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Reconceiving autoimmunity: An overview

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ABSTRACT

Three interconnected positions are advocated: (1) although serving as a useful model, the immune self does not exist as such; (2) instead of a self/nonself demarcation, the immune system 'sees' itself, i.e., it does not ignore the 'self' or attack the 'other;' but exhibits a spectrum of responses, which when viewed from outside the system appear as discrimination of 'self' and 'nonself' based on certain criteria of reactivity. When immune reactions are conceived in terms of normal physiology and open exchange with the environment, where borders dividing host and foreign are elusive and changing, host defense is only part of the immune system's functions, which actually comprise two basic tasks: protection, i.e., to preserve host *integrity*, and maintenance of organismic *identity*. And thus (3) if the spectrum of immunity is enlarged, differentiating low reactive 'autoimmune' reactions from activated immune responses against the 'other' is only a matter of degree. Simply, all immunity is 'autoimmunity,' and the pathologic state of immunity directed at normal constituents of the organism is a particular case of dis-regulation, which appropriately is designated, *autoimmune*. Other uses of 'autoimmunity' and its congeners function as the semantic remnants of Burnet's original self/nonself theory and should be replaced. A new nomenclature is proposed, *concinnity*, which more accurately designates the physiology of the animal's ordinary housekeeping economy mediated by the immune system than 'autoimmunity' when used to describe such normal functions.

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1. The immune self

The functional difference that determines recognition of the foreign may result from some quantitative antigen affinity difference, the context in which the antigen is seen, or the degree of interruption in network dynamics induced by such an antigen. Accordingly, the overall function of the immune system may be defined as maintenance of molecular (antigenic) homeostasis (Poletaev et al., 2008). On this general view, a systems-wide analysis of reactivity – not the discriminatory power of individual lymphocytes – determines identity and immune specificity.[1] In other words, the immune system's overall state, its collective behavior or network pattern, produces a group property, which specifies, in traditional terms, 'self' and its disruption—designated 'nonself' or the 'other.' Such integrated (or connected Pradeu and Carosella, 2006; Pradeu, 2012) states are quiescent and disrupted ones, induced by 'foreign' elements, generate immune activation. Such properties are thus determined by a self-regulated system controlled by a group phenomenon of interactions among several components comprising a vast interactive system of antigen-presenting cells, effector T and B cells, regulatory T cells and a diverse soup of molecular signals (Kim et al. 2007).[2]

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[1] The exquisite specificity that seemed conclusively demonstrated by Landsteiner's research with haptens, but has recently proven to be highly degenerate in terms of T-cell receptor (TCR) recognition of different peptide/MHC ligands, is referred to as 'polyspecificity' (Wucherpfennig et al., 2007; Wooldridge et al., 2011; cited by an anonymous reviewer). Why these monoclonal TCRs are dramatically less specific than whole immune sera is unexplained, but the finding seems clear: "Although individual clones can be demonstrated to be less than specific, the immune response, at the population level, is manifestly specific" (Cohen, 2001). Although no 'solution' has been offered, perhaps collective, cooperative molecular and cellular interactions are required for high degrees of immune specificity, which re-enforces the notion that capturing the immune system as a whole will reveal more subtle aspects of regulation.

[2] One such regulatory mechanism awaiting further elucidation is the role of exosomes. Exosomes, containing a variety of proteins and mRNAs, are secreted membrane vesicles (30–100 nm), which are formed by inward budding of late endosomes. Epithelial cells, dendritic cells, B and T cells, mast cells and tumor cells release exosomes, which have been found in human plasma, urine breast milk, broncoalveolar lavage and malignant effusions (reviewed in Wahlgren et al., 2012; Wendler et al., 2013). They have been implicated in cell-to-cell signaling including antigen presentation (Sprent, 2005) and RNA transfer (Valadi et al., 2007). The ability to impact immune signaling between antigen presenting cells and T cells, as well as between T cells (Wahlgren et al., 2012) implicates a significant role for exosomes in immune regulation. Of particular interest, given the renewed excitement about immune therapies for cancer (Couzin-Frankel, 2013), is the largely undefined role of exosomes in modulating the immune response to tumors (Zhang and Grizzle, 2011; Clayton and Mason, 2009; Bobrie and Théry, 2013). Besides anti-tumor immune suppression resulting from malignant cell secretion of exosomes

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Given the highly contextualized nature of immunity dependent on a dynamic system, the borders of the *self* and the identity of the *other* are increasingly appreciated as inconstant, and often elusive (Tauber, 2000). Bountiful evidence has shown that so-called 'autoimmunity' is a normal, *active* process, and in these newer views, such functions are regarded as integrated within a more complex normal physiology (Schwartz and Cohen, 2000; Horn et al., 2001; Coutinho, 2005). (Chimeric transplants are an example of active tolerance mechanisms Starzl and Demetris, 1995). "Natural autoantibodies" have been characterized and quantified in both normal (Avrameas, 1991; Coutinho et al., 1995) and disease states (Notkins, 2007). Serving a key role in normal immunological physiology, autoimmune-sensing mediates the body's normal processing of senile cells, repair of damaged tissues, and immune destruction of malignancies (Huetz et al., 1988; Poletaev and Osipenko, 2003).

Such self-surveillance may well be the original function of the immune system, and so some have suggested that the primordial role of the immune system was to serve perceptive and communicative functions of the body's own physiology to establish and then maintain host *identity* (Stewart, 1992, 1994b; Tauber, 2003; Ramos et al., 2006). Given the striking correlations of shared receptors and mediators, intimate anatomic relationships, and ontogenetic origins, that earlier phylogenetic function might descend from a common neuro-endocrine communicative function (Rabin, 1999; Ader, 2006). Accordingly, under pathogenic pressure, the immune system may have developed specialized capacities as a defensive system, which largely explains the evolutionary forces that have molded the immune system in higher vertebrates. In the host defense scenario, the immune system distinguishes between pathological nonself and benign nonself by recognizing microbial patterns and certain evolutionary-conserved pathogenic markers, which trigger the immune response (Janeway, 1992; Medzhitov and Janeway, 2002). However, if we are to understand the immune system's basic function (and ultimately its organization and regulation) normal "house-maintenance" functions must be further elucidated. Accordingly, autoimmunity, originally conceived as aberrant regulation, must now be re-conceived, which begins with examining the status of the self, that organizing precept of contemporary immunology.

By the mid-1990s, some critics argued that 'the self,' having served a useful metaphorical function, had irretrievably weakened under the weight of experimental and critical review (Matzinger, 1994; Tauber, 1994a, 2000; Pradeu 2010, 2012). One aspect concerns the difficulty of defining the immune self, itself, which has several general meanings: (1) the "organismal self"—the epistemological functional category immunologists typically employ; (2) the "immunological self"—an ontological construction which draws from molecular definitions and builds upon Burnet's theory of tolerance; and (3) the "immune self"—a metaphysical formulation of the system-as-a-whole (Ulvestad, 2007 pp. 88ff.). Definition #1 has proven problematic: There are at least half a dozen different conceptions of what constitutes the immune self (Matzinger, 1994, p. 993): (1) everything encoded by the genome; (2) everything under the skin including/excluding immune "privileged" sites; (3) the set of peptides complexed with T-lymphocyte antigen-presenting complexes of which various sub-sets vie for inclusion; (4) cell surface and soluble molecules of B-lymphocytes; (5) a set of bodily proteins that exist above a certain concentration; (6) the immune network itself, variously conceived. While these versions may be situated along a continuum between a severe genetic reductionism and complex organismal constructions (Tauber, 1996, 1998, 1999), each shares an unsettled relationship to a dichotomous model of self and other that lie at the very origins of immunology (Tauber, 1991, 2003).

With so much dispute surrounding the definition of self, a growing counter position suggests that the "self" might be better regarded as only a metaphor for a "figure" outlined by the immune system's silence, i.e., its non-reactivity. That figure is inconstant and modified upon certain conditions. For instance, in pregnancy, the fetus clearly differs genetically from its maternal host, yet enjoys immunological indifference. If 'silence' designates immune selfhood, what constitutes the threshold or borderline of activity that differentiates the 'other?' Is such a demarcation artificial, inasmuch as so much of immune activity is on-going background 'noise' of immune surveillance, lymphocyte turnover, and basic physiological processing of abnormal cells? Inasmuch as the immune response is by and large defined by studies of the activated state, we have little insight about baseline immune activity. Simply stated, the gradations of the immune response, from resting to various conditions of primed or pre-activated conditions to full blown responses offer different characterizations of the immune system, one in which *the self* is enfolded in obscurity. Perhaps the immune system itself will have to suffice. And if that view is adopted, the self/nonself mantra of contemporary immunology requires radical redress, of which definition #3 above (the system-as-a-whole) must suffice.

While the 'immune self' governs the practice and theoretical orientation of most practicing immunologists, the neat boundaries of 'self' and 'other' continue to be broken and replaced by a spectrum of functions based on a gradation of immune responses that do not neatly fit the self/nonself division.[3] Various paradoxes demand explanation (Pennisi, 1996), and the self's epistemological standing in immune theory has been roundly critiqued (e.g., Varela et al., 1988; Tauber, 2000). Indeed, despite the appeals of the prevailing paradigm, the criteria for establishing the immune self have not been established, and, furthermore, the self/nonself dichotomy cannot account for various immune functions. Aside from incomplete accounts of immune tolerance, discrepancies arising from a continuum of 'autoimmune' reactions – ranging from normal physiological and inflammatory processes to uncontrolled disease initiated by an immune reaction gone awry, i.e., a dis-regulated state of normal surveillance – have destabilized the self/nonself dichotomy. Indeed, immune reactivity against the organism's own constituents is an ordinary finding intrinsic to the behavior of the surveillance functions of the immune system and thus an important component of normal physiology. Immune reactivity is, in fact, bidirectional—the immune system becomes

(*footnote continued*)
(Yu et al., 2007; Marleau et al., 2012), dendritic-derived exosomes can directly kill malignant cells (Munch et al., 2012). Given the apparent non-uniformity of exosome contents and the apparent diversity of their secretory patterns and context-dependent effects, these mediators are likely to prove most difficult factors to characterize. However, the importance of discerning their role in immune system dynamics seems self-apparent, given their likely role as supplementary to the cytokine network, which has served as the primary regulatory apparatus of the immune system.

[3] Given the historical antecedents to the self question, when the centrality of such discrimination has been contested, much controversy has ensued, which is perhaps best represented by a special issue of *Seminars in Immunology*, in which a wide spectrum of opinions emerged (Langman, 2000): Some detractors generously called for a pluralistic approach; others regarded the crisis over the self as overblown; most agreed that immune selfhood is increasingly a polymorphous and ill-defined construct, but immunology required the dichotomous construct. The controversy had gained its major momentum as a result of presentation of the "danger theory" by Polly Matzinger and Ephraim Fuchs (Podolsky and Tauber, 1997, pp. 361–366), which generated much comment and signaled to *The New York Times* that the self paradigm was being threatened. Reporting on three different experimental scenarios appearing in a single issue of *Science* (Forsthuber et al., 1996; Ridge et al., 1996; Sarzotti et al., 1996), the general public was alerted to the apparent failure of what were heretofore well-accepted self/nonself discriminatory boundaries (Johnson, 1996, p. C3).

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