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Ecoimmunity: immune tolerance by symmetric co-evolution

Uri Nevo[a,*] and Ehud Hauben[b]

[a]Section on Tissue Biophysics and Biomimetics, Laboratory of Integrative and Medical Biophysics, National Institute of Human Health and Child Development, National Institutes of Health, 13 South Drive, Bethesda, MD 20892, USA
[b]San Raffaele Telethon Institute for Gene Therapy (HSR-TIGET), Via Olgettina 58, 20132 Milan, Italy
*Author for correspondence (email: nevouri@mail.nih.gov)

SUMMARY It is widely accepted that immune tolerance toward "self" is established by central and peripheral adaptations of the immune system. Mechanisms that have been demonstrated to play a role in the induction and maintenance of tolerance include thymic deletion of self-reactive T cells, peripheral T cell anergy and apoptosis, as well as thymic and peripheral induction of regulatory T cells. However, a large body of experimental findings cannot be rationalized solely based on adaptations of the immune system to its environment. Here we propose a new model termed Ecoimmunity, where the immune system and the tissue are viewed as two sides of a continuously active and co-evolving predator–prey system. Ecoimmunity views self-tolerance, not as an equilibrium in which autoimmunity is chronically suppressed, but as a symmetrical balanced conflict between the ability of immune cells to destroy tissue cells by numerous mechanisms, and the capacity of adapted tissue cells to avoid predation. This balance evolves during ontogeny, in parallel to immune adaptations, embryonic tissue cells adapt their phenotype to the corresponding immune activity by developing the ability to escape or modulate damaging local immune responses. This phenotypic plasticity of tissue cells is directed by epigenetic selection of gene expression pattern and cellular phenotype amidst an ongoing immune pressure. Thus, whereas some immune cells prey predominantly on pathogens and infected cells, self-reactive cells continuously prey on incompetent tissue cells that fail to express the adapted phenotype and resist predation. This model uses ecological generalization to reconcile current contradictory observations as well as classical enigmas related to both autoimmunity and to tolerance toward foreign tissues. Finally, it provides empirical predictions and alternative strategies toward clinical challenges.

INTRODUCTION: THE ENIGMA OF SELF-TOLERANCE

Immune tolerance has been defined as unresponsiveness to an antigen that is induced by previous exposure to that antigen (Abbas et al. 2007). Multiple molecular mechanisms are known to participate in the maintenance of immune tolerance. Central tolerance mechanisms of deletion in primary lymphoid tissues operate during T cell maturation by elimination of self-reactive clones, based on their high affinity recognition of self-antigens (Hogquist et al. 2005), and for B cell maturation in the bone marrow by receptor editing and apoptosis (Reth et al. 2000). Despite these mechanisms, some self-reactive T and B cells escape deletion in primary lymphoid tissues and are part of the normal repertoire expressed by the mature, healthy immune system (Gallegos and Bevan 2006). Various peripheral immunoregulatory mechanisms have been proposed to prevent autoreactive T cells from promoting immune responses toward self. These mechanisms include: (a) the dependence of a response on the requirement for antigen presentation in the context of a co-stimulatory signal, without which T cells become dysfunctional (anergic) (Van Parijs and Abbas 1998). (b) Repeated stimulation by persistent antigens results in deletion of T cells by activation-induced cell death. (c) Regulatory T (Tr) cells restrain immune responses toward both self- and foreign antigens (Sakaguchi et al. 1995). Different subsets of Tr cells have been characterized, including CD4+Foxp3+Tr cells, type 1 Tr (Tr1) cells, T-helper type 3 (Th3) cells, CD8+CD28−, CD4−CD8−, and natural killer T cells (reviewed in (Hauben and Roncarolo 2005)).

The other side of the tolerance equation is the role of the tissue in suppressing harmful immune responses and inducing protective ones (Boonman et al. 2005; Moffett and Loke 2006). Tissue-resident cells were shown to actively evade immune-mediated damage, and exert profound immunosuppressive properties. As an example, Fas (CD95) expression by tissue-resident cells (e.g., pancreatic islet β cells) has been shown to actively induce T cell apoptosis (Hill et al. 2007). Similarly, cell resistance to cytotoxicity was demonstrated and correlated with genetic background: β cells in mouse strains that are not susceptible to autoimmunity were shown to display resistance to cytotoxic cytokines that destroy islets in susceptible strains (Mathews et al. 2001). Sequestration of

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immunogenic self-epitopes in EAE-resistant mice was shown to result in degeneration of the respective immune clones (Lehmann et al. 1992). Moreover, active induction of immune tolerance by different cell subsets has been demonstrated in many systems, including embryonic progenitors, hematopoietic stem cells (Sykes and Nikolic 2005), as well as adult tissue cells such as sinusoidal endothelial cells, hepatocytes, and keratinocytes (Arnold 2003).

Despite our knowledge of the molecular mechanisms involved in maintaining immune tolerance, a comprehensive model of the immune system–tissue relationship that will define the overall control of the immune response is lacking. Earlier models of self-tolerance suggested the discrimination of self from non-self, by the expression of specific markers of non-inherited maternal, or inherited paternal HLA antigens (Ichinohe et al. 2005). Alternatively, evolutionarily conserved microbial features (pathogen-associated molecular patterns—PAMPs), were suggested as markers for distinguishing "infectious non-self" from "non-infectious self" (Janeway 1989). These markers differ from markers of both normal- and altered-self, and determine the induction of an immune response. The "danger model" (Matzinger 1994) emphasizes the role of the local tissue in the induction of tolerance by suggesting that danger signals, rather than foreignness of an antigen, stimulate and maintain an immune response. Conversely, antigen presentation in the absence of danger signals results in immune tolerance. The "immunological homunculus" view (Cohen and Young 1991) suggests that the immune system, through a constant dialogue with the tissues, has a dynamic perception of the condition of each tissue, and the presence of pathogens. This allows the immune system to make a pseudo-cognitive decision in each context dictating the nature of its response (Cohen and Young 1991). Tuning of activation thresholds, that is sensitive to changes in the level of antigen, was suggested as a mechanism that may allow T cells to be ignorant of "self" although highly sensitive to changes in pathogen levels (Grossman and Paul 1992).

Although each of the above models addresses most of the manifestations of immune tolerance, the explanation for a wide spectrum of phenomena related to "tissue tolerance" remains unclear (Talmage 1986; Coutinho et al. 1992; Coutinho 2002). A representative set of such phenomena includes: (a) Tolerance toward foreign antigens: this is demonstrated by maternal tolerance toward allogeneic embryos, where the expression of target genes such as heme oxygenase-1 (HO-1) and indolamine 2,3 dioxygenase (IDO) by cells of the tissue has been shown to modulate immune responses (Billingham et al. 1953; Oliveira et al. 2006; Trowsdale and Betz 2006), fraternal twins tolerance (Owen 1945), tolerance toward commensal bacteria, and acceptance of some embryonic xenografts during the embryonic stage (Billingham and Medawar 1953; Billingham and Silvers 1964; Dekel et al. 2003). (b) Rejection of autologous and syngeneic tissues, as demonstrated by syngeneic graft versus host disease (Latif et al. 2003) or by rejection of autografts that were "parked" externally during development (Triplett 1962). (c) The demonstration that tolerance depends on factors that are irrelevant to the definition of "self": grafts with regenerative capacity may be accepted (Dresske et al. 2002), graft acceptance depends on graft size (Silvers 1968; Jones et al. 2001) and innate immune cells can manifest tolerance (Janeway 1989; Hargreaves and Medzhitov 2005). (d) The presence of autoimmune T cells does not necessarily imply autoimmune pathology: healthy individuals host autoimmune cells (Gallegos and Bevan 2006) and tolerance is developed toward tissues formed during adulthood (Matzinger 1998). (e) Active autoimmunity is important to maintain homeostasis. This was shown by the observation that in animals with a healthy immune response, physiological tolerance toward grafts demands an active immune response (Lechler and Batchelor 1982; Salaun et al. 1990; Bishop and McCaughan 2001), and independently by the surprising results of T cell vaccination against autoimmune diseases (Cohen 1989, 1991), and of protective autoimmunity (Moalem et al. 1999; Schwartz and Cohen 2000; Zohar et al. 2006).

This article addresses enigmatic immunological phenomena, using a new framework in which the immune system and the tissue interact as species in a macroscopic ecological system. We shall present this framework and describe its relevance to immunological mechanisms and the resulting empirical predictions.

ECOIMMUNITY: A MODEL FOR TISSUE–IMMUNE INTERACTION

Ecosystems manifest self-tolerance and respond to foreign invaders

The role of evolution in shaping the immune system was established with the understanding of the process of clonal selection (Talmage 1957; Burnet 1959). We propose to extend the ecological insight to include any type of immune activity toward self- or foreign antigens, and by doing so, to avoid the need for self–non-self discrimination. For the sake of this discussion we will temporarily disregard the protective role of the immune system and suggest that, as in other biological systems, a symmetric relationship exists between the power of immunity—as a predator—to attack, and the capacity of any local tissue to protect itself. Namely, immune cells respond against any target they are able to identify and attack. Indeed, observing population dynamics, common predator–prey interactions may be viewed as manifesting some form of tolerance: despite the fact that lions can (and do) attack gazelles, gazelle populations may fluctuate but do not change drastically (as long as other environmental factors

remain relatively constant). How is this form of tolerance preserved in these systems? Evidently, no ad hoc mechanism of suppression or regulation of the predators operates here. The stable balance of the two species' populations results from their adaptation to one another (and to other local species) through evolution. Both species symmetrically impose a selective pressure by continuously removing the incompetent individuals that fail to hunt, or to escape predation (Darwin 1859; Schaller and Keane 1972). The co-evolving nature of this interaction maintains homeostasis in the habitat by an additional mechanism—the rejection of foreign invaders. Foreign organisms cannot easily colonize new habitats, even if their physiology fits the local abiotic conditions. For instance, species that originated in a habitat that lacked carnivores would have a low chance of surviving and colonizing a new habitat populated by carnivores. This is true even if such a species returns to a habitat it had been relocated from a few generations previously.

How can ecology be used to describe the relation of immune and tissue cells that share the same genome? To use an ecological metaphor, one should verify that the studied system is composed of an environment occupied by living and co-existing species that maintain feedback mechanisms. Are these conditions met in the immune–tissue interaction? We will now describe the assumptions that promoted us to apply the ecological metaphor, and suggest that it can be valid in the immune–tissue setting.

Assumptions of Ecoimmunity

I Different types of cells can be illustrated as species: The definitions of species that are commonly used for multi-cellular organisms are irrelevant in the study of microorganisms (regardless of the discussion of the immune system and the tissue). Species of microorganisms cannot be defined by the ability to have fertile offspring by successful sexual reproduction, nor can the genome serve as the basis for taxonomy. On the other hand, tissue cells of the same multi-cellular organism, like other microorganisms, fulfill most of the characteristics that define species. Cells of different tissues fit the definition of *Typological species*, the cells of each tissue conform to certain fixed properties, and different types of cells can be differentiated according to variations in their phenotypes. For these characteristics, the old definition of *Morphological species* also agrees with the speciation of tissue cells. However, in line with our ecological reasoning we find Darwin's vague definition of species to be the most applicable to our case. All the cells of an organism emerge from the same zygote, but then diverge one from another to create sufficiently significant differences that are based on their phenotype. Consequently, tissue cells of the same type share a common ancestor and a lineage that maintains their integrity as a group. Lineages differ one from the other, not only by their phenotype, but also spatially, as they develop in different organs.

II Tissues can be viewed as habitats with limited resources: Tissues fit the definition of habitats as the environment in which an animal, or a plant, naturally develops and lives. Different tissues may be regarded as different habitats, as they vary in their abiotic and biotic conditions. Each of these habitats is dynamic, containing conditions, and cellular interactions that change throughout life, and is limited in its resources, especially following insults and, in some cases, during development (both marked by cell death) (Henson and Hume 2006; Penaloza et al. 2006).

III Immune cells and pathogens interact as predators and prey: The interaction with active immune cells (innate and adaptive) is usually harmful to the target organism (be it a bacteria, a virally infected cell, or a parasite). On the other hand the interaction is positive for the immune cell in the sense that it facilitates its survival, differentiation, and proliferation (a +/− interaction). Indeed, models of predator–prey population dynamics that incorporate competition and selection of immune cells and predation of pathogens serve as the basis for analysis of the kinetics of immune responses to counter pathogens (Nowak and May 2000; Frank 2002; Wodarz 2006).

IV The cellular phenotype can be varied, passed to daughter cells, and induced to neighboring cells: Through the action of different transcription factors and post transcription/translation modifications, the phenotype, even within the same genome, is modified. The transcription profile varies and is adapted to environmental cues of the dynamic local tissue (phenotypic plasticity). Some of these epigenetic variations occur stochastically due to changes in gene/protein expression, which provide cells with the flexibility required to respond and adapt to environmental changes and stresses, and can prevent cells from being trapped in suboptimal epigenetic states and phenotypes (Kaern et al. 2005; Meshorer and Misteli 2006). Different transcription profiles can fit differently based on the dynamic tissue's habitat (Dekel and Alon 2005). Importantly, epigenetic information is heritable during cell division although it is not contained within the DNA sequence itself (e.g., DNA methylation, post translational modifications, acetylation and phosphorylation, etc). Therefore, gene expression and epigenetic modifications, which determine the local cellular phenotype, represent heritable tissue-specific traits: prospering cells can transfer nuclear, cytoplasmic and membrane components to daughter cells and modulate signaling pathways in neighboring cells. This inheritance of phenotype allows cellular commitment and is also the basis for cellular adaptation.

V Molecular immune specificity is not perfect: Basic chemical and physical considerations imply that the molecular specificity attributed to the T cell receptor and to monoclonal antibodies cannot be perfect (Greenspan 2001). Indeed, the

interaction between the TCR and the short peptides presented by MHC molecules is highly flexible and allows a specific TCR to interact with a broad range of different peptide ligands. TCR degeneracy is the base for cross recognition and has been associated with autoreactivity and autoimmunity (Hemmer et al. 2000).

Resulting principles of Ecoimmunity generalize ecological interactions

By virtue of the above assumptions we suggest the following principles of operation within the Ecoimmunity framework:

I Selection of Phenotype: The limited resources within a tissue (assumption II) imply that the environment cannot support all newly differentiating cells, and therefore the potential for survival, differentiation and proliferation cannot be fulfilled by all cells. As the genome is relatively fixed in most healthy somatic cells (excluding the adaptive immune cells), the epigenetic cellular phenotype is the basis for differences that define the chance to survive (Kaern et al. 2005). Recent studies have demonstrated that heritable environmentally induced epigenetic molecular modifications to both DNA and chromatin have a range of effects on gene expression and thus on cell phenotype (Jirtle and Skinner 2007). In the term "phenotype" we include the specific gene expression patterns that result in the particular characteristics of this cell. We thus have a Darwinian system: a relatively stable, and yet limited, cellular environment, and a phenotype, which is a heritable trait that can be changed (assumption IV) via natural selection—selection of phenotype. Cells adapt their phenotype in response to environmental changes and may expand it through inheritance and induction. Moreover, the efficiency of adaptation and selection of a phenotype is better than that of genetic mutations: changes in the phenotype can take a continuous rather than a discrete nature, they can be done "purposefully" rather than randomly, and they can be induced in neighboring cells, not only in daughter cells.

II Immune and tissue cells can interact as predator and prey: Assumption V suggests that immune activity inevitably includes cross-reactive clones that may be harmful to self. Thus, unless additional assumptions are added (that include a mechanism of self/non-self discrimination), the direct interspecific interaction between self-reactive immune cells and other cells is that of predators and prey (assumption III).

III Tolerance may be an immune-tissue co-evolution through symmetric adaptation: Finally, based on the first two principles, we suggest that selection of phenotype in the face of the pressure of predation may result in the selection of an immune-resistant phenotype. This adaptation and selection is similar to the selection of adaptive immune clones except that the latter involves mechanisms of genetic alterations. Thus, it is possible that in parallel with the variance in immune affinity of lymphocytes clones, the cells of each tissue vary in the transcription level of cytokines and receptors. Immune cells that are best fit to prey on vulnerable tissue cells and tissue cells that are most fit to resist immune predation survive, proliferate, and further differentiate. (Naturally, this phenotypic variability and inheritance applies also to immune cells.) Such co-evolution may result in what is commonly viewed as "self-tolerance." The continuous co-existence of immune and tissue cells is the outcome of a "well balanced conflict" rather than the outcome of a unilateral suppression.

The emphasis given in the above to the selection of phenotype does not imply that, theoretically, any given cell may adapt and develop in the host's habitat. Evolution (this time we refer to phylogenetic evolution) selects only tissues able to express the protective phenotypes and phenotypic plasticity during ontogeny, and during challenging periods, and still maintain their function.

Healthy tissue cells use immune-evasion strategies continuously

Tissue cells adopt multiple strategies to avoid destructive immune responses. In the broader community-ecology view, these mechanisms are extensions of known defense strategies to counter predators. Some examples of these mechanisms are: (a) Hiding by minimization of chemical affinity, such as sequestration of receptors and antigens, the down-regulation of MHC-I molecules and co-stimulatory molecules expression (Algarra et al. 2004), or the secretion of paracrine inhibitors that down-regulate cell adhesion molecules (CAMs) by adjacent endothelial venules, thereby inhibiting lymphocyte infiltration (Tomescu et al. 2003). (b) Signaling to inhibit predation by, for example, secreting soluble factors such as TGF-β, IL-10 or VEGF, which locally modulate the immune response (Ohm and Carbone 2001). (c) Reducing activity and changing behavior in accordance with a predator's activity, for example, when tissue cells detect local inflammation by sensing increased levels of antibodies and inflammatory mediators originating from both immune and neighboring cells. Accordingly, these tissue cells can secrete factors that increase resistance and suppress more vulnerable cellular activities such as differentiation or growth (Rolls et al. 2006). (d) Counterattack by expression of different factors and receptors that damage immune cells (e.g., Fas (Apo-1/CD95), Fas ligand (FasL, CD95L), and TNF receptor (TNFR)), leading to T cell apoptosis (Van Parijs and Abbas 1996). (e) Saturation of the predator when, in the first stages of development, cells in some tissues differentiate and proliferate in overwhelming number, thereby gaining a numerical advantage until a competent phenotype is established (Nathens et al. 1995; Butcher and Picker 1996; Rosenblum et al. 2006).

Are these defense mechanisms genetically encoded? Is their expression independent of immune activity? Or are they acquired amid immune pressure? Cancer cell evasion techniques

demonstrate that various immune-defensive phenotypes may indeed be adaptive. Cancer cells that can adapt by actively suppressing tumor-specific immunity survive and proliferate (Pardoll 2003; Uyttenhove et al. 2003; Tlsty et al. 2004; Feinberg et al. 2006).

For example, this suggested dynamic adaptation is restricted by the expression patterns defined genetically. Structures such as major and minor histocompatibility complex proteins play a major role in the immune–tissue interaction, and their expression can be dynamically adapted. Any cellular disparity in their level of expression that can be "sensed" by the immune system reflects on the interaction. As the histocompatibility complex plays a major role in the immune–tissue interaction, and because it has such a high relative variance, it is highly relevant to our framework. The ability of the tissue to adapt to the presence of an active immune system by acquiring a suitable expression level of MHC molecules can prevent immune-mediated destruction (Kaufman et al. 1993; Maeurer et al. 1996).

Similar to ecological systems, the importance of adaptation and selection is more significant when the habitat changes. In our case, this is when the tissue is damaged by a pathogen or by any external injury. Damaged cells are incapable of hiding or escaping; consequently, they express markers and secrete soluble factors that stimulate the immune system in a manner which, in the short run, promotes clearance of damaged and of neighboring cells and, in the long run, provides the basis for tissue repair and regeneration.

ECOIMMUNITY FINDS COHERENCE IN IMMUNOLOGICAL ENIGMAS

Co-evolution is most effective in shaping embryonic tissues

Ecoimmunity suggests that by default, tissues, and microorganisms can survive in the presence of active immunity, if they co-evolved with the selective pressure of the respective immune system. Adaptation and selection can operate through cellular response to environmental cues or through stochastic differences across cells (Kaern et al. 2005). The favorable phenotype can be popularized either by inducing a change in phenotype in neighboring cells, or by heritage during cell division to daughter cells. In either case the selection of phenotype probably occurs in the optimal way during development, by virtue of the high rate of differentiation and the high-phenotypic plasticity of pluripotent embryonic stem cells (Meshorer and Misteli 2006). In these conditions, competent tissue cells survive as they adapt their phenotype to counter immune predation. Notice that this adaptation results in cellular resistance toward adaptive, as well as innate immune cells (innate-immunity tolerance) (Janeway 1989; Medzhitov and Janeway 2002; Kobayashi and Flavell 2004; Hargreaves and Medzhitov 2005). This adaptation through co-evolution results in tolerance towards tissues that evolved during adulthood. In addition, since this cellular adaptation is not uniquely defined by the genetic similarity or foreignness of the tissue relative to the immune system, it may facilitate tolerance toward commensal bacteria (Kelly et al. 2005), and toward allogeneic and xenogeneic embryonic transplants (Billingham and Silvers 1964; Dekel et al. 2003)

Fraternal dizygotic twin tolerance and maternal tolerance are two classical, and yet enigmatic, manifestations of immune tolerance (Owen 1945; Trowsdale and Betz 2006). It is now evident that the placenta does not act as an immune barrier and maternal immune cells do patrol the tissues of the developing embryo. Multiple mechanisms of immune modulation in the mother–fetus interface were demonstrated to maintain immune tolerance (e.g., IDO inhibition, expression of FAS ligand, CRRY, CD25+ regulatory cells [Trowsdale and Betz 2006]). However, surprisingly, the absence of these mechanisms (excluding the IDO) was shown to result in rejection of the fetus, in allogeneic as well as syngeneic fetuses. Ecoimmunity can explain the absence of immune tolerance toward these syngeneic fetuses without further assumptions. The placenta bridges the developing tissues and the maternal immune system (Trowsdale and Betz 2006), and in fraternal twins, the placenta allows fusion and an inter-embryo exchange of cells. Thus, the maternal immune system applies selective pressure on the developing tissues, which display a high capacity to differentiate, adapt and modulate the immune response. In the context of Ecoimmunity, the rejection of fetuses in the absence of the tissue's immune-modulatory mechanisms is not surprising: the maternal immune system attacks whichever vulnerable tissue it encounters, and so failure to modulate and avoid this system is detrimental to the fetus, regardless of whether it is syngeneic or allogeneic. Along the same line, Ecoimmunity predicts that this inherited replication of the maternal immune–tissue interaction may be preserved after birth. Indeed, clinical mother-to-child grafting has been shown to be preferable to father-to-child grafting (Kalia et al. 1988; Neu et al. 1998; van Rood and Claas 2000).

Transplants that colonize new ecosystems: adaptation or extinction

Tissues that co-evolved in the presence of one immune system face difficulties when encountering a different immune environment in adulthood, similar to species that colonize new habitats. Accordingly, Ecoimmunity attributes the acute rejection of grafts to their inability to adapt and cope with the immune system of the recipient. Phenotypic plasticity can be gained primarily by stem cells, which display higher ability to

modulate immune activity compared with terminally differentiated adult cells. It is therefore anticipated that the overall rate of adaptation of the adult tissue is much lower than that of developing tissues. However, co-evolution during development is not a necessary condition in all cases: like species that colonize a new habitat, tissues may survive in the presence of a foreign immune system, if they can adopt an appropriate protective phenotype, while under attack. Following are some of the known factors that influence the chances of species to colonize a new ecological habitat, and their equivalent (and yet unexplained) observations in the study of tolerance to grafts. (a) The size of the colonizing group (propagule size) (Ahlroth et al. 2003): equivalently, bigger allografts have a higher rate of acceptance (Silvers 1968; Jones et al. 2001; Yasunami et al. 2005). (b) The reproduction rate of the colonizing species (Griffith et al. 1989); equivalently, transplanted tissues with a high regenerative capacity have a better chance of survival, even if they are fully MHC-mismatched (Dresske et al. 2002). (c) The presence and competence of local predators (Griffith et al. 1989); equivalently, survival of grafts from wild-type donors in immune-deficient animals is easily achieved, and immune suppression can prolong graft survival in clinical settings; however, it prevents the induction of immune tolerance. (d) The past experience of the colonizing species: equivalently, grafts that co-evolved with the active presence of an immune system similar to that of the recipient may adapt to the immune environment of the recipient. However, a suppressed immune system cannot apply selective pressure on tissue cells. Consequently, chronically held grafts that never encounter the active immune system cannot adapt to it and are rejected once immunosuppression is withdrawn. (e) The residence of individuals of the same species facilitates fast adaptation of the colonizing individuals in the new habitat; equivalently the chances for acceptance increase as the interaction between the immune system of the host and the tissues was already set, and can be induced by the pre-grafted resident cells (Martin et al. 1991; Mezrich et al. 2005). (f) Physiological limitations of the colonizing species versus its capacity to adapt; equivalently, the genetic background may impose obvious limitations on the ability of cells to express an appropriate phenotype.

On the other hand, foreign carnivores that appear in a new habitat may reduce the population of resident species. This is equivalent to the immune–tissue interaction in graft-versus-host disease (GVHD) (Buckley 2000). In accordance with the ecological analogy, GVHD is more problematic in immune-deficient individuals, presumably due to the reduced capacity of the local tissue to deal with any immune activity (Buckley 2000). Resident tissues have a much higher chance of avoiding GVHD when bone marrow is transplanted in the early stages of development (allowing the developing tissues to adapt) (Buckley 2000). The ecological view can also resolve the unexplained occurrence of GVHD in syngeneic immune-deficient patients (Latif et al. 2003). In all these cases, Ecoimmunity suggests that GVHD results not from the foreignness of the host's tissues, relative to the immune system of the graft, but rather from the inability of the host's tissue cells to handle predators. Ecologically, the tissues of the immune-deficient host are the dodos that encounter predators for the first time.

Multiple experiments involving immune-deficient mice provide direct evidence for the critical role of tissue adaptation in the maintenance of homeostasis. Autoimmune disease—with no apparent change in the phenotype of affected cells (Cabbage et al. 2006)—was induced in immune-deficient mice by transplanting syngeneic T cells from transgenic mice expressing solely T cell receptors reactive to myelin basic protein. Similarly, transfer of T cells into immune-deficient mice grafted with skin or heart tissue resulted in graft rejection, even in the absence of apparent markers of inflammation before the transfer (Bingaman et al. 2000). The role of the graft in establishing transplantation tolerance (Karim et al. 2002) has been demonstrated by the finding that IFN-γ also promoted graft acceptance in knock-out mice that lacked T cell expression of the IFN-γ receptor. Namely, IFN-γ promoted the adaptation of graft cells to the local immune response (Coley et al. 2006). Furthermore, we have recently shown that transplantation of pancreatic islets from immune-deficient (SCID) mice into syngeneic wild-type mice (given the known uncertainties concerning an experiment involving knock-out mice) results in reduced graft survival compared with transplantation of wild-type syngeneic islets (Hauben et al., 2007).

One of the most elegant pieces of evidence for the role of co-evolution in establishing tolerance is the classical set of puzzling experiments performed by Triplett in 1962 (Triplett 1962), and then by Rollins-Smith and Cohen (1982). On the face of it, these works seem to contradict one another. Triplett removed pituitary glands from frog embryos and parked them externally in allogeneic frogs. Upon re-grafting into their original host, post maturation, most of these grafts were rejected. However, in a similar experiment Rollins-Smith and Cohen reported complete acceptance of the relocated pituitary glands, and questioned Triplett's results. A re-evaluation of both experiments in light of Ecoimmunity theory reveals the coherence of these two experiments. Triplett's experiments demonstrate the critical role of epigenetic adaptations during development: the externally parked tissues were not exposed to their original immune system during development, and were thus rejected upon regrafting. In the Rollins-Smith experiment, however, the glands were parked orthotopically in syngeneic animals, thus giving rise to the conflicting observation. According to Ecoimmunity, the development of these parked tissues in an identical immune system was the perfect pre-experience to facilitate easy survival upon relocation. In the same line Ecoimmunity handles the unresolved observa-

tion, in Triplett's experiment, of successful regrafting of half of a gland (where the other half was not relocated). As in pre-existing species that facilitate the colonization of individuals from the same species, pre-existing donor grafts in the host have a critical role in the induction of immune tolerance.

Active species regulate one another without chronic suppression

How can Ecoimmunity be reconciled with the role of immune cell apoptosis, anergy, and regulatory cells in the maintenance of self-tolerance? Despite the consensus on the role of immune suppression in maintaining tolerance, observations interpreted as evidence for chronic anergy and suppressive regulation can actually reflect the net attenuation of autoreactivity. This could be the result of competition between different predator species, which consequently suppress each other. Multiple observations on autoimmune T cells demonstrate that the same cell subsets can induce both tolerance and autoimmune diseases, without apparent change in phenotype. CD25+Foxp3+Tr cells, whereas suppressing certain types of immune responses may serve a specific effector function through promoting other responses (Belkaid et al. 2002). In fact it was demonstrated that functional tolerance in vivo cannot be achieved in the absence of immune activity (Lechler and Batchelor 1982; Bishop and McCaughan 2001). Considering the ecological analogy, the role of different subsets of Tr cells can possibly be described as competition or parasitism between predators that is disadvantageous to one side (or both sides) of the interaction and is protective for the prey (i.e., the tissue). Results obtained by tracking the dynamics of the interaction between Tr cells and other cell subsets demonstrated the possible role of such competition between predators (Thornton et al. 2004; Tang et al. 2006).

Common views of Tr cells assume that they operate by chronic and absolute suppression of autoreactive T cells. Such suppression implies that autoreactivity is necessarily destructive. However, it has been shown that priming of autoreactive T cells accompanies scenarios of secondary degenerative processes triggered by various types of insults (Popovich et al. 1996). This response has been demonstrated to be a purposeful protective physiological mechanism (Yoles et al. 2001). This tissue-repair mechanism can be boosted by vaccination counter antigens associated with various degenerative processes (Moalem et al. 1999; Wildbaum et al. 2003; Benner et al. 2004; Frenkel et al. 2005; Zohar et al. 2006). Ecoimmunity reconciles the above observations on the destructive and protective faces of autoimmunity, with no need for special protective phenotype, with regard to the individual activity of immune cells toward their prey. Autoimmune cells, as predators, fulfill a key role in regulating the population of the prey in times of stressful conditions such as trauma, oxidative stress, or infection. Predators remove the sick and the vulnerable individuals and by doing so maintain the population of the prey to fit the carrying capacity of the habitat, and prevent an arbitrary infection from becoming an endemic disease. The protective role of predators, in such scenarios, has been demonstrated in multiple systems. (Schaller and Keane 1972; Anderson and May 1981; Sih et al. 1985; Cote and Sutherland 1997; Packer et al. 2003; Johnson et al. 2006).

Species populations fluctuate when ecosystems change

According to the ecological reasoning proposed by Ecoimmunity, an autoimmune disease is equivalent to a scenario in which a predator–prey interaction is shifted and becomes destructive. In macroscopic ecological systems, the cause for such a shift is usually not that the predators achieved an instant quantum leap in their hunting talents. More commonly the trigger is some external factor that weakens the prey and their ability to protect themselves or that affects a third species that has a key role in the interacting network (keystone species). This analogy fits the external-trigger hypothesis, according to which, many cases of autoimmune diseases are triggered by an environmental or a pathogenic factor that initiates a self-perpetuating degenerative process (Barnett and Prineas 2004; Dunne and Cooke 2005; Hauben et al. 2005; Opsahl and Kennedy 2005). We suggest that such an external factor not only stimulates an immune response, but in addition, renders the tissue susceptible to immune predation. A direct example for the role of tissue malfunction in reducing affinity in the context of autoimmune disease came from the study by Barin et al. which demonstrated how iodine triggers autoimmune thyroiditis by elevating the expression of intracellular adhesion molecules of tissue cells that enhance the affinity of the immune–tissue interaction (Barin et al. 2005).

The stability of a desired lifelong tolerance is tested especially in scenarios of changing conditions. In these cases cells respond to the environmental cues, and are likely to change their phenotype. Tolerance that is based on suppression of autoimmune cells runs the risk of being broken or abused by foreign microorganisms or by altered immune cells. Such events may be potentially fatal because the broken suppression lacks a balancing mechanism, and once individual immune cells break it, it can hardly be regulated. On the other hand, a well-balanced conflict can still be stable: even if individual immune cells "get mad", healthy tissue cells are always on guard to resist predation. In that sense immune cells that act as predators choose an evolutionary stable strategy (ESS)—relative to the strategy of suppression. In a complementary way, tissue cells that adopt a protective phenotype choose an ESS relative to the strategy of indefensibility.

Open issues: difficulties and predictions of ecoimmunity

Ecoimmunity describes a possible framework for the analysis of phenomena related to immune tolerance in general and specifically to immune self-tolerance. This interdisciplinary view attempts to bridge ecological, developmental, and immunological dynamics. As such, it encompasses multiple issues and ideas that should further be explored and validated. While some of the assumptions about Ecoimmunity presented here are not as radical, the suggested principle of selection of phenotype deserves attention. We should verify that the exact parameters that define the rate of differentiation and of cellular phenotypic changes are sufficient to allow phenotypic plasticity, before cells are predated. The question of the degree of phenotypic plasticity, and of the rate of possible changes, should specifically be tested in mature tissues, and in tissues that develop before the immune system. We have not addressed here the exact molecular mechanisms that operate in each tissue, in its interaction with autoimmunity. What makes different tissues apply different types of immune-resistant mechanisms? How do these molecular mechanisms reflect on the chances of various tissues to be grafted successfully? Why are some tissues more susceptible than others to destructive autoimmunity?

The second principle stating a predator–prey interaction of the immune system and the tissue, may be the most difficult to accept, especially in the context of current views of the immune–tissue interaction. Wouldn't symbiosis fit better as an interaction of two sides that share the same genome and the same "goal"—the well-being of the host? Commonly observed predator–prey and immune–tissue interactions are indeed different, but we find that none of these differences overrides the generalization suggested by our model. Both systems are composed of a complex interaction between living entities that differ (either genetically or phenotypically) and co-evolve in the same limited habitat. In both cases they become mutually dependent, and their continuous adaptation to the environment contributes to the well being of the entire ecosystem (be it a forest, a coral reef, or a multi-cellular organism). There is thus no reason to assume additional interactions or different rules and kinetics of operation.

Despite these unresolved issues, we can already suggest a few counter-intuitive predictions. Ecoimmunity implies that genetically identical cells that develop in different immune environments will differ in their capacity to resist immune-mediated destruction. At the molecular level, it is suggested that the expression level of genes that are related to the immune–tissue interaction will differ, in between cells from adult wild-types versus immune-deficient animals of the same background. The use of gene arrays may aid in revealing the specific adaptations accumulated by cells that develop under different selective immune pressure. The outcomes of these phenotypic differences may be further tested by various experimental models, such as the transplantation of tissue from an immune-deficient donor into a wild-type recipient of the same genetic background. Contrary to the expected graft acceptance, Ecoimmunity predicts partial or complete rejection (Hauben et al. 2007) depending on the graft size (that correlates with the tissue's capacity to withstand damage, while adapting) and the tissue regenerative capacity. Other possible manipulations may involve the "parking" and relocation of grafts between wild-type and immune-deficient mice, development in an allogeneic maternal environment and grafting, etc. On the other hand, if genetic identity does not necessarily result in immune tolerance, then the complementary case is also implied: genetic differences do not necessarily result in immune destruction. Additional experimental manipulations, in addition to those reviewed above, that will test this prediction may include, for example, transfer of tissue between two allogeneic fetuses that develop in syngeneic mothers. The traditional expected result of such an experiment would be complete rejection, whereas Ecoimmunity predicts graft acceptance as a result of epigenetic adaptations.

In accordance, Ecoimmunity suggests various possible implications for clinical scenarios. For instance, it is hypothesized that for tissue grafts with correct tissue typing and pre-conditioning, successful allogeneic transplantation may be achieved without chronic immune suppression. The correct tissue typing should be based on the genes that are involved in the immune–tissue interaction, and that influence the ability of the graft to adapt. In addition, conditioning could be performed by gradually exposing the graft to the recipient's immune system, in vivo or in vitro. Pre-conditioning may allow the graft to establish the correct dialogue with the immune system and the correct protective phenotype, thus avoiding annihilation. We further hypothesize that possible therapies for autoimmune diseases, in addition to treatments that target the immune system, should target the tissue, by increasing its resistance to immune predation or amplifying the degree of phenotypic plasticity.

CONCLUDING REMARKS

We propose a new way to address enigmatic phenomena related to immune tolerance by suggesting selection of a tissue's phenotype against a continuous immune pressure. Seemingly a violation of the search for simplicity, this added dimension is not a unique interaction that was set ad hoc, but rather a direct extension of common interactions that appear in all multi-species systems. Ecoimmunity uses Darwin's definition of species to generalize the immune responses against pathogens to include autoimmunity. By doing so, Ecoimmunity is shown to explain various phenomena, while fulfilling a few important criteria (Livio 2000): (a) It is simple: it includes no

additional assumptions other than that the tissue is an ecological Darwinian system. (b) It is symmetric: the tissue and the immune system are interchangeable with respect to all the rules that define their dynamics. And (c) it obeys the Copernican principle: in the broader context of biology of multispecies systems, some of the classical models of tolerance violate a *Biological Copernican Principle*, that is, tolerance is achieved by setting unique rules that are not applicable to other ecological systems. These rules include the existence of species that have no purpose and should remain inactive throughout their entire existence (anergized autoreactive T cells), the establishment of a system to keep these species silenced (Tr cells), and even species (local tissue cells) that are normally resistant to any predation within their own habitat (as long as pathogens are not colonizing). Ecoimmunity suggests that the immune–tissue interaction is universal and invariant to scaling. Insights stemming from macroscopic ecological systems can be applied to the immune–tissue interaction and vice versa. Moreover, the immune system itself is viewed here as non-unique with respect to its development and role, relative to other organs. It is simply a resident species of the host's inner microhabitats that obeys the laws of co-evolution. In other words, imagine a tiny cellular-sized alien zoologist/microbiologist—ignorant of Darwin—who is actually able to study first hand the immune system–tissue interaction. This microbiologist views ontogeny as an evolutionary time, and will most likely converge on the same typological/Darwinian definition of species. Among other interspecific interactions, he observes, for instance, immune cells' species preying on colonizing pathogens, and different species of T cells competing over the same prey. Now let us assume, hypothetically, that he also finds protection of tissue cells (regardless of their fitness), and suppression of autoimmune cells (however fit they are) throughout the evolutionary time. In such a case he would probably never agree with the idea of selection of the fittest in the struggles of life (Darwin 1859). He might, however, accept this idea if he found immune–tissue predation and co-evolution.

Ecoimmunity revisits our approach to the general aim of immune activity. If the immune system is analyzed not only as a defense system, but also as an ecological system, then intercellular interactions are universal and relatively fixed. The factors that commonly change and that shift ecosystems from homeostasis to a different working-point (extinction, abnormal population, etc.) are usually external. This article presented only a sample of what can be understood by "borrowing" ecological insights on the dynamics of inter-specific interactions to autoimmunity. The vast vocabulary, definitions, and dynamics studied in ecosystems can refresh our approach to autoimmunity and enrich our set of analysis tools. The mathematical quantification of ecological dynamics (that is already applied to immune–pathogen interactions) can be applied to autoimmunity. The generalization suggests that other aspects of immune response (immune-memory, stimulation, surveillance, etc.) should also be analyzed with ecological tools to improve our understanding of the immune system.

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