



Immune System,
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Introduction

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Abstract

The idea that the immune system distinguishes between self and non-self was one of the central assumptions of immunology in the second half of 20th century. This idea influenced experimental design and data interpretation. However, in the face of new evidence there is a need for a new conceptual framework in immunology.

Keywords: immune self; philosophy of immunology; self/non-self discrimination.

In the last several decades, immunology has become a subject of attention of several branches of humanities. This successful and rapidly developing branch of biology served as an exemplar of a paradigm change and conceptual development in the history of science (Silverstein 1989, Tauber 1994; Tauber & Chernyak 1991). Its political and military discourse was studied extensively in the context of political science and anthropology (Cohen 2009; Haraway 1989; Martin 1990; Napier 2003). Reproductive immunology attracted the attention of gender studies (Howes 2008), while social interactions within the field were investigated from the point of view of epistemology of science (Fagan 2007). The immune system has become a subject of philosophical reflection on the nature of an organism and the character of self (Howes 1998; Pradeu 2010; Pradeu 2012; Tauber 1994). Cognitive properties of the immune system have provoked a discussion about the nature of cognitive systems (Hershberg & Efroni 2001; Varela et al. 1988; Varela 1994; Cohen 2001).

One leitmotif that runs through most of these humanistic studies of immunology is the question of the immune self. Indeed, the idea that the role of the immune system is to ignore self and attack non-self was central to immunology for several decades after the Second World War (Tauber 1994; 2012). It was first introduced by

Macfarlane Burnet as a part of the Clonal Selection Theory (Burnet 1959), but its implicit presence in immunology can be traced back to Elie Metchnikoff and his concern with an organismal identity in the context of immunology and development (Tauber 1994; Tauber & Chernyak 1991). The importance of the self/non-self model is illustrated by the fact that immunology has often been defined as the science of self or as the science of self/non-self discrimination (Klein 1984; Lopez-Larrea 2012; Wilson 1971).

The idea that the immune system discriminates between self and non-self is intuitively appealing. If the immune system can protect an individual from infection and pathology, it must have the power to tell the individual from the foreign, pathogenic agents. How, otherwise, could the immune system serve as a sentinel for an organism? This simple idea also seemed useful in explaining phenomena like organ graft rejection and autoimmunity. From the point of view of the self/non-self model, an autoimmune disease is a form of misrecognition of self-tissues as foreign. Infection and pathology result from the failure to respond effectively to non-self (Khalturin & Bosch 2007)

Additional support for the realism regarding the immune self came from the empirical observation that the immune system protects the individual rather than individual cells. In fact, individual cells of the body may be sacrificed to protect the self. Cytotoxic T cells or NK-cells can kill infected or pathologically transformed cells of the body to prevent pathogen spread and disease (Trambas & Griffiths 2003). Apoptosis, regulated cell death, has also been found to be an effective defense strategy in various forms of the actions of the immune system (Barber 2001). Thus, it is only multicellular organisms that can be equipped with an immune system. The presence of the system is indicative of a certain degree of unification, which, together with other distinctive features, can constitute an organism as a biological individual (cf. Ben-Neriah & Karin 2011; Domazet-Loso & Tautz 2010). From this perspective, immunogenicity could be considered as criterion of inclusion for the organism (Pradeu 2010) and the immune system might seem to be involved in protecting and defining some weakly emergent (reducibly emergent) higher level individual rather than its lower level parts. (The idea of weak emergence was developed and applied in a biological context by Bedau 1997; 2008).

Despite its long history and intuitive appeal, the paradigm of self/non-self discrimination in immunology has been in crisis since the 1980s. The reason is not that the concept of the immune self proved to be vague or ambiguous (Matzinger 1994). (In fact, most key biological concepts like gene, organ, immunity or life are chronically ill-defined). Rather, it was the empirical evidence that undermined its credibility. On one hand, it has been found that autoimmunity is an important part of an organism's physiology (Cohen 1992; Coutinho et al. 1995; Quintana & Cohen 2004). On the other hand, it became clear that the recognition of innocuous foreign bodies as parts of the organism is crucial for maintaining integrity and health. Indeed, the power to respond to non-self as self turns out to be essential in protecting an individual from allergy (McFadden & Basketter 2000); it serves as a basis for oral toler-

ance and ensures the maintenance of a defined population of commensal microbes in the gut. This unexpected, from the point of view of self/non-self model, function of the immune system also proved to be a form of a defense strategy against opportunistic microbes. If recognized as foreign, some opportunistic agents could induce inflammatory-derived tissue damage opening themselves a route to infection and colonization of the host (Hill & Artis 2010).

The crisis of the self/non-self paradigm in immunology has inspired many researchers to look for an alternative framework that could accurately capture the reactivity of the immune system. It has been proposed that instead of distinguishing self and non-self, the system is involved rather in discrimination between infectious non-self and non-infectious self (Janeway 1992). Despite being able to address some of the concerns of the original model, the revised model by Janeway was not able to take into account such phenomena as sterile inflammation, in which the immune system responds despite the lack of an infectious agent. Thus, Polly Matzinger formulated the so-called “Danger Model,” according to which the immune system is more concerned with protecting the individual from damage than with discriminating between self and non-self. From the point of view of this model, the immune system recognizes and responds to molecules released during stress or tissue damage that serve as danger (alarm) signals (Matzinger 2002). This model was supported by the finding that endogenous ligands of innate immune receptors initiating inflammatory responses are abundantly present during infection and tissue damage. Nevertheless, most recent data put this model in question because there is accumulating evidence that innate immune receptor agonists can induce the receptors to promote tolerance and inhibit inflammatory responses in certain circumstances (reviewed in Kubinak & Round 2012)

One should note that most of the attempts to provide general model of the reactivity of the immune system were based on the assumption that the immune system can be either switched on or off, active or inactive. However, accumulating data indicates that the immune system is never really off and that discriminatory powers of the active system are very subtle and irreducible to a simple binary logic (Eberl 2010; Leng and Bentwich 2002; Świątczak et al. 2011). Instead of occupying two alternative states, the immune system produces uniquely tailored responses to counterbalance effects of the fluctuations in the biochemical and microbial micro-environment (Garret et al. 2010; Barbosa & Rescigno 2010). This is particularly evident in the context of the gut immune system, which is constantly involved in antigen sampling, IgA antibody release and antimicrobial peptides production. In addition, differentiation of pro-inflammatory T-cells is an integral part of tolerance induction in the immune system and it is the balance with other types of T-cells (Regulatory T cells, Th2 cells) that prevents these cells from inducing intestinal inflammation (Lohner et al. 2008).

The activity of the immune system is not limited to initiating immune responses. It also participates in modulating strength of the intraepithelial tight junctions, in regulation of the functions of other bodily systems, and in the body maintenance

by removing dead, damaged and mutated cells. The activity of the immune system thus appears to be highly dynamic and complex. Indeed, the power of the system to neutralize the effects of biochemical and microbial fluctuations depends on a network of cells and molecules that integrate information about various aspects of the environment in a given anatomical niche (Cohen 2000). Crucial players in this systems-level integrative process are dendritic cells that collectively translate immune recognition into an active response (Rimoldi et al. 2005; Rescigno 2011; Świątczak 2012).

Since the self/non-self model is doomed to failure, there is a need for new overarching framework that could capture the function of the immune system. Cognitive approach provides one possible source of metaphors and concepts that could help to make sense of the action of the immune system and would help to appreciate the richness and sophistication of the states of the immune system. Humanities, with their abstract conceptual framework, could contribute to the ongoing debate on the conceptualization of the activity of the immune system.

The present issue of AVANT is a small step towards an interdisciplinary debate about the foundational issues in immunology. It contains reviews and review-like papers written by well-recognized scholars, whose work is dedicated to theoretical foundations of immunology. The Authors integrate extensive knowledge of the immune system with a deep understanding of social, historical, theoretical and philosophical aspects of immunology. The commentary by Alfred Tauber addresses the current status of the self metaphor in immunology. He emphasizes the need for an ecological sensibility and points out that the immune system cannot be studied in isolation from its context of interactions with commensal bacteria and other bodily systems. The interview with Uri Hershberg helps to understand the role of metaphors in immunology and addresses important questions regarding the status of the immune self. Neeraja Sankaran reviews historiography of immunology since 1999, demonstrating that it is no longer an immature field of study, but a flourishing and fascinating discipline. Yair Neuman comments on his own original approach to immune self that he considers as an interpretative process. In the introduction to his recently published book on the development of the concept of immunity, Ed Cohen argues that the political and legal connotations of this concept are still implicitly present in the conceptual structure of immunology. The series of articles by our guests is completed with a short review of selected books and papers dedicated to the foundational issues in immunology, prepared by Jacek Podgórski.

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