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Antigen-receptor degeneracy and immunological paradigms

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Abstract

This paper discusses some consequences of the discovery that antigen receptors are degenerate: Immune specificity, in contrast to the tenets of the clonal selection paradigm, must be generated by the immune response down-stream of initial antigen recognition; and specificity is a property of a collective of cells and not of single clones.

Keywords: T cells; T-cell receptor; Inflammation; Specificity; Degeneracy; Clonal selection; Cognitive paradigm

1. Degeneracy problems

Degeneracy, in the present discourse, refers to the capacity of any single antigen receptor to bind and respond to (recognize) many different ligands. The Oxford English Dictionary (Second Edition, 1989) defines the primary meaning of *degeneracy* as:

> Having lost the qualities proper to the race or kind; having declined from a higher to a lower type; hence, declined in character or qualities; debased, degraded.

The multi-functionality of antigen receptors, one imagines, might have been called by any number of more virtuous names, but *degeneracy* was the chosen term. Is the slur apt? Is nature herself debased, or is it only that our expectations of her have been disappointed?

Degeneracy of antigen receptors leads to two different but related complications: Any single antigen epitope will be able to activate a great many different lymphocyte clones (*poly-clonality*) and any single lymphocyte clone will be able to recognize many different antigen epitopes (*poly-recognition*).

The first complication, poly-clonality, is experimentally proven by the observation that a mouse thymus engineered to express an MHC molecule that presents only a single peptide is still able to positively select a very large T-cell receptor repertoire (Ignatowicz et al., 1996); given the right conditions, extreme poly-clonality can be activated by a single epitope. Nevertheless, immune responses are not, as a rule, characterized by extreme poly-clonality; in fact, most natural T-cell responses are oligo-clonal (Douek et al., 2003). So, there must be a mechanism or mechanisms that operate to restrict poly-clonality in wild-type adaptive immune systems. The inherent potential for extreme poly-clonality, in practice, may be tempered by clonal competition. Competition among clones for access, energy or space will most likely reward the fast and the avid. Since the best clones should win, clonal competition does not threaten the logic of the clonal selection theory (CST) of adaptive immunity.

The second complication of degeneracy, poly-recognition, is more problematic for the CST. Poly-recognition is experimentally proven by the capacity of a single T-cell clone to respond to perhaps millions of peptides (Maverakis et al., 2001). Since the antigen receptor of any clone is not strictly specific, a clone, down-stream of its initial selection, may be activated by unpredictable epitopes. The CST is based on the strict specificity of immune system clones; without strict specificity of recognition there could be no self-nonself discrimination and no reliable immune memory. Receptor degeneracy challenges a basic tenet of the CST paradigm.

In this article, we shall explore how the discovery of receptor degeneracy affects our understanding of the organization and function of the immune system. We shall discuss seven fundamental features of the immune system. To clarify the issues raised by degeneracy, we shall compare the classical view of the CST (Burnet, 1969) at each point with the view of what has been called the *cognitive paradigm* (Cohen, 1992). There are other paradigms that take positions intermediate between classical CST thinking and the cognitive paradigm; but here we shall contrast only these two extreme positions for the sake of brevity. The seven

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Table 1
Seven features of the immune system and their interpretation according to the classical CST Paradigm and the cognitive paradigm

No.	Feature	Specificity paradigms	
		CST paradigm	Cognitive paradigm
1	Specificity	Intrinsic property	Emergent property
2	Functional unit	Individual clone	Cell collective; anatomy
3	Action	Clonal response	Co-response; modeling
4	Discourse	Monolog	Dialog–symposium
5	Output	Discrimination	Inflammation
6	Objective	Defense	Maintenance
7	Genetics	Meta-germline	Germline & meta-germline

points are summarized in Table 1, and will be itemized below.

1.1. Specificity

The CST assumes axiomatically that antigen receptors are specific for specific antigen epitopes; specific lymphocyte clones, by virtue of their specific antigen receptors, could only be activated by specific antigens. Specificity was thought to be an *intrinsic property* of the antigen receptor. Thus, the CST attributed the specificity of an animal's immune response to the antigen specificity of the antigen receptors of its lymphocyte clones. Immune specificity needed no explanation other than reduction to receptor specificity. For this reason, the discovery that antigen receptors are degenerate, damages the foundation of CST thinking; degeneracy means that immune specificity cannot be *reduced* to receptor specificity.

The cognitive paradigm presents a more complex view of immune specificity; the cognitive paradigm perceives immune specificity as an *emergent property* of the immune system (Cohen, 1992; Cohen, 2000). An emergent property is a characteristic of a system that cannot be explained merely by the properties of the system's component parts. Emergent properties are not reducible to the discrete properties of individual components; emergent properties arise from *collective interactions* between individual components (Cohen, 2000; Shnerb et al., 2000). Since antigen receptors are intrinsically degenerate, the strict immune specificity manifested by immune responses at the level of the whole animal cannot be reduced to clonal selection, but must emerge by interactions subsequent to clonal degeneracy (Cohen, 2000). Specificity, therefore, must emerge from how the immune system *behaves* after clonal selection, and not automatically from the act of clonal selection itself. In other words, specificity is not given to the immune system, but is created by the immune system, despite the degeneracy of its component clones.

1.2. Functional unit

According to classical CST thinking, the basic operating unit of the adaptive immune system is the independent lymphocyte clone; a clone is either selected (to proliferate and differentiate) or not selected by an encounter with antigen, and that's that. No single clone is concerned with other clones or is even aware of them. The cognitive paradigm, in contrast to the CST, sees specificity as emerging from the collective interactions of many different agents. This is the gist of point 1, above. Moreover, the anatomy of the immune system organizes the discrete contacts necessary for collective cell interactions (Cohen, 2000). The emergence of immune specificity involves the movements of immune cells in defined anatomical compartments. The immune system's anatomy is part of the functional immune unit.

1.3. Basic action

The CST teaches that the basic activity of the immune system is the clonal response.

The cognitive paradigm, as we said above, proposes that immune specificity emerges from the interactions of a cell collective. These collective reactions generate what has been termed a co-response (Cohen, 2000; Cohen, 2000). Briefly, the concept of co-respondence expresses the fact that clones of T cells and B cells respond to more than the epitopes that interact with their antigen receptors; in addition to antigen epitopes, lymphocyte clones respond to each other, to the state of the antigen presenting cells (APC: dendritic cells, macrophages, etc), and to the state of the tissue in which they interact. Cytokines, chemokines, heat shock proteins (Zanin-Zhorov et al., 2003), and other innate receptor–ligand interactions generate a web of mutual cellular interactions. The cytokine environment, for example, integrates information about the responses of adjacent cells to their antigen epitopes and to the innate signals they see. Chemokines tell cells where to go. Additional innate receptor interactions also influence the phenotype of the collective response. In this way, the responses of individual clones are fine-tuned (Grossman and Paul, 2001) by the collective; each cell modifies its response in the light of the collective response of the others. Co-respondence thus generates a collective *meta-response* (Cohen, 2000). The specificity of the collective meta-response *emerges* from the web of mutual interactions that influences each cell, despite its degenerate antigen receptor.

Immunology needs precise mathematical modeling and computer simulation to help us understand the emergence of immune specificity from the collective co-response (Meier-Schellersheim, 1999; Louzoun et al., 2003; Kam et al., 2001). The interactions are simply too complex to be grasped by intuition.

1.4. Discourse

The CST describes a monolog of autistic lymphocytes; each lymphocyte hears only the voice of its own antigen receptor. The cognitive paradigm, in contrast, describes a dialog between lymphocyte clones, APCs and the

tissues—perhaps a more apt word would be a symposium—leading to the emergence of a group decision, which is the expressed phenotype of the immune response (Cohen, 2000).

1.5. Output

The output of the CST monolog is the discrimination between specific antigens; receptor specificity allows the immune system to separate the foreign from the self (Burnet, 1969)—or perhaps to distinguish between danger from non-danger (Anderson and Matzinger, 2000). But rather then specific discrimination, the output of the immune system, according to the cognitive paradigm, is the management of the process called *inflammation* (Cohen, 2000; Cohen, 2000). Inflammation is the response of the multi-cellular creature to any form of injury—a response that usually leads to healing (Florey, 1970). Molecules of inflammation are required to facilitate wound healing, bone repair, connective tissue formation, angiogenesis, regeneration of cells and tissues, apoptosis of damaged or aberrant cells, as well as to activate host defense. The immune system detects the need for inflammation and applies the necessary molecules and cells in the right amount, order, dynamics and site. The immune system is not merely the CST department of defense, it is the cognitive paradigm's department of the health, education and welfare (Cohen, 2000).

1.6. Objective

Discrimination between antigens, according to the CST, allows the immune system to defend the self against foreign invaders; the immune system specializes in recognizing the foreign (Cohn, 2003). The cognitive paradigm, in contrast to the CST, proposes that the aim of the immune system is to manage inflammation so that it maintains the body (Cohen, 2000; Cohen, 2000; Efroni and Cohen, 2002). This difference in perceived aims is the essential difference between the CST and cognitive paradigms (Cohn, 2003; Efroni and Cohen, 2003): The CST proposes that the immune system exists to search out and destroy pathogens. The degeneracy of the antigen receptors thus constitutes a serious obstacle to any absolute discrimination between the self and the world of pathogens.

The cognitive view, in contrast to that of the CST, is that rejecting pathogens is just one aspect of the physiology of body maintenance; the immune system is responsive primarily to the state of the self (Coutinho et al., 1984). The immune system, in a word, is concerned mostly with the physiology of body maintenance. Receptor degeneracy does not threaten the cognitive paradigm to the degree to which it disturbs the CST. Receptor degeneracy, in fact, is an opportunity for the emergence of specificity down-stream of antigen recognition.

Color vision provides an example of the power of receptor degeneracy (Cohen, 2000). The human retina has only three different kinds of color receptors (red, green and blue cones) that are very degenerate; each kind of cone responds to a broad range of overlapping photon energies. Nevertheless, we are able, down-stream of the retina, to recognize specifically many thousands of different colors. The cones do not encode color specificity. Rather, the patterns of neuronal firing distal to the retinal color receptors encode the specificity of color vision. So too do patterns of degenerate, co-responding lymphocytes and their allied cells encode the specificity of the immune response; the patterns generated by co-respondence are down-stream of initial clonal activation (Cohen, 2000).

1.7. Genetics

The CST foresaw the meta-germline generation of antigen receptors and motivated the research that led to the discovery of the recombinatorial mechanism of antigen–receptor genetics (Efroni and Cohen, 2003). At the same time, it drew attention to the antigen receptors, the CST relegated innate immunity to the back seat of immune interest. The cognitive paradigm, in contrast to the classical CST, depends on the germline; the cellular dialog-symposium relies on germline (innate receptor) interactions to connect the web of co-responding cells (Atlan and Cohen, 1998). The cognitive paradigm suits the immunological attention recently directed to the innate receptors (Medzhitov and Janeway, 2002).

2. Living with degeneracy

Degeneracy is blameworthy when it comes to human behavior. But at the molecular and cellular scales, degeneracy is essential. The degeneracy of molecular interactions allows for the evolution of new functions from old molecules and, thus, for the complexity of the living organism (Solomon and Shir, 2003). The plasticities of the brain and the immune system arise from the degeneracy of cell signaling. Antibiotics and other pharmaceuticals work by virtue of degenerate receptors. No, molecular degeneracy is not a *debasement* or *deline* from a higher to a lower type; molecular degeneracy is the vehicle of nature's progress (Cohen, 2000). It's just that we have to learn how to understand it better.

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