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Oncogenic inflammation and autoimmune disease

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Abstract

Many models exist to explain the induction and perpetuation of autoimmune diseases. Despite their validation in a variety of animal models, the basis for autoimmune disease in humans remains unknown. Here, we propose that an important aspect of autoimmune disease is the active participation of the target organ due to endogenously produced co-stimulatory factors that cause prolonged antigen presentation and lymphocyte activation. Evidence suggests that a major source of such endogenous signaling comes from newly transformed cells within the target organ that produce pro-inflammatory factors.
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Contents

Autoimmune diseases are a major growing health problem worldwide with some showing dramatic variations in incidence and severity [1]. In the US alone, roughly 8.5 million people are afflicted with at least one of the common autoimmune diseases [2]. There are two major frustrations with autoimmune diseases. First, as with cancers, clinical treatment is marginally effective and/or considerably burdensome. Second, for most autoimmune diseases, the mechanism behind disease etiology remains a mystery. This

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situation is distinct from cancer where our understanding of how genetic mutations lead to disease, is increasing at a tremendous rate. Ironically, these advancements in cancer biology may have provided a very important piece to the autoimmunity puzzle. Cancers and autoimmunity are often coincident—more coincident than is generally appreciated. Despite minimal supporting evidence, the standard model for explaining this coincidence is that autoimmunity leads to cancer due to the rapid cell division associated with the regeneration of damaged tissues at the site of inflammation [3]. The alternative model that we will model in this review is: that cellular transformation within a tissue alone can initiate autoimmunity and influence the progression of the cancer. In this review, we put forward our alternative model that is based on several lines of evidence.

1. Overview of the mechanisms controlling tolerance: central and peripheral

Broadly defined, tolerance is the lack, or absence, of an immune response to a given antigen. In the context of this review, we will restrict its definition to the state of health that individuals enjoy when cells of the immune system ignore host tissues. As with immune responses to foreign pathogens, tolerance involves the orchestrated interaction of T cells, B cells and antigen-presenting cells (APCs). However, the mechanisms of regulating self-tolerance are largely unsolved. From a large body of work, it is now clear that tolerance is a complex phenomenon that is shaped at multiple levels. The first step in T-cell tolerance is central deletion in the thymus. Animal models have consistently supported the role of clonal deletion in restricting the T-cell repertoire against self antigens by interactions with thymic epithelial cells [4]. Indeed, thymic selection eliminates most, but not all, of the potentially autoreactive T cells during their development. Although the specifics of this process are not well understood, the notion that protein expression in the thymus can lead to T-cell deletion is well accepted. The extent to which the thymus can mediate tolerance to tissue-specific proteins and how organ-specific tolerance is mediated remains an open question. While some tissue-specific proteins might reach the thymus via the circulation, this mechanism may be unnecessary due to expression within the thymus of the recently discovered autoimmune regulator protein AIRE, which functions as a promiscuous ubiquitin ligase with the potential for controlling transcription of a broad array of tissue-specific target genes in thymic epithelial cells [5].

Despite central tolerance mechanisms, many low-affinity self-reactive T cells exit the thymus become activated in the periphery [6]. Additional mechanisms are required for keeping these potentially destructive T cells in check. Mechanisms of peripheral tolerance can be divided into two general types: passive and active. Passive suppression appears to be based primarily on the requirement of two separate signals for T-cell activation, with the first ("signal 1") being provided by recognition of peptide/MHC complexes. The second signal ("signal 2") is delivered mainly through ligation of the co-stimulatory receptor CD28 on the T-cell surface with CD80 (B7.1) and/or CD86 (B7.2) on the surface of an activated APC [7]. Other co-stimulatory molecules such as 4-1BB, OX40, CD40 and members of the CD2 superfamily can similarly complement signal 1 [8]. An important aspect of signal 2 is that co-stimulatory molecules are not constitutively expressed on APCs but are induced by pro-inflammatory factors, such as bacterial products [such as lipopolysaccharide (LPS) and CpG-biased DNA], pro-inflammatory cytokines [such as tumour-necrosis factor (TNF) and IL-1] or other molecules often referred to as "adjuvants" or "danger signals" [9]. These endogenous danger signals may also be produced in response to injury-induced tissue damage, apoptosis or necrosis [10] and, as discussed herein, neoplastic transformation. One key feature of these pro-inflammatory factors is that they stimulate common pathways that ultimately lead to nuclear translocation of the NFκB complex and transcription of pro-inflammatory cytokine genes. The danger model, as originally proposed [9], predicted that conditions such as cancer might not stimulate immune responses due to lack of co-stimulatory signals. However, this notion was based on cancers at late or advanced stages of disease, when tumor-induced immunosuppression may be at its highest [for example, through production of the regulatory cytokines, transforming growth factor-β (TGF-β) and IL-10]. In fact, there is considerable potential for newly transformed cells to evoke danger signals through the engagement of pro-inflammatory signaling pathways.

Given the signal 1/signal 2 paradigm, one model for the initiation of autoimmune responses entails presentation of a self protein (self signal 1) in the context of signal 2. In fact, this could occur in almost any infection, as some self proteins may now be presented in the context of NFκB-activating danger signals induced by the pathogen. Indeed, infection-induced self-reactive responses can be easily observed with a sufficiently sensitive detection system in place [11]. However, since

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