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MINIREVIEW

The *self*/*non-self* dualism is still so marked as it was considered for a long time?

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Abstract

For several decades the immune system has been described mainly as a molecular machinery aimed to recognize and eliminate all the *non-self* molecules or organisms. Actually, recent evidences support the presence of a constant cross talk between the immune system and microorganisms that live within the host as symbionts resulting in the tolerance of *non-self* bacteria and yeasts. As a whole, the "defensive" role of immunity, described as highly prominent in several contexts of the modern biosciences, should be revised taking into account that the immune system defined during evolution which organisms have to be excluded and killed, and which have to be maintained. These new evidences support the idea that each animal is a dynamic and context-dependent entity with a mixed and tolerant *self*.

Key Words: self/non-self; immunity; individual; symbiosis

Introduction

The main property of the immune system is its ability to distinguish between not dangerous endogenous and exogenous structures (*self*) and harmful endogenous or exogenous entities (*non-self*). Medzhitov and Janeway (2002) reported three modalities of recognitions: "*microbial non-self*", recognition of "*missing self*" and recognition of "*induced or altered self*" allowing to the innate immune system to discriminate between "*infectious non-self*" and "*non-infectious self*". The recognition of "*missing self*", is based on the recognition of "*markers of normal self*" in which gene products and products of metabolic pathways are unique to the host and absent from microorganisms**.** The last strategy, *i.e.,* the recognition of "*induced or altered self*", allows the detection of markers of abnormal *self* that are induced by infection and cellular transformation.

The discrimination between *self* and *non-self* occurs at the molecular level and it is mediated by specific cell structures, such as Toll-like receptors (TLRs), receptors of T lymphocytes, MHC complexes and immunoglobulins (Fig. 1).

The microbial recognition is based on the presence of conserved molecular patterns produced by microorganisms referred as pathogen-associated molecular patterns (PAMPs), which include Gram negative lipopolysaccharide and Gram positive peptidoglycan. These and other PAMPs are recognized by receptors of the immune system and they are called pattern recognition receptors (PRRs), also including TLRs. These receptors do not recognize and do not bind directly PAMPs, but act through other molecules resulting in a specific response for the different classes of pathogens.

In mammals the recognition of LPS by the macrophage receptor is realized by means of TLR4 and it involves the co-receptor CD14, localized on the membranes of macrophages, and the LPS-binding protein (LBP), present in the serum (Perera *et al.*, 2001). In *Drosophila melanogaster*, the Toll co-receptor is represented by Spätzle. However, this molecule is in the form of pro-Spätzle and the cleavage to Spätzle and the binding to Toll require the intervention of recognition molecules secreted by micetes or Gram positive bacteria, that, in turn, activate a protease called Spätzle-processing enzyme (SPE) (Lemaitre and Hoffmann, 2007).

A phylogenetic panorama

In the social amoeba *Dictyostelium discoideum* a specific cell type, called sentinel (S)-cells, has been suggested to play a role in both detoxification and immunity (Chen *et al*., 2007). In particular, S-cells phagocytize bacteria and sequester toxins, through a Toll/Interleukin-1 receptor (TIR) domain protein, TirA. These findings suggest that an old cellular foraging mechanism is utilized for defensive functions and it supports the hypothesis about the

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Fig. 1 The Toll-like receptors and the nucleotide-binding oligomerization domain containing protein 2 (NOD2) are involved in host defense and tissue repair responses so that their proper functioning promote the mucosal maintenance and the commensal homeostasis. In the presence of pathogens, the Toll-like receptors and NOD2 stimulates a pro-inflammatory response. Modified from Cario (2005).

presence of an active system of pathogen recognition in eukaryotes before the appearance of multicellularity.

Sponges represent a very ancient form of multicellular animals, with filter-feeding behaviour. Sponges are normally exposed to bacteria and TLRs are essential in mediating their innate immune responses among many different receptors that participate in the recognition of microbial pathogens. Indeed, Wiens *et al.* (2007) identified a TLR, a serine/threonine protein kinase (IRAK-41) and a novel effector caspase in the sponge *Suberites domuncula*.

Alongside these studies, Toll homologues have been found in arthropods, annelids and mammals (Medzhitov and Janeway, 2000; Underhill and Ozinsky, 2002; Akira, 2003).

The "Danger" model

"Danger" theorists proposed the equivalence of "danger" with un-programmed tissue destruction, necrosis, or other signs associated to cellular distress (Matzinger, 1998). On the basis of this "threat", the immune system would be able to recognize *self* from *non-self* avoiding the processes described by the "self-non-self" theories. The question posed by "Danger" theory is indeed what happens when self changes. For example, the immune reactions against the changed tissues are not observed in organisms that undergo metamorphosis, puberty, pregnancy or aging. Another example is provided by several tumors that are not rejected although many of them clearly express new or mutated proteins.

Even if intriguing, the "Danger" theory has not been fully accepted and numerous criticisms arose by the scientific community. As reported by Vance (2000) this perspective seems not only unnecessary, but potentially misleading. Furthermore, the concept of "danger" is unable to support the three criteria used in rejecting the concept of *self-non self* because: 1) is not well defined, 2) there are many exceptions and 3) it does not consider fully the broad immunological phenomena that take part.

A support in favour of the "danger" hypothesis has been obtained in experiments performed on the human eosinophilis that recognized and activated "danger" signal derived from damaged (necrotic) epithelial cells (Stenfeldt and Wennerås, 2004). Furthermore, a relationship between degree of activation of eosinophils and the dose of necrotic epithelial cells has been observed (Stenfeldt and Wennerås, 2004).

Looking for an agreement: the interaction between the microbiome and the immune system

According to a common view of immunity, the immune system should recognize and eliminate all *non-self* molecules or organisms. However, several evidences support the presence of a constant molecular dialogue between microorganisms and the host immune system in order to favour, for instance, both the establishment and maintenance of the intestinal gut homeostasis by promoting the tolerance of *non-self* bacteria and yeasts (Medzhitov and Janeway, 2002; Cario, 2010; Kaser *et al*., 2010).

As a consequence of this interaction, the innate immune system in the gut, which includes many innate leucocyte populations and several types of intestinal epithelial cells, maintains a balanced immune response to the microbiota, despite its *non-self* nature (Maloy and Powrie, 2011). At the same time, the dysregulation of immune responses versus the commensal microbiota is related to intestinal inflammations occurring directly in consequence of disequilibria between the finely tuned pro- and anti-inflammatory mechanisms within the gastrointestinal tract (Dupaul-Chicoine, 2010; Maloy and Powrie 2011).

According to what observed in several mammals, the immune system activates tissue-protective innate defences that inhibit colonization and invasion by pathogens, but at the same time myeloid cells control circuits preventing harmful immune responses towards the intestinal microbiota (Harrison, 2011). Therefore, a selective modulation of the innate immune activation of downstream mediators presents an ongoing challenge to effectively target deleterious inflammatory responses whilst sparing host-protective immunity in the intestinal tissues (Harrison, 2011).

Recent studies greatly advanced our understanding of the mechanisms through which the gastrointestinal innate immune system can mediate differential host-microbial interactions in recognition and sorting of the broad luminal spectrum of diverse microbial products. In particular, Toll-like receptors and NOD2 are emerging as key mediators of innate host defense in the intestinal mucosa, crucially involved in maintaining mucosal as well as commensal homeostasis (Cario, 2005, 2010).

As reported in human gut, Toll-like receptors may activate distinct signalling events via diverse cofactors and adaptor proteins mediating specific immune responses (Cario, 2005). For instance, at least five different adaptor proteins have been identified in humans (MyD88, Mal/TIRAP, TRIF/TICAM-1, TRAM/Tirp/TICAM-2, and SARM) (for review see O'Neill *et al*., 2003) and they regulate different downstream signalling modules and interacting complexes resulting in activation of several transcription factors, such as NFκB, AP-1, Elk-1, CREB, STATs, and the subsequent transcriptional activation of genes encoding pro- and anti-inflammatory cytokines and chemokines as well as induction of costimulatory molecules (Cario, 2005). All of these diverse downstream effects are critically involved in the control of pathogen elimination, commensal homeostasis,and linkage to the adaptive immunity (Cario, 2005).

Similarly, the expression of some genes related to the immune response is highly related to the microbiome composition since, for instance, microbial symbionts provide developmental signals that limit the proliferation of basophil progenitor cells and thereby prevent basophil-induced allergic responses in vertebrate, so that multiple populations of intestinal immune cells require the microbiota for their full development and function (Gilbert *et al*., 2012; Hill *et al*., 2012).

As described by Gilbert *et al*. (2012), the immune system may be formulated as having two "limbs": an outward-looking limb that defines the organism that has to be protected from foreign pathogens, and an inward-looking arm that looks for potential dangers arising from within the organism itself (Tauber, 1994, 2000, 2009; Eberl, 2010; Pradeu, 2010). This dualistic vision of immunity should be at present revised as a continuous negotiation of numerous interactions between the organism and its biotic environment (both "internal" and "external"). The "immune self" model of individuality, based on a clearly distinction of *self* and *non-self* reflecting the portray of the immune system as a defensive network against an hostile exterior world (that rejects anything that is *non-self*) should be revised considering animals as a sort of "mixed self", using the metaphor suggested by Pradeu (2010) or distinguishing three (in place of two) counterparts: *self*, *non-self* and *nearby self*, the last referring to *non-self* entities that are accepted as *self* by the immune system.

Interestingly, this last result is not due to an immune tolerance toward microbes nor to a strategy whereby the defensive factors are minimalized to prevent damage to the infected organism, but it relies on an active recruitment of symbiotic bacteria by the immune system (Tauber, 2008a, b). In squids (McFall-Ngai *et al.,* 2010) and mammals (Hooper *et al.,* 2012), elements of the host immune system have been co-opted to support the colonization, limitation, and persistence of symbiotic bacteria within the host.

Interestingly, if the immune system cannot be properly regulated to "accept" some symbionts, they need to be sequestered into specialized bacteria-bearing host cells, such as the bacteriocytes, as reported in aphids (Buchner, 1965).

Concluding remarks

In accordance to the concepts reported above, the distinction between *self* and *non-self* may be today not so clear-cut as frequently thought. The "self-non-self" theory captures the favour of the majority of immunologists however, on the basis of the data reported by different laboratories, the existence of other modes of recognition should not be excluded.

As Lewis Thomas (1974) commented discussing the concepts of *self* and symbiosis: "This is, when you think about it, really amazing. The whole dear notion of one's own self - marvellous, old free-willed, free-enterprising, autonomous, isolated island of a Self - is a myth". As commented by Gilbert *et al*. (2012), the immune system does not merely guard the body against other hostile organisms in the environment, but it also mediates the body's participation in a community of "others" that contribute to its welfare (Tauber, 2000; Dale and Moran, 2006). The "defensive" role of immunity, so prominent in the medical and agricultural contexts, should be balanced considering that the immune system has evolved the capability to discriminate which organisms it has to exclude and kill, and which allow to maintain. From this evolutionary point of view, each animal is not a circumscribed and autonomous entity that is *a priori* designated as "the self", but it is a dynamic and context-dependent entity with a mixed and tolerant *self*.

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