Why Autoimmunity?

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We have been addressing the rules and the required conditions by which the organism loses its characteristic control of self-reactivity, allowing it to transform to dangerous autoaggression. In this summary of how we view the various conditions underlying autoimmunity and the lack of regulation which we now know is a necessary component in causing disease, we will be referring mainly to our own work.

The autoimmune T cell repertoire

A *large self-directed repertoire exists against subdominant and cryptic selfdeterminants.* Most dominant determinants on a protein antigen induce tolerance during thymic development, but subdominant and cryptic (poorly expressed) determinants fail to do so. Since only about a third of antigenic determinants are dominant, this leaves a rather large majority of T cells available for later self-reactivity, either of the unwanted, aggressive type (autoimmunity) or of the valuable, protective type (cancer). These potentially reactive T cells remain ignorant for a variety of reasons, but in general because their complementary antigenic determinants are not displayed at a sufficient level on the cell surface of antigen presenting cells in a major histocompatibility complex (MHC) context. The crypticity of these determinants relates to the individual's MHC and the processing of the native antigen, rather than to structural features of the protein molecule. Thus, determinants in every area of the antigen can be either dominant or cryptic, depending on the MHC [1]. The cryptic, poorly expressed determinants on self antigens also fail to engage T cells to perform negative selection, just as they will not activate T cells after immunization with the native antigen in adjuvant. Another general subpopulation of self-reactive T cells remaining in the repertoire has insufficient avidity for the displayed complexes between the MHC and well expressed dominant determinants, and thereby it escapes to tolerance induction.

Degeneracy of T cell receptor recognition

The T cell receptor is degenerated in specificity and therefore, a variety of molecules may initiate autoimmunity; when a dominant determinant on a microorganism cross-reacts with a cryptic determinant of a self-antigen, this is called "molecular mimicry".

Molecular mimicry can often explain the initation of autoimmunity. It is an underappreciated fact that a single T cell can bind to a wide variety of different ligands for two separate reasons: first, approximately 30% of T cells express two different α chains, but more importantly, each T cell receptor (TcR) can bind to a multiplicity of peptide-MHC ligands. There need not be sequence identity between the mimicking peptide and a cross-reactive self-peptide [2]. The critical feature is that the small number of T cell receptor-interacting residues within an MHC context should be cross-recognizable. Accordingly, whenever a foreign virus or bacterium has a dominant determinant that activates a T cell from the ignorant repertoire (which has been protected from negative selection), and a TcR can react with a self-determinant leading to the induction of a Th1 response, autoimmunity may be initiated.

For example, the table represents a set of peptides that can activate T cell hybridomas raised to the amino-terminal nanomer determinant from myelin basic protein (MBP) in the B10.PL (H-2^u) mouse. The acetylated nanomer Ac-Ala-Ser-Gln-Lys-Arg-Pro- Ser-Gln- Arg can elicit T cells from a highly restricted V gene repertoire (e.g. Vb8, Va2.3), inducing experimental autoimmune encephalomyelitis (EAE); likewise, LDVMR(2-5) and 7-11:35-44 can induce EAE symptoms.

The relationship of antigen processing to dominance/crypticity

Processing creates the self: flanking residues as well as flanking determinants are crucial in establishing dominance hierarchies and "deciding" which T cells are to be protected from negative selection. The key specificity issue in the induction of tolerance is the same as in the induction of immunity: those determinants which are most available, having a reasonable affinity for the MHC, will become involved. Various difficulties related to processing will affect the establishment of the hierarchy of those determinants able to make an impact and to relegate others to obscurity. Hindrance of access to the MHC by a residue flanking a determinant can lead to the protection of specific T cells from ablation during thymic development, or later, from tolerance induction in the periphery [3]. Similarly, a residue hindering access between T cell receptors and particular MHC-antigen complexes will also act to

Table. Cross-reactive peptides for Ac1-9 specific hybridomas.

Designation of peptide	Sequence																
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Ac1-9	AcA*	S	Q	K	R	P	S	Q	R								
Ac1-11	AcA*	S	Q	K	R	P	S	Q	R	S	K						
G (1-11)	G A	S	Q	K	R	P	S	Q	R								
7-11:35-44	S	Q	R	S	K	I	L	D	S	I	G	R	F	F	S		
LDVMR(2-5)	L	D	V	M	R	S	Q	K	R								

*The amino-terminal alanine is acetylated.

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preserve this repertoire from tolerance induction [4]. Flanking residues also have an important part to play in providing favored target sites for processing enzymes. For example, dibasic motifs are readily attacked by endoproteases, which can open up tightly folded molecules and render binding determinants available for interaction with the MHC [5, 6]. The first determinant(s) rendered available during the unfolding process will bind to one of the ambient class II MHC molecules, becoming protected from enzymatic attack [7] to thereby emerge as the dominant determinant(s) on the antigen [6]. Other determinants distant from the groove may have further opportunities to bind to other class II MHC molecules. Peptides involved in the competition for class I MHC binding follow different rules and usually compete as relatively short peptides for class I binding sites in the endoplasmic reticulum. An important conclusion is that the hierarchy of response to different determinants on the antigen may be established from the display hierarchy. However, a second feature which must always be factored into the overall hierarchy of response is the nature and availability of the T cell repertoire.

Propagation of the response—"determinant spreading"

Once a response begins leading to inflammation, this response can spread to involve other determinants on the same molecule (intramolecular spreading) or determinants on other molecules (intermolecular spreading). Such an initiating determinant inducing IFNγ and TNFα production results in upregulation of MHC display as well as in enhanced antigen processing. It has recently been shown that IL-6 can reveal a previously cryptic determinant on hen lysozyme (amino acids 2-16) in the H-2d mouse, ostensibly by lowering pH in the early endosomes [8]. It is important to note that IL-6 knockout mice are unable to contract EAE, as it had been previously reported [9]. This interaction is further enhanced by the arrival of memory cells at localized sites of inflammation, with a greater density of surface adhesion molecules (such as ICAM, LFA-1, etc.) and costimulatory molecules. Therefore, previously cryptic determinants become visible to the immune system and in the local, heightened interaction environment gain the opportunity to initiate new responses, further driving the response. Because of regulatory systems to be discussed below, the spreading response may be stopped in its tracks, as it appears that a strong and continuous Th1-propelling response is required to maintain determinant spreading [10]. B cells with their ability to highly concentrate antigen at the site of class II MHC processing are also able to promote spreading [11]. Occasionally, a spreading response becomes controlled because the cells recruited are themselves regulatory [12].

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Autoimmune disease represents a failure of regulation

Most autoimmune reactivity is short-lived and quickly down-regulated. The failure to regulate such reactivity is one of the attributes of autoimmune disease. The very well-balanced immune system tends to be able to avoid the excesses of heightened or defective responsiveness. One general regulatory mechanism is antigen-centered, involving Th1/Th2 (CD4 T cells) or Tc1/Tc2 (CD8 T cells) balance and mutually inhibitory reactivity. A possibly distinct antigen-centered mechanism involves the direct interaction of CD8 suppressor cells with antigen-specific CD4 T cells. This type of interaction was extensively studied in the 1970's and 1980's and is summarized in an earlier review [13]. Another very effective mechanism is TcR-centered and utilizes determinants on the system's own receptors as elements in the regulation. In one circuit we have studied, after antigen exposure, that both CD4 and CD8 T cells are spontaneously activated to TcR determinants of the predominant T cell involved in autoreactivity (Vb8.2 in both EAE and collagen-induced arthritis [CIA]). Prevention of activation of either of the regulatory populations leads to a chronic autoreactivity, and under exacerbated conditions, even to death. As postulated earlier by Cohen [14], certain responses are hard-wired into the immune system (comprising an "immune homunculus") allowing these TcRs to be highly expressed and thereby able to induce self-regulatory activity. Once the aforementioned regulatory circuit becomes established, the homuncular, aggressive CD4 T cells are neutralized.

Our conclusion is that a coordinated series of events as described above must occur before an autoimmune response will ensue and be propagated. A companion conclusion is that some flaw in regulation must also be present to permit rampant and dangerous autoreactivity: self-reactive responses are usually transient and well-regulated. A complex combination of the five reasons above may provide an answer to the question "why autoimmunity?"

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