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Rethinking individuality: the dialectics of the holobiont

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Abstract Given immunity's general role in the organism's economy—both in terms of its internal environment as well as mediating its external relations—immune theory has expanded its traditional formulation of preserving individual autonomy to one that includes accounting for nutritional processes and symbiotic relationships that require immune tolerance. When such a full ecological alignment is adopted, the immune system becomes the mediator of both defensive and assimilative environmental intercourse, where a balance of immune rejection and tolerance governs the complex interactions of the organism's ecological relationships. Accordingly, immunology, which historically had affiliated with the biology of *individuals*, now becomes a science concerned with the biology of *communities*. With this translocation, the ontological basis of the organism is undergoing a profound change. Indeed, the recent recognition of the ubiquity of symbiosis has challenged the traditional notions of biological individuality and requires a shift in the metaphysics undergirding biology, in which a philosophy of the organism must be characterized by ecological dialectics "all-the-way-down."

Keywords Immunity · Individuality · Holobiont · Organism · Symbiosis · Ecosystem

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Introduction

At the base of contemporary immunology resides an ontological ambiguity: In most biological disciplines—developmental biology, evolutionary biology, physiology, anatomy, genetics—'individuality' has relied on an intuitive grasp of that which is characterized or counted, a designation that in fact may be quite arbitrary (Martin and Lynch 2009; Goodnight 2013; Godfrey-Smith 2013). And immunology has assumed this same construction, i.e., the individual has been perceived as an insular entity, a genetically uniform organism that must be protected from an environment that is teaming with potentially pathogenic microorganisms. Accordingly, immunology has traditionally been the study of those mechanisms by which the individual defends itself from this hostile environment. That model of immunity was amplified in the public domain during the AIDS epidemic by the opportunistic infections that resulted from a weakened immune system (AIDS.Gov. 2010), which re-enforced popular conceptions of the correspondence between immunity and individual identity (Haraway 1989; Martin 1990, 1994; Goodsell 2016; Tauber 2016).

However, this autonomous notion of individuality has proven inadequate both in terms of current understanding of organismic organization and more specifically in regards to immune functions in various capacities beyond its defensive role (Tauber 2000; Pradeu 2012). Beyond the difficulties of defining the individual immunologically, the recent surge of interest in immune processes mediating mutualistic relationships has further challenged the notion of immune mediated individuality (under the guise of the 'immune self') (Eberl 2010; Tauber 2012). Following this line of criticism, the challenge of reconsidering immunology's guiding precepts is that most (if not all) "individual" animals are increasingly appreciated as being organized consortia of hundreds of species living in a symbiotic commune. What had been previously described as "individual organisms" are, in fact, multi-species/multi-lineage "holobionts," composite organisms, whose physiology is a co-metabolism between the host and its microbiome, whose development is predicated upon signals derived from these commensal microorganisms, whose phenotype is predicated on microbial as well as host genes, and whose immune system recognizes these particular microbes as part of its "self" (McFall-Ngai et al. 2013; Gilbert et al. 2012).

As we previously noted, "we were never individuals" (Gilbert et al. 2012), and in that quip we sought to capture a fundamental shift in our understanding of the organism, one that displaces the genetically homogenous individual as a governing concept for the life sciences. In this setting, immunity then expands from its exclusive defensive function to assume the broadened role of distinguishing benign from deleterious microbes and then allowing beneficial intercourse with the organism's environment. Such exchanges require active immune tolerance and so immunity becomes the net result of balancing rejection and assimilation. This latter element must account for the mutualism characterizing the presence of a vast population of diverse microorganisms that are required for the body's construction and maintenance. The immune system, on this view, is the mediator of holobiont

homeostasis. In short, we raise here the following question: Does the conclusion that animals are constructed as holobionts mean that the current defense-dominated view of the immune system requires revision and then, what will constitute an adequate conceptual re-formulation? From our perspective, the newly acquired knowledge of symbiosis has effectively re-defined the conceptual frame of the organism and, correspondingly, evolution, development and physiology must be re-conceived in consideration of the organism's full ecological context (Gilbert and Epel 2015; Tauber 2017): Accordingly, the holobiont can be seen as both organism and ecosystem, and the immune system acts as the arbiter between the host and its microbial environment, and its protective functions are a subset of a much larger agenda of host-symbiont détente.

Rethinking the 'individual'

Throughout the history of biology, an organismic individual has been regarded as possessing anatomic borders, harmonious balance characterized by communication between its parts, division of labor for the benefit of the whole, and a system of hierarchical dominance and control (see Nyhart and Lidgard 2011). Moreover, such an individual reproduces as a unit to replicate itself, and "[e]very cell of your body was generated by cell division forming a lineage tree that goes back to the fertilized egg" (Linnarsson 2015). Symbiosis challenges this well-entrenched definition of the individual organism, not only because physiological autonomy has been sacrificed, but because anatomic borders have lost clear definition, and development becomes intertwined among several phylogenetically defined entities. Many insects have outsourced much of their amino acid-synthesizing machinery to their microbes, and in numerous invertebrates, microbial signals are needed for embryonic cell division and morphogenesis (McCutcheon and von Dohlen 2011; Landmann et al. 2014; Moran and Yun 2015). Neither termites nor cows can digest grass or wood. Those abilities are provided by enzymes encoded in symbionts, not in the mammalian genome. Symbiont-free vertebrates must often live in antiseptic chambers, since the microbes are responsible for forming their gut-associated lymphoid tissue, gut-associated capillaries, and, in the case of zebrafish, the gut tissue, themselves (Rawls et al. 2004; Viney and Riley 2014; Gilbert and Epel 2015). These complex consortia, "holobionts" (Rosenberg et al. 2007), defy any singular definition of organismal individuals as monogenomic agents. In mice, "normal" gene expression is that of the holobiont, not that of the animal alone (Hooper et al. 2001). The phylogenetic trees mimic biological trees—full of symbiotic organisms from various phyla and kingdoms.

And while the biological individual has served as a crucial basis to studies of genetics, immunology, evolution, development, anatomy, and physiology, these demarcations of individuality have been challenged by the finding that symbiosis is a signature of life on earth (Gilbert et al. 2012; McFall-Ngai et al. 2013; Bordenstein and Theis 2015). "Animals" (i.e., metazoan eukaryotes) cannot be considered as genetically pure individuals. Rather they are holobionts, multi-genomic individuals (see Pradeu 2010). Similarly, these new studies have shown that the symbionts

constitute a parallel mode of genetic inheritance, providing selectable genetic variation for natural selection. And the immune system, the putative discriminator between "self" and "nonself" also develops, in part, in dialogue with symbionts, and thereby functions as a mechanism for integrating microbes into the animal-cell community (Gilbert et al. 2012).

One might construe a new level of individuality—the "holobiont"—as the multicellular eukaryote plus its colonies of symbionts. However, this is a particularly problematic type of "individual" for biologists concerned with immune functions and evolutionary mechanisms. First, unlike our traditional view of animals, the holobiont is multi-genomic and a genetic signature alone is insufficient for immune discrimination, which is a system-wide (collective) response (Kim et al. 2009; Daëron 2014). Second, the holobiont changes its component parts over time. These two features make it antithetical to neo-Darwinist accounts of selection, which presuppose genetically homogeneous entities that do not change their genomes over time. The idea that the holobionts constitutes a unit and level of evolutionary selection is being argued in a separate series of papers (Rosenberg and Zilber-Rosenberg 2016; Gilbert et al. 2017). The third major problem is that a holobiont, conceived as an organism, calls into question the fundamental basis of immunology—that the immune system exists to protect the genetically homogenous and developmentally autonomous animal from pathogens. We argue that this defensive function falsely restricts the role of immunity, which not only destroys the deleterious, but also assumes the larger ecological task of mediating *both* rejective and assimilative processes. To establish mutualistic relationships and to maintain holobiont integrity constituted by organisms of different genotypes requires active immune tolerance (Tauber 2017). This view, wherein immunity must be studied as a function of a multigenomic holobiont organisms and not merely their animal components, has been discussed from physiological (McFall-Ngai et al. 2013), medical (Sansonetti and Medzhitov 2009; Khosravi and Mazmanian 2013), and philosophical points of view (Pradeu 2010; Tauber 2008). Here, we review the role of immunity in a developmental construct.

Reconceiving organismal integrity: the death of the clinic

The history of immunology, and for that matter, microbiology, has taken place in the clinic. But let's consider another "proper" context of immunology, developmental biology. Developmental biology is another science intimately involved in "self" formation, and it, too, is presently contending with the new holobiont construction of the organism. To a large extent, developmental biology is a dialectical discipline. In such a dialectical world,

> parts and wholes evolve in consequence of their relationship, and the relationship, itself, evolves…that one thing cannot exist without the other and that one acquires its properties from its relation to the other, that the properties of both evolve as a consequence of their interpenetration. (Levins and Lewontin 1985, p. 3)

Such dialectics are found at every level of mammalian development. First, *fertilization* has been shown to be the interaction between two *cellular* entities, the sperm and the egg, such that the egg and female reproductive tract activate the sperm, and the sperm activates the egg. The sperm and egg are two cells at the verge of death. Their interaction creates a new entity, the zygote, whose progeny can persist for decades. This interaction is highly specific, and competition thereby comingles with cooperation. Once one sperm has bound to the egg, all other sperm perish.

Second, *organogenesis* has been shown to be the dialectical interaction of two or more *tissues* that then allow generation of new cell types. Thus, when a bulge from the forebrain touches the head surface ectoderm, it interacts in a way such that the head ectoderm is instructed to form lens rather than epidermis. As the ectoderm becomes the lens, it then sends signals instructing the forebrain bulge to differentiate into the retina. The two tissues interact repeatedly, eventually becoming the lens and retina of the eye. Similarly, the kidney is generated by two different groups of cells, both of which would die without the presence of the other. But by their meeting, interactions occur to make the ordered structure of the dozen or so cells of the kidney tubule. Competition and cooperation comingle here, as well, inasmuch as the interaction of epithelium and stroma provide the signals to inhibit cell division. Malignancies may originate when these instructions are not given, misread, or not received (Maffini et al. 2004; see Gilbert 1991).

In the adult organism, such dialectical interactions determine the emergence of immunocompetent lymphocytes. Basically, the development of specific immunocompetence occurs in the adult and this process follows the same dialectical rules. Central to this maturation process is the interaction between antigen, B-cells, T-cells, and macrophages that ultimately transform the immature B cell into the antibody-producing plasma cell. The plasma cell is thus a product of a multi-cellular interactions and as it differentiates, some of its genes mutate to create a set of genes that differ from those of all the other cells in the body. This is an example of cooperation and competition characterizing the interpenetrating elements of the immune system, where elaborate mechanisms of clonal anergy and clonal selection occur through the cooperation of epithelia, lymphocytes and macrophages.

A newly discovered, third level of interaction involves *symbiotic* interactions between *cells of different species*—the holobiont in operation—to generate the cells of the gut, capillaries, and the immune system of the host. Without the symbiotic microbes, mammals possess a poor capillary system to absorb nutrients. The symbiotic bacteria in the gut induce gene expression in the gut tissues, and this gene expression makes the paracrine factors (such as angiogenin-4) that instruct the mesoderm surrounding the gut to become capillaries (Hooper et al. 2001). In addition, the bacteria are especially important in establishing communities of the gut-associated T-cells and B-cells of the immune system (Lanning et al. 2005; Lee and Mazmanian 2010; Ardeshir et al. 2014; Wesemann et al. 2013).

Fourth, *ecological interactions* between *organisms* are responsible for the niche construction seen in the biosphere. Organisms are not keys that fit into pre-existing locks, but rather actively construct their own environments (Levins and Lewontin 1985; Odling-Smee et al. 2003). The basis for these reciprocal interactions between

the organism and its environment are based on the universal phenomenon of developmental plasticity. One might even posit a fifth interaction—on the molecular level: There is no lock and there is no key. This model, that was so critical to biochemistry, was shown to be wrong when Koshland presented the evidence for "induced fit." The substrate helps make the enzyme fit it (Koshland 1958, 1995). Stereo-specificity is the basis for all of biology—antigens/antibody, substrate/enzyme, ligand/receptor, sperm/egg, tRNA/amino acid, transcription factor/DNA (Gilbert and Greenberg 1984; Kupiec 2009). However, these interactions are not between metallic keys, but rather a set of interactions that induces a fit—dialectics all the way down and all the way up. In sum, whatever is counted as a "biological individual," it must be regarded as a concrescence of several levels of dialectical processes. The immune-mediated holobiont fits well into this context.

Immunity as ecological management

Microbes are commonly seen as pathogens and the immune system is conceived as providing the capacity for host defense against them. This was certainly reinforced in the 1980s, during the AIDS epidemic, when the lack of immune function allowed otherwise harmless microbes to become "opportunistic pathogens" and the very basis of human identity threatened (Martin 1994). However, much of what has been called 'autoimmunity' and immune 'ignorance' ('anergy') of the other, in fact, includes active *tolerant* sentinel functions both of host tissue and tolerance of substances at the interface of host and its external environment. *Autoimmunity* is immune attack launched against normal constituents; *concinnity* ("ordering" functions) provides normal immune 'housekeeping' services; microbial symbionts are actively tolerated by the immune system (Pradeu and Carosella 2006; Eberl 2010, 2016; Tauber 2015).

Thus the *active* resting or "conservative" immune surveillance functions comprise normal physiological activity (Tauber 2003; Vaz et al. 2006). Indeed, immunity is constituted by dynamic functions in which immune responses arise from a complex calculus of environmental (internal and external) factors, historical and developmental history, and evolutionarily derived identifications of 'safe' (and thus tolerated) and 'dangerous' (and thus attacked) substances (Grignolio et al. 2014). Accordingly, immunity is a collective product of myriad factors, which elicit a spectrum of responses along a continuum stretching from the unrecognized to active immune tolerance to various degrees of immune destructive activation (Tauber 2017). So despite the organizing power of a simplified self/nonself discriminatory model of immunity, by the end of the twentieth century such a dichotomous formulation could not account for the full array of immune activities. Other organizational constructs are being sought to better comprehend the structure of the immune system and its regulation.

The multiple functions of the immune system, especially its ability to achieve states of *tolerance* for assimilative processes expands the self-defensive role of immunology into a larger "ecological" context of promoting organismal identity through dialogue with both the internal and external environments. In other words,

the original clinical orientation of immunology is being supplemented with an expanded ecological orientation where immunology is joining the environmental sciences. On this view, the defensive conception of immunity becomes a subset of an ecological view that focuses on the fundamental character of information processing and integration of the organism with its larger ecology, both internal and external. Immune reactivity (rejection or tolerance) therefore becomes *a second order response* to the immune system's 'cognitive' functions (Tauber 1997, 2013, 2017). Accordingly, the immune system fundamentally is a cognitive faculty (Cohen 1992a, b).[1]

This ecological view regards the immune system as being the manager of individuality, in that it is connected to the endocrine and nervous system to create an integrated sensory network (i.e., a cognitive system) that monitors the potentially competitive components of the internal environment as well as the potentially competitive components in the external environment and adjudicates contenders for inclusion (Tauber 2008). So, if immunity-as-defense is balanced with immunity-as-tolerance, the primary concerns of immunology shifts from defending the insularity of the organism to placing the organism in its environment, where useful exchange of nutrients and exposure to myriad substances must not only be tolerated, but encouraged. Assuming such an account presents immunity as determining the overall intercourse of *all* relationships in the organism's economy and thus the commune becomes the organizing frame of study.[2]

Eco-immunology

As biological notions of *agency* shift from independent entities to complex co-operative collectives the investigative interests move from discerning mechanisms of insularity to those concerned with how the organism becomes an integrated constituent of a larger community. And, correspondingly, even the 'relaxed' use of *individuality* becomes a remnant of an eclipsed semantics. To examine these ecological relationships in their full complexity, attempts are underway to integrate immunology, developmental biology, and ecology (Demas and Nelson 2011; Gilbert and Epel 2015). Indeed, symbiosis dissolves the boundary between development and ecology. The bacteria permitted and encouraged to enter the body are those that help construct the body, and which even help construct the immune system (discussed in the next section). This new inter-disciplinary field—

[1] The cognitive metaphor is not a new development in immunology's conceptual formulation. This cognitive orientation is seen in immunologists descriptions of macrophages "seeing" antigen, antibodies "recognizing" epitopes, T and B cells possessing "memory;" and adaptive immunity comprising a "learning" process (Tauber 1997). Indeed, at the level of cell communication, the immune system, neural system, and endocrine system coalesce to constitute an integrative sensory network for the body (Gilbert 2003; Ader 2006; Sotelo 2015). In ecological developmental biology (see below), this molecular sensing network is critical for integrating the developing organism with its biotic and abiotic environments as well as mediating competition within the organism (Nijhout and Emlen 1998; Bonett et al. 2010).

[2] Much of this re-orientation revolves around understanding the mechanisms of immune tolerance that have allowed symbiotic relationships to take hold (a topic reviewed by Chiu and Eberl in this special issue).

eco-immunology—seeks to explain natural variation in immune functions, and to do so, several agendas are at play: (1) an adaptationist approach to investigate the costs and benefits of investment in immune activity; (2) the potential role of pathogens in shaping life history variation; (3) the evolutionary mechanisms operating to establish genomes determined by environmental factors; and (4) the direct contributions of ecological factors—nutritional, pathogenic, reproductive, cultural and psychosocial—to human immune functions (McDade 2005; Schulenburg et al. 2009; Maligoli and Ottaviani 2014; Wodarz 2014). The environment and the organism are 'locked together' and the boundaries are less important than understanding how interchanges between the organism and the world occur. (This expansion of course includes the organism's inner ecology as well.) In short, immunology conceived as a member of the ecological sciences dramatically widens conceptions of immunity (Tauber 2017). Indeed, *immunity* is more than immunity, i.e., as *immunitas*.

This new science of eco-immunology has an ongoing relationship with its cognate and syncytial discipline, ecological developmental biology (Tauber 2009). Whereas eco-immunology emphasizes the role of the immune system in the integration of bodily identity, ecological developmental biology emphasizes the role of symbionts and plasticity in shaping the differentiation and morphogenesis of organ systems within the holobiont organism (Gilbert and Epel 2015). Symbiotic microbes are responsible for helping generate organs throughout the animal kingdom. Specific microbes are needed for mammals to have normal gut and brain development, and they are needed for metamorphosis and reproductive tissue formation in numerous animals (Hadfield 2011; Sampson and Mazmanian 2015). Indeed, the development of the holobiont is predicated on the ecological relationships among and between symbionts and the larger "host." Each provides the context for the development of the other (Chiu and Gilbert 2015). Organisms develop as and through numerous ecosystems.

Ecological developmental biology merges with eco-immunology to provide evidence for four principles necessary for understanding holobiont individuality (Gilbert et al. 2015).

1. *The immune system is active in permitting the entry of some microbes into the body and preventing the entry of others* While actively eliminating some microbes from the holobiont, the immune system actually encourages the symbiotic microbes to enter the body and provides niches for their subsequent growth (Peterson et al. 2007; Obata et al. 2010; Round et al. 2010; Chiu and Gilbert 2015). This is true in both vertebrates and invertebrates, where the innate recognition of microbes is necessary for host-microbe symbiosis (Chu and Mazmanian 2013).
2. *Microbes are active in creating the immune system and other tissues* The symbiotic microbes residing in areas such as Peyer's patches become critical for generating immune tissue and for normalizing the T-cell and B-cell repertoire (Duan et al. 2010; Wesemann 2015). On one level, we are discussing co-development, wherein two or more species cooperate to generate the holobiont.

At another level, we are observing ecological succession and the generation of an ecosystems that depends on symbiotic relationships.

3. *The immune system plays a critical role in regulating bacteria and in regulating the "social ecology" of an organism* Both innate and acquired immunity are critical in maintaining the animal holobiont, and the immune system has evolved as a form of ecosystem management that regulates the composition, diversity and localization of the microbiota (Salzman et al. 2003; Oh et al. 2013). Recent research suggests that when this immune system fails, the "social contract" among the cells is abrogated and the host organism becomes more vulnerable. This is not only the case for autoimmunity and opportunistic infections, but also for cancer (Campisi and Robert 2014.) One must also keep in mind that each of the symbionts has its own immune system and that these immune networks may be interlocked symbiotically.[3] Simply, the microbial species are capable of modifying their niche. Indeed, new research (Root-Bernstein 2016) suggests that mutualistic microbes may accomplish this networking and niche construction by evolving cell surface molecules that mimic the T-cell receptors.

Fourth, biological sciences, which had been about the biology of *individuals*, must now become a science concerned with the biology of *communities*. The holobiont is an individual (for the purposes of discussing development and evolution), but that individual is actually a community of different organisms that are in various degrees of constancy and flux.

In sum, development, evolution, immunology, and ecology are all being blended in the holobiont organism. The holobiont is constructed by several interacting and potentially competing lineages. Animals, literally, in the most corporal manner, embody the notion of "becoming with the other."

Individuality revisited

The *use* of 'individuality' relies on an intuitive grasp of that which is characterized or counted (Goodnight 2013), which in fact may be quite arbitrary (Martin and Lynch 2009). Indeed, vague and multiple criteria obstruct the development of precise and inclusive definitions of individuality (Clarke and Okasha 2013). Moreover, attempts to define biology's key concepts lodged within an individualistic formulation—from *species* to *gene*—characteristically exhibit ontological ambiguity, which then require intuitive separation (e.g., Sarkar 1998, 2005; Beurton et al. 2000; Wilson 2005; Dupré and O'Malley 2009; Clarke and Okasha 2013; Goodnight 2013). Nevertheless, biologists must use such designated entities as objects of discovery and investigation (Bouchard and Huneman 2013; for historical case studies in immunology, see Löwy 1991; Crist and Tauber 1999; Cohen 2001).

[3] For instance, *Bacteroides the taiotomicron* induces *angiogenin-4* gene expression in mouse's intestinal cells. This angiogenin-4 not only instructs the mouse's gut mesenchyme to organize itself into capillaries; it also is bacteriocidal for *Listeria* and *Enterococcus*, two of the major competitors of *Bacteroides* as well as being human pathogens (Hooper et al. 2003; Cash et al. 2006).

In terms of using *individuality* in immunology, the same general difficulties arise and some particular to the discipline. Most generally, the weakness of the formulation rests on its adherence to a notion of identity conceived in terms of defending a host (a finite *entity*), where immunity is defined in terms of an autonomous *self*. Alternatively, the immune system may be conceived as *establishing* the very identity in question over time by defining that which must be identified, i.e., the *what* to be defended over the lifespan of the organism. Such a revised theory originates with Ilya Metchnikoff, who (at the end of the ninetieth century) proposed that evolution's dynamics also occurred *within* the organism, and that biological identity resulted from immune-mediated dynamic processes at two levels: (1) between host eukaryotic cell lineages, and (2) in the intercourse with microbial symbionts that he believed essential to the healthy physiology of the individual (Metchnikoff 1968, 2000; Buss 1987; Gourko et al. 2000; Tauber and Chernyak 1991; Tauber 2003). On this view, the organism was not a given, but rather a 'work-in-progress' that underwent lifelong development in dialectical exchange with other potentially competing intra-organismal elements. He thus re-conceived the immune system from a defense network to the physiological mediator that negotiates the integration of numerous cell lines and species into the multi-lineage non-essentialist organism.

If immunity is conceived as an on-going developmental process, then borders are tentative and identity evolves. In other words, immunity is not restricted to some pre-established self/other discrimination, but (as already argued) rather functions as an information processing system in an ever-challenging environment. Accordingly, the immune system 'negotiates' the traffic of potentially beneficial against noxious encounters on a reactive spectrum of tolerance and rejection. That spectrum forms a continuum, shifting in time and space, and it is on this basis that immunity is characterized by its dynamic character. Indeed, immunity includes diverse processes that maintain the organism's normal body economies. These range from processing cell turnover, arbitrating nutrition, and partaking in the integration of homeostatic mechanisms mediated by the immune, nervous, and endocrine systems (Gilbert 2003; Ader 2006). Such inputs, whether nervous, hormonal, or immune, then cascade into an integrated sensory network of functionally supportive elements whose "rules" determine whether actions are initiated, or not.[4]

With this re-orientation, the status of *individuality* becomes an explicit problem in systems-wide modeling of the immunity (Kim et al. 2009; Wodarz 2014). Where are boundaries drawn? Like human communities, collectives trail off and then co-mingle with other communities that have similar 'fuzzy' borders. So then, what constitutes self and nonself when an irreducible reciprocity is at work? The holobiont is made possible by the immune system and this very negotiator is created

[4] To capture the complex intercourse between the human and non-human living world, Latour (1999) regards the ecosystem as a polity in which all constituents participate in a constant negotiation of belonging and elimination. To recognize shapes on the microbial surface, immunocompetent vertebrate cells alter their genomic DNA and become "diplomats" in the sense Latour describes, namely they 'negotiate' or mediate rejection or assimilation. "Diplomacy," writes Stengers (2005 93), "is a technology of belonging," which, especially in the case of the holobiont, determines who "we" are.

by interactions between the eukaryotic tissues and the microbes, themselves. Thus the immune system is not only made by the "host;" the "other" helps construct it.

So, we agree with those who state that immunity is widely understood as the most important mechanism to explain the evolution of the multicellular organism's individuality. On that general view, immune functions are dominant in the emergence and perpetuation of genetically pure individuals, or in other words, individuals that are in large measure individuals by traditional criteria. However, we contest that consensus opinion. Symbiosis, especially developmental symbiosis and immune-mediated tolerance of the holobiont consortium, challenges this classic orientation. While designations of individuality are pragmatically useful and possess powerful heuristic appeal, *individuality* nevertheless suffers ontological ambiguity because of indistinct categories that would define borders and thereby define individuals. Simply, lexical plasticity is integral to the life sciences, but the commitment to a biology built on individuality offers a high philosophical threshold to overcome.

Conclusion

In summary, immunology's agenda must add to its study of immunity-as-defense, (a construction based on a self-contained entity) the more expansive ecological context in which immune functions are ultimately configured. The challenges posed by the 'ecological imperative' highlight the science's evolution and the complexity of the language that refracts those developments. *Individuality*, residing at the nexus of this transformation, is left in a conceptual limbo. While this problem has already attracted the attention of some philosophers (Tauber 1994, 2008; Moulin 2012; Pradeu and Carosella 2006; Pradeu 2012; this special issue), and of several researchers interested in disease etiology (e.g., J. I. Gordon and S. Mazmanian), it is only beginning to attract those scientists interested in how this ecological approach could lead to new insights into the organization and regulation of the immune system within its larger environmental context (Sansonetti and Medzhitov 2009; Round et al. 2010; Sotelo 2015; Wesemann 2015; Tauber 2017).

This shift in immunology's conceptual orientation is in line with a general trend in biology, one that is turning a molecular-centered science towards ecological considerations. This is not to say that molecular biology will lose its hegemony (see Joyner et al. 2016), but taking immunology as a case study, it seems reasonable to conclude that the guiding issues governing major strategic goals are increasingly framed by a systems analysis, where diverse inputs must be accounted, which in turn requires expanding methodological boundary conditions. Here an ecological approach (understood in terms of collective behaviors and exchange relationships) increasingly influences models of organization and their modes of regulation.

Over the past 25 years, a growing numbers of immunologists are questioning the utility of an insular definition of autonomous identity and have instead introduced contextual models to depict immune function (Tauber 1997; Demas and Nelson 2011; Wodarz 2014). In such formulations, agency shifts its conceptual grounding to an organism without firm demarcations. Thus, the notion of individuality that

grounds immune identification is being challenged by a combination of several agents, including a scientific reassessment of autoimmunity and tolerance (Tauber 2015; Eberl 2016) and an emerging awareness of an 'ecological imperative,' in which entities "are what they are because of the environment in which they are found" (Birch and Cobb 1981, p. 94). Whatever these interactions are between microbe and host, the holobiont is being continuously constructed. Harmony is not something given, but rather something that requires interactive agency throughout the lifespan of the organism.

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