deficient mice show greater depletion of peripheral B cells and only negligible immunoglobulin M (IgM) responses after challenge with T cell–dependent and T cell–independent antigens (*3*). Immunization of A/WySnJ mice results in largely normal IgM titers (*10*). To explain these differences, the authors speculate that A/WySnJ B cells either express a marginally functional BAFF-R or partially compensate for a nonfunctional receptor by using BCMA or TACI. Taken together, these findings underscore the importance of BAFF and BAFF-R in the survival of transitional B cells and maintenance of mature follicular and marginal zone B cells. These mice further reveal that APRIL is not a survival factor for these B cell populations, and that B1 cells are maintained in a BAFF-independent manner.

Although the mystery of transitional and mature B cell survival has been resolved, questions about the involvement of BAFF and BAFF-R in the selection of developing B cells and in the activities of mature B cells still remain. Because BAFF is a potent survival signal, questions arise as to whether excess signaling through the BAFF receptor can divert negative selection in the bone marrow and allow the emergence of self-reactive B cells.

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Such an effect would explain the development of a lupus-like disease in transgenic mice that overexpress BAFF (*12–14*). BAFF attenuates apoptosis of mature B cells, heightens humoral responses, and costimulates the response of mature B cells to CD40L (*15*). Thus, BAFF and BAFF-R may be important for the survival of antigen-activated B cells as well as resting mature B cells. Further work is also required to resolve how BCMA and TACI are involved in B cell activities. That TACI may be a positive regulator of T cell–independent responses or a negative regulator of B cell activity awaits clarification. Given the B cell–selective expression of this subfamily of TNFRs, future studies should provide insights into how these receptors guide transition of emergent B cells into the mature pool, sustain antigen-specific immune responses, and support the longevity of post–germinal center B cells.

References and Notes

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PERSPECTIVES: ENERGY LANDSCAPES

Flirting with Catastrophe

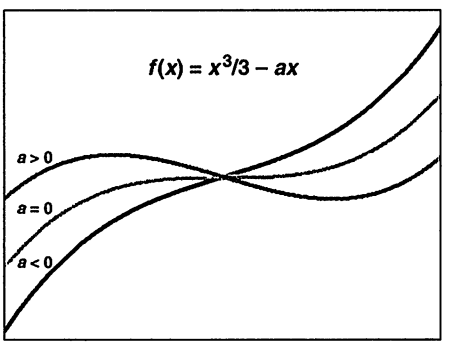
Robert H. Leary

The behavior of atomic and molecular assemblies is governed by potential energy surfaces, which describe the complex interactions between the components and determine how chemical reactions progress or whether a material forms a glass or a crystal. On page 2067 of this issue, Wales (*1*) brings a new analytical tool—catastrophe theory—to the study of potential energy surfaces. He shows that neighboring stable states and the reaction paths that connect them can often be described by universal functional forms dictated by catastrophe theory.

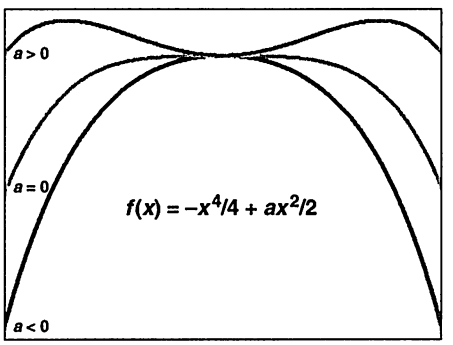
A potential energy surface is commonly described as a landscape. Mountain peaks (local maxima), valley bottoms (local minima), and passes (saddle points representing a minimum in one direction and a maximum in a second, independent direction) are critical points where the gradient vanishes. Except for certain degenerate cases (called non-Morse points), these are the only possible types of critical point for smooth functions of two variables. Smooth functions of one variable typically have only minima and maxima. But in higher dimensions, we must distinguish between different types of saddles.

In 1931, Morse developed a general characterization of nondegenerate critical points (*2*, *3*) in what is regarded as one of the most important contributions to 20th century mathematics (*4*). Morse showed that in the vicinity of any nondegenerate critical point, the potential can be decomposed by a smooth coordinate transformation into a sum of simple, one-dimensional quadratic terms in the individual coordinates. The critical point represents a local maximum along coordinates associated with negative coefficients and a local minimum along coordinates with positive coefficients. In higher dimensions, saddle points are thus distinguished by an index d that represents the number of independent directions for which the potential is at a maximum. Local minima ($d = 0$) are of special interest because they represent stable bound states.

The simplest degenerate case resisting such a decomposition is the one-dimensional cubic polynomial $f(x) = x^3/3$, for which $x = 0$ is a non-Morse critical point that is neither a minimum nor a maximum. This function is a special member of the family of cubic polynomials $f(x) = x^3/3 - ax$ (see the first figure). For $a > 0$, there are two Morse critical points, a minimum at $a^{1/2}$ and a maximum at $-a^{1/2}$. For $a < 0$, there are no critical points. The non-Morse $a = 0$ case separates these two regions where Morse theory applies.



The simplest fold catastrophe.



The simplest cusp catastrophe.

In higher dimensions, the potential around a non-Morse point may be split into a Morse part (which itself may be decomposed into quadratic pieces) and a non-Morse part. For singly degenerate critical points, an M-dimensional potential splits into an $(M - 1)$-dimensional Morse part and a one-dimensional non-Morse part. The analysis of the non-Morse parts at singly and doubly degenerate critical points and their classification into universal forms is the stuff of Thom's celebrated [and, with respect to models of prison riots and stock market crashes (*5*), controversial] elementary catastrophe theory (*5–8*).

For families of potentials with up to five parameters, there are only 11 structurally stable non-Morse universal functional forms or catastrophe functions. For one-parameter families, the situation is even simpler. In the absence of special symmetry conditions, the cubic example (see the first figure)—the fold catastrophe—is the only possible such function. Occasionally, nature restricts the class of applicable functions to those with even symmetry, for example, to describe a reaction path between geometrically equivalent local minima that is symmetrical about the intermediate transition point. The quartic cusp catastrophe function $f(x) = -x^4/4 + ax^2/2$ (see the second figure) and its negative then form the universal family of one-parameter catastrophe functions.

Wales (*1*) uses catastrophe theory to analyze the reaction path followed by atomic and molecular clusters that are undergoing a conformational change from one local minimum to another. Such a path passes through a transition point (a saddle of index $d = 1$). If the local minima are geometrically and energetically distinct, the path is asymmetrical and the transition point generally more closely resembles the energetically higher of the two minima.

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