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If the ‘Adaptive’ Immune System Can Recognize a Significant Portion of the Pathogenic Universe to Which the ‘Innate’ Immune System is Blind, Then...

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Abstract

The ‘adaptive’ immune repertoire functionally recognizes pathogens (and their toxic products) that the ‘innate’ defense system misses. This requires that the self–nonself discrimination and the regulation of effector output be dependent primarily on somatic learning mechanisms (i.e. on the somatically generated, large, random ‘adaptive’ immune paratopes repertoire).

The ‘adaptive’ immune system (henceforth referred to simply as immune system) was evolutionarily derived by coupling a somatically generated, large and random paratopic (combining site) repertoire to the existent effector mechanisms used by the ‘innate’ immune system (henceforth referred to as the ‘defense system’). The recognitive elements of the defense system [e.g. alternate pathway C’lysis, Toll, lipopolysaccharide, mannose, etc. receptors] were retained in vertebrates expressing an immune system.

This coupling of a large, random, somatically generated repertoire to a small family of effector mechanisms introduced two new problems:

1. The somatically generated repertoire had to be sorted into these specificities which, if expressed, would debilitate the host, and those specificities which, if not expressed, would result in the death of the host by infection.
2. The sorted paratopic repertoire had to be coherently coupled to an effector mechanism that would effectively destroy and rid the pathogen. In addition to coherence, each pathogen had to be treated independently.

The recognitive elements of defense systems are germline-encoded and precoupled to their respective effector mechanisms (e.g. the alternate pathway of C’lysis or the particle sensors and carbohydrate receptors of macrophages). The paratopic repertoire of the immune system is somatically generated and requires a mechanism to appropriately couple it to an effective effector function.

I will refer to the sorting of the paratopic repertoire as Decision 1 and to the regulation of the magnitude and class of the response as Decision 2. Both sets of decisions require a somatic learning process, which means that the mechanism determining the outcome must be dependent on the somatically generated paratopic immune repertoire for recognition of antigen. If the recognitive elements of defense systems cannot see a significant portion of the pathogenic universe, then they cannot make an antigen-specific contribution to regulating the response to these antigens.

What is the reason to believe that there is a significant portion of the antigenic universe to which the defense system is blind? There are two arguments.

Firstly, mutants deleting the paratopic repertoire of the immune system (e.g. Rag^{-/-}), but leaving the recognitive repertoire of the defense system intact, succumb to 'opportunistic' infection and accept grafts between disparate individuals. 'Opportunistic' infection is a euphemism for pathogens held at bay by the repertoire of the immune system. Mutants, such as athymic, which delete effector T-helper activity and consequently immune system responsiveness, also die of opportunistic infection and accept disparate grafts. Unlike the immune system, which is effector T-helper dependent, the defense system operates effector T-helper independently.

Secondly, the selective pressure during evolution for a somatically generated random paratopic repertoire must have been the limitations faced by germline-encoded repertoire of defense systems. As the jawed vertebrates emerged, the germline evolution of the recognitive elements of their defense systems became too slow to keep pace with the ability of mutants of pathogens as well as new pathogens to escape recognition. The only solution was to somatically generate a repertoire that divided the antigenic universe into epitopes that were combinatorially distributed on antigens. In this way, no pathogen could escape recognition due to limitations in the paratopic repertoire.

What are examples of antigens not dependent on defense system recognition? All of the monomeric toxins like diphtheria, tetanus, cholera, botulinus, streptolysin, *Cl. Welchii* lecithinase, α - and β -haemolysins of streptococci, etc. escape defense system recognition. Also, there is the viral universe dependent on recognition of a vast family of major histocompatibility complex-bound peptides which the defense system ignores. The requirement that Decisions 1 and 2 operate for these antigens means that they also operate for all antigens. Predictably, if all of the antigen-recognizing sites of the defense system were deleted, the functions referred to as Decision 1, the sorting of the repertoire, and Decision 2, the regulation of magnitude and class of the effector response would remain operative.

In sum then, the immune system repertoire sees everything that the defense system sees; the defense system repertoire is blind to a significant portion of the antigenic universe that the immune system sees. The fact that there exists a proportion of the pathogenic universe seen uniquely by the immune system's repertoire sets the way in which Decisions 1 and 2 can be made.

The consequence of the limited recognitive potential of the defense system is that the response behaviour of the immune system becomes dependent on somatic learning mechanisms. The arguments that recognitive elements of the defense system like pathogenicity [1,2] and danger [3,4] determine whether Decision 1 or Decision 2 is brought into question because these characters are properties of germline-encoded recognitive elements that are, in large measure, blind to the 'opportunistic' pathogenic universe and to their toxic products (often monomers).

If the immune system sees a significant proportion of the pathogenic universe to which the defense system is blind, then a significant body of work needs reinterpretation.

No self-component can be immunogenic effector T-helper (eTh)-independently. Any host component that is immunogenic eTh-independently would be inductive-only and that would be lethal. The defense system operates eTh-independently because its antigen-recognizing receptors have been selected in the germline, not to see the components of the host species.

Suppression cannot be used to sort the immune paratopic repertoire (Decision 1), because inactivation of a response to a self-component on the antigen-responsive cell itself will

inactivate the response of that cell to a pathogen. Suppression can only play a role in regulating the class of response (Decision 2), because it is somatically selected to express an anti-nonsel repertoire [5].

Idiotyp network regulation as a general mechanism is ruled out because (1) it denies the necessity for Decision 1, the sorting of the repertoire, and (2) any antibody at a sufficient concentration to regulate is also at a sufficient concentration to activate the biodestructive and ridding effector mechanisms. There is no way to sort the repertoire (Decision 1) by mechanisms operating at the level of Decision 2, the regulation of effector function.

Antigen-specific regulation of the immune repertoire by the recognitive elements of the defense system could only operate for antigens seen by both. In this case, one or the other recognitive system would be redundant. One reason that the defense system's recognitive elements have been maintained by evolutionary selection is that the effector response to the pathogens that they do see is immediate. The immune system must be induced to an effective threshold level of effector activity and that takes time. As the immune repertoire was superimposed on the effector mechanisms of the defense system, it is this repertoire that regulates the effector output, certainly for those antigens that the 'innate' defense system cannot see. This latter has a fixed, germline-selected relationship between recognition and effector function, which therefore does not require the two somatically operating Decision sets.

An 'innate' system that misses much of what the 'adaptive' system sees has as its consequence that somatic learning at two levels (Decisions 1 and 2) must operate.

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