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Review

Regulation of lupus-related autoantibody production and clinical disease by Toll-like receptors

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Abstract

Autoantigens that contain DNA, RNA, or self-IgG are preferred targets for autoantibodies in systemic lupus erythematosus (SLE). B cells promote SLE pathogenesis by producing autoantibodies, activating autoreactive T cells, and secreting cytokines. We discuss how certain autoreactive B cells are selectively activated, with emphasis on the roles of key Toll-like receptors (TLRs). Although TLR7, which recognizes ssRNA, promotes autoimmune disease, TLR9, which recognizes DNA, unexpectedly regulates disease, despite being required for the secretion of anti-chromatin autoantibodies. We describe positive feedback loops involving B cells, T cells, DCs, and soluble mediators, and how these networks are regulated by TLR signals.

Keywords: Systemic lupus erythematosus; Autoantibodies; Toll-like receptor-7; Toll-like receptor-9; Anti-Sm; Anti-chromatin; B cell; Autoimmune disease

1. Introduction

Systemic autoimmune diseases, such as systemic lupus erythematosus (SLE), are chronic—typically waxing and waning—syndromes that result in damage to diverse organ systems by a variety of immune mechanisms. They are undoubtedly the product of multiple and stepwise failures of immune regulation, leading to a complex scenario of established disease. Nonetheless, this does not mean that in lupus there is simply global immune activation. Rather, there is clearly specificity both in terms of lymphocyte activation, and also in the pivotal role of certain cell types and cytokines. The clues to better understanding and therapy of these diseases must come from a better understanding of the specific nature of aberrant immune activation and the temporal relationship of these events. What stimulates and what sustains autoimmunity? What specific immune circuits are dysregulated? What are the targets of self-reactivity and why?

2. Positive feedback in autoimmunity

Normally, the immune system is autoregulatory in the sense that the immune response is damped by a variety of counter-regulatory mechanisms that are induced at the time of immune activation. It is reasonable to assume that among the many genetic factors that contribute to disease are alterations in regulatory molecules or circuits, essentially reducing the brakes on (auto)immune responses [1–8]. In the context of a positive feedback loop, small changes in tuning based on genetic factors could be amplified, converting a transient response into one that is sustained and pathogenic. In addition, the immune response to foreign antigens is typically limited by the clearance of those antigens. In autoimmunity, the autoantigens are never cleared, thus driving the response indefinitely.

Another implication of positive feedback is that the signals and stimuli that sustain a response need not be the same as those that initiate it. Thus, an environmental stimulus, such as a toxin or an infectious agent, could initiate an anti-self-response due to temporary immune dysregulation or cross-reactivity; such a response could then be sustained without the need for the initiating stimulus. Self-amplifying loops are also consistent with the waxing and waning nature of many systemic autoimmune diseases, as exemplified by the lupus "flare". A fundamental aspect of the positive feedback concept in autoimmunity is that once self-tolerance is lost and effector function is generated, subsequent tissue damage leads to release of more self-antigen,

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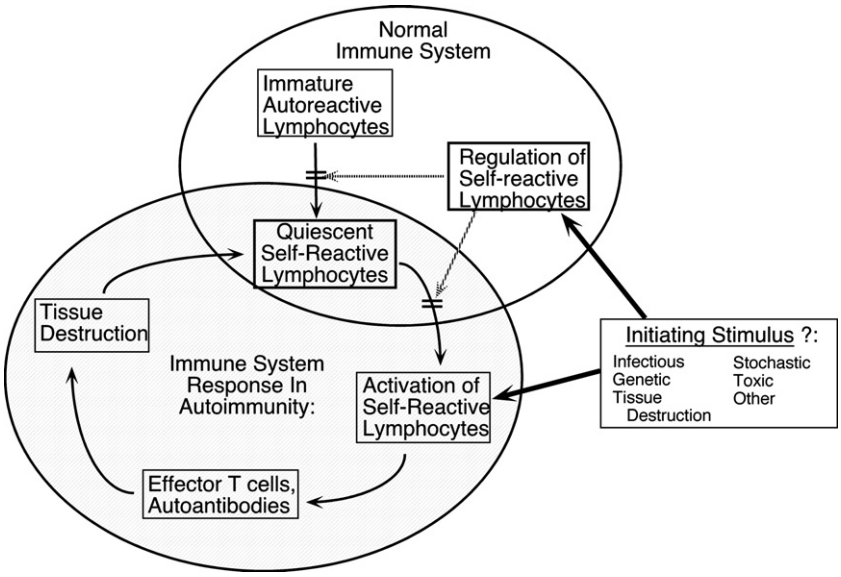

Fig. 1. An early model of positive feedback in the genesis of systemic autoimmunity. Normally, the immune system (upper right large ellipse) generates autoreactive lymphocytes via the stochastic rearrangement of receptors, but tolerance mechanisms, now known to include clonal deletion and receptor editing, prevent the maturation of some of these. However, some of these autoreactive cells will develop and mature, where they are normally held in check by a variety of peripheral tolerance mechanisms. One or more initiating stimuli or preconditions (such as genetic predisposition) can subvert either central or peripheral regulation of autoreactive cells, allowing them to be activated. Chronic autoimmunity will ensue if these lymphocytes generate effector functions, cause tissue injury and inflammation and autoantigen release that is able to promote further activation of autoreactive lymphocytes. It is envisioned that an initial insult could thus be converted to a self-sustaining autoimmune condition, with endogenous stimuli proving sufficient to provide dynamic and continuous activation of autoreactive lymphocytes.

potentially in an immunogenic form. Resultant inflammation also increases the chances that this self-antigen will lead to activation of autoreactive lymphocytes. We first proposed a general version of positive feedback in autoimmunity in the mid-1980s (Fig. 1).

As conceptually useful as this construct might be, however, it lacks mechanistic detail (perhaps not surprising given its 1980s vintage). If feedback loops do in fact exist, then they have to be embodied by particular cell types and inflammatory mediators that communicate among these cells. In addition, specific antigens have to be incorporated as initiators and sustainers of the reaction. Connections, and the forces that regulate them, need to be identified at the cellular and molecular level. A better understanding of these circuits in a more detailed and accurate model of positive feedback should enable more intelligent design of specific inhibitors or modulators that will effectively dampen or interrupt disease.

3. B Cells are central to SLE pathogenesis

The discovery in the mid to late 1990s that B cells played central roles in the pathogenesis of lupus [9–13] and other autoimmune diseases [14–16], gave some specific detail to the concept of positive feedback. In particular, T cell activation and target tissue infiltration were both decreased in lupus-prone MRL/Mp mice, either in the presence or absence of the Fas$^{lpr/lpr}$ mutation, when B cells were eliminated by genetic means [9,10,13]. This elucidated one mechanism of positive feedback, in that B cells could promote T cell activation. Moreover, these data suggested a new function, beyond secretion of autoantibodies, for the role of B cells in lupus pathogenesis. Subsequent work confirmed this formally by demonstrating that B cells that could not secrete antibodies could nonetheless support spontaneous T cell activation, T cell tissue infiltration and early mortality in the MRL/Mp$^{lpr/lpr}$ lupus model [11]. This connection has been extensively discussed in a prior review [17].

It has been widely assumed that B cells are important APCs for autoreactive T cells [15,17–20], a concept supported by direct investigations on the potential of autoreactive B cells to activate T cells in vivo and in vitro [21–25]. However, the relative importance of B cell APC function has yet to be determined, and there may be additional roles for B cells, including secretion of cytokines and maintenance of lymphoid architecture (reviewed recently in Ref. [26]). Emerging studies in humans suggest that depletion of B cells in vivo can be an effective therapy for lupus [27–29]; analogous studies have demonstrated this clearly in the case of rheumatoid arthritis [30]. Intriguingly, in one study of B cell depletion in SLE patients, clinical response correlated with a decrease in T cell activation in blood, suggesting the existence of a T-B positive feedback loop [28].

From these studies, a new view of feedback loops also emerged, which attempted to incorporate both classical pathogenesis mechanisms as well as novel roles for B cells (Fig. 2, adapted from Ref. [12]). This model places B cells at the center of an amplification loop in which they activate CD4$^+$ T cells, which in turn expand and activate additional autoreactive naïve B cells. The loop is further amplified by the inflammation and release of self-antigen that accompanies both T cell-mediated and antibody-mediated immunopathology. These results focused on the B cell as an important component, and possibly central to the regulation of autoimmunity. However, they did not shed light on the initiating factors—genetic or