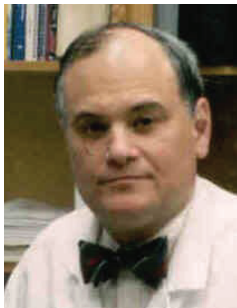


Is a common therapy for autoimmune disease possible?



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‘Identifying the mechanisms common to related autoimmune diseases might prove advantageous for the purpose of drug development.’

Continuing to improve our management of patients with autoimmune disease remains one of many substantially unmet challenges confronting modern medicine. At its heart, this effort relies heavily on accessing an ever-expanding knowledge of normal immunology and the molecular and cellular basis of disease. Integrating the evolving concepts rooted in emerging technology at the bench and bringing these to the field of clinical autoimmunity must be thoughtfully coupled with the diverse needs of our patients. Yet in many instances we encounter difficulty in categorizing our patients, describing them with precision to our colleagues or predicting their response to therapy. Despite these severe limitations, great advances in therapy have taken place over the last decade. Clearly, we must gain greater understanding of the basic disease mechanisms in play before we can create more effective and safer therapies.

Let me begin this editorial with a brief review of what pieces of this complex puzzle we currently seem to understand. Adaptive immune responses usually protect us against infection. These are thought to be initiated by antigen-specific T cells. Sometimes they occur instead against noninfectious agents and may be directed against self-antigens, resulting in serious, potentially catastrophic consequences. Why reactivity to self, which undoubtedly occurs with great frequency in states of health, should begin to pose problems remains uncertain. A number of mechanisms for dampening this process and rendering it clinically silent have been identified. These include T-cell editing, clonal anergy, which effectively precludes activation, and clonal deletion [1–4]. Human autoimmune diseases comprise a group of maladies arising from the loss of normal tolerance. When adaptive immune responses occur against infectious agents, the immune system attempts to clear the foreign antigen. When the identical reaction occurs against a self-antigen, complete clearance

is usually impossible and the immune response culminates in the activation of effector-cell pathways and chronic inflammation. Thus, a perfectly good, normally protective process is corrupted and causes harm by virtue of its exaggerated amplitude and duration.

The incidence of common autoimmune diseases, such as rheumatoid arthritis, Type 1 diabetes mellitus and Graves’ disease, appears to aggregate in certain families, suggesting genetically related susceptibility to multiple diseases. In fact, individuals and families manifesting one of these diseases have a substantially greater risk of developing another. Thus, a common genetic basis for multiple autoimmune diseases seems very likely and is currently supported by substantial evidence. The contribution of genetics to many of these diseases is probably relatively modest in some and more substantial in others. This insight is derived from identical twin studies [5,6]. It is thought to be in the 10–30% range.

Thus, the environment must be considered as an important contributor to autoimmune disease susceptibility. Shared immunological mechanisms linking several diseases were proposed more than 40 years ago for autoimmune thyroid disease, Type 1 diabetes mellitus, systemic sclerosis and Sjögren’s syndrome [7,8].

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Underlying all forms of autoimmune disease resides the same cast of mechanistic suspects. The fundamental immune reactions in autoimmune disease do not differ from those found in normal responses. Cellular components of the professional immune system and the small molecules they generate (e.g., cytokines and lipid mediators) have been implicated in the pathogenesis of these diseases. Of particular importance in autoimmune tissue damage is the activated CD4⁺ T cell and the B cells with which it interacts. Thus, these diseases might be thought of as resulting from corruption of normal and vitally important functions.

How does this realization impact on our designing therapeutic strategies? Obviously the risks attached to altering normal immune responses should heighten our sense of caution. One approach might involve targeting antigen-specific T cells in a manner analogous to that of naturally occurring regulatory T cells. A concerted effort is currently underway to determine the usefulness of CD3-depletion in Type 1 diabetes mellitus [9,10].

Several pathways have been identified thus far that appear instrumental in the cross-talk between B and T cells. These support specific functions of the lymphocyte and, thus, their interruption might represent an effective strategy for reducing immune activity. These pathways include CD28, CD80 and CD86. In addition, T cells display CD154 (aka CD40 ligand) on their surface and this protein activates CD40 on the surface of target B cells [11]. Interfering with the CD40/CD40 ligand bridge dampens antibody generation. Besides its importance in B-cell function, CD154 can activate other cells bearing CD40, such as fibroblasts, epithelium and endothelial cells. Blocking CD40/CD154 signaling has been examined as a therapy for lupus [12] and may be useful in other forms of autoimmunity [13]. B-cell participation in these diseases might be considerably broader than previously suspected [14]. These cells not only represent the precursors of self-antibody-producing plasma cells but also efficiently present self-antigens to autoreactive T cells. Moreover, they produce several important cytokines and express costimulatory molecules that support T-cell function.

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B-cell depletion has been used initially to treat non-Hodgkin’s lymphoma, where it currently serves as a mainstay of therapy [15]. But it has also been found to be helpful in rheumatoid arthritis and lupus erythematosus [16,17]. Rituximab (anti-CD20) has also been studied in Graves’ disease [18] and thyroid-associated ophthalmopathy [19], although no large, well-controlled studies have thus far been reported. It is currently undergoing further clinical evaluation [20]. Other targets considered or already utilized for therapy include manipulating the inhibitory Fc receptor,

FcγRIIB, which may serve a critical role in maintaining self-tolerance. The RANK/RANKL pathway has been implicated in the transdifferentiation of monocyte lineage cells into osteoclasts. Thus, targeting this pathway might yield an important tool for modulating bone resorption in rheumatoid arthritis.

Identifying the mechanisms common to related autoimmune diseases might prove advantageous for the purpose of drug development. Recognizing overlapping therapeutic targets could be exploited by directing novel agents against those pathways involved in the pathogenesis of multiple diseases. But common signaling pathways are likely to serve important functions in states of health. Thus, their disruption might prove detrimental with regard to infection control, wound healing and tumor surveillance.

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We have witnessed the downside to this approach with the anticytokine agents recently introduced to the marketplace. These interrupt well-traveled pathways central to the inflammatory response. Increased incidence of opportunistic infections and iatrogenic tumors has plagued the extensive use of the anti-TNF-α drugs. Thus, while I believe that development of common therapies for multiple diseases is entirely possible, a one size fits all approach to drug design might come at a particularly high cost. It might be argued, therefore, that agents targeting more specific pathways, namely those involved peculiarly in the pathogenesis of individual diseases, rather than drugs designed against targets shared by several diseases, might prove to be a preferable approach. Clearly we must exercise great caution as allied autoimmune diseases and the common threads that tie them together become better understood. While executives in the pharmaceutical industry might dream of creating magic bullets that exhibit activity in multiple diseases, the potential for these agents to cause untoward effects must not be underestimated.

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