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Escaping from Rejection

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Summary

Those engaged in clinical transplantation and transplantation immunology have always taken as a central objective the elucidation of means to prevent graft rejection by the recipient immune system. Conceptually, such mechanisms stem from the concept of Paul Ehrlich that all organisms can selectively avoid autotoxicity; i.e. they exhibit *horror autotoxicus*. Some mechanisms of *horror autotoxicus* now understood. T lymphocytes and B lymphocytes recognize foreign antigens but not some auto-antigens. Clonal deletion generates lacunae in what is otherwise a virtually limitless potential to recognize antigens. We call this mechanism structural tolerance. Where imperfections in structural tolerance allow self-recognition, the full activation of lymphocytes and generation of effector activity depends on delivery of accessory signals generated by infection and/or injury. The absence of accessory signals prevents or even suppresses immunological responses. We call this dichotomy of responsiveness conditional tolerance. When, despite structural and conditional tolerance, effector activity perturbs autologous cells, metabolism changes in ways that protect against injury. We use the term accommodation to refer to this acquired protection against injury. Structural and conditional tolerance and accommodation overlap in such a way that potentially toxic products can be generated to control microorganisms and neutralize toxins without overly damaging adjacent cells. The central challenge in transplantation, then, should be the orchestration of structural and conditional tolerance and accommodation in such a way that toxic products can still be generated for defense while preserving graft function and survival.

Since the earliest days of transplantation, immunobiologists have sought means by which to prevent recognition and rejection of foreign tissue. The goal of these strategies is the retention of recipient immune function while selectively avoiding graft injury. While considerable theoretical and technical problems remain, an analogous problem and solution already exists in nature. Here, we discuss the mechanisms by which organisms preclude or control auto-toxicity, and for each, consider the corollaries between prevention of auto-toxicity and graft rejection. Further study of these controls, including structural and conditional tolerance and accommodation, will offer insight into new therapies for allo- and xenotransplantation.

Keywords

tolerance; accommodation; T Cell; allograft rejection; host defense

The immune system of higher vertebrates recognizes and neutralizes a broad range of environmental threats. Although these reactions contain commensal organisms, destroy non-commensal organisms and block toxins, the same responses might, but manifestly do not, injure

autogenous tissues or interfere with physiologic processes. The paradox of a powerful, but restrained, immune system has long a subject of study and commentary. Paul Ehrlich (1854–1915) postulated that organisms have an inherent *horror autotoxicus* and asserted that understanding the means by which injury is avoided is a matter of the “greatest importance (1).” Today, the mechanism of *horror autotoxicus* is usually considered to be tolerance.

Understanding *horror autotoxicus* is especially pertinent for the fields of transplantation immunology and clinical transplantation. Transplant immunologists have long sought to understand what makes a foreign graft “foreign,” and to determine why a foreign graft cannot be accepted as fully as autologous cells and tissues. Similarly, clinical transplant specialists seek a method of manipulating either the recipient or the graft to prevent rejection and promote acceptance without attenuating the remainder of the recipient’s immune capability. We think a more expanded understanding of *horror autotoxicus*, and particularly its role of accommodation, might aid in accomplishing both aims.

Structural tolerance

The first mechanism of *horror autotoxicus* we shall call “structural tolerance,” refers to the means by which lymphocytes recognize foreign organisms and toxins, but not autologous cells (Figure 1A). The most important (or at least most elegant) example of structural tolerance is represented by the diverse repertoire of T lymphocytes and B lymphocytes with antigen receptors directed at a broad array of antigens, but not those displayed on autologous cells. Thus, ELISPOT analyses consistently show few or no lymphocytes specific for self in normal individuals (2), (3). The lack of self-specificity in TCR and BCR repertoires is generated at least in part by clonal deletion during lymphocyte genesis and maturation.

The concept of structural tolerance can be traced to Ehrlich. Ehrlich postulated that antibodies interact with targets like “a lock and a key” (4) and that a normal individual does not make self-reactive antibodies. Thus, the “side chains” of cells, which he thought to be antibodies, could recognize microorganisms, toxins and foreign blood cells but not the cells themselves (4). Owen (5) and Burnett (6) proposed a more dynamic concept, where receptors that recognize self might be made, but either the autoreactive receptor or the cell bearing it would subsequently be eliminated. This process, now called clonal deletion, results in “lacunae” corresponding to self epitopes in the repertoires of lymphocytes (7). Consistent with this concept, one can detect in ELISPOT tests an absence of T cells and B cells capable of recognizing antigen to which an individual is tolerant (8). For example, we showed that infants receiving ABO-incompatible heart transplants acquire tolerance to A or B blood groups carried by the graft but not the recipient and that tolerant subjects lack B cells capable of producing antibodies directed against the graft blood group (9).

While undoubtedly important, structural tolerance fails to fully explain avoidance of self-injury by the immune system. Roughly one million T lymphocytes and B lymphocytes bearing distinct antigen receptors with random sequences (10) are produced each day, and of these, at least a few lymphocytes with autoreactive receptors must escape deletion. Further gaps in the structural tolerance model include the discordance between the presence of autoreactive receptors and autoimmune disease. Though there is a high probability of at least transiently having autoreactive antibody, less than 20% of individuals develop autoimmune disease (11), and persistent autoantibodies are detected in healthy individuals (12), (13). Even if clonal deletion is more effective than we think, evolutionary pressure would be expected to generate pathogens with antigens fitting entirely within a host’s immune repertoire lacunae; yet, with the exception of a few viruses, such organisms have not been found. Thus, some mechanism (s) other than structural tolerance must contribute to *horror autotoxicus*.

Conditional tolerance

To address the limitations of structural tolerance, another, and rather compelling, mechanism preventing auto-immunity has been proposed, which we shall call “conditional tolerance” (Figure 1B). Conditional tolerance refers to the set of mechanisms governing whether or not antigen recognition eventuates in an active immune response. In contrast to structural tolerance, which precludes antigen recognition, conditionality posits that antigen recognition occurs, but that the response is contingent on circumstances associated with the interaction. For example, presentation of an antigen under baseline conditions, such as by unstimulated dendritic cells, leads to no response or to anergy while presentation of the same antigen under conditions of inflammation generates immunity (14).

The concept of conditional tolerance can be traced to early studies of haptens. In 1932, Freund (15) described how injection of colloidal mixed with a purified extract of *B. anthracis* immunized animals against bacterial products, but exposure to un-bound bacterial compounds did not. An unexpected finding of this work was that antibodies could be raised against the innocuous colloid by injection of hapten-colloid, suggesting that circumstance, and not merely structure, defined antigenicity. At a cellular level, lymphocytes stimulated under non-inflammatory conditions and in the absence of tissue damage undergo anergy or suppression, while lymphocytes stimulated under conditions of tissue injury, infection or “danger” become activated (16).

The idea of conditionality was formalized by Bretscher and Cohn (17). They proposed that antibody responses depend on the antigen being marked as foreign by the presence of another signal, which they took to be delivered by a ‘carrier antibody.’ “Associative recognition” evolved into the “danger hypothesis (18)” and gained support with the greater appreciation that cells presenting antigen can determine the direction of lymphocyte responses and that the function of these cells is governed by accessory receptors such as toll-like receptors’ capable of recognizing exogenous and endogenous markers of injury (19), (20). One example, stimulation of toll like receptor-9 with a foreign agonist such as CpG DNA drives antigen presenting cells to prime auto-reactive T cells leading to autoimmune encephalitis (21). As another example, some who experience pituitary ischemic hemorrhage as a result of Sheehan’s syndrome later develop auto-immune hypopituitarism (22).

If failure of conditional tolerance explains some types of autoimmune disease, such failure does not explain allograft rejection. While ischemia/reperfusion injury in transplanted organs may promote alloimmune responses, such injury is not essential for those responses. Alloimmune responses to major histocompatibility antigens and acute rejection do not apparently depend on ‘danger’ or inflammatory stimuli. Allogeneic skin grafts and kidneys allowed to heal for several days following transplantation into immunodeficient animals are quickly rejected by adoptively transferred T cells (23), (24). Despite the strict need for inflammatory stimuli, the alloimmune reaction is dramatically more universal, rapid, and severe than the immune response to viruses or bacteria (25).

Fully effective structural and conditional tolerance might preclude the mounting of a protective immune response against common pathogens. Control of infection by T lymphocytes requires recognition of autologous cells expressing MHC with peptides from intracellular microorganisms, and failure of T lymphocytes to recognize self-MHC heightens susceptibility to infectious agents (26), (27). Yet, the CD8+ T lymphocytes recognizing foreign peptides were selected in the thymus and preserved in the periphery by recognition of self-peptides. Although the self-peptides plus MHC are thought to interact weakly with TCR, large amounts of self peptides might be generated in some circumstances, allowing the corresponding T

lymphocytes to be activated and self-reactive. Importantly, while recognition of foreign peptides can lead to cytotoxicity, in most instances it does not (28).

Accommodation

B lymphocyte functions do not require self-reactivity; however, antibody-mediated responses, which might injure autologous cells by ‘reactive lysis,’ actually protect against the most lethal bacteria. Thus, something beyond structural and conditional tolerance is needed to explain how immunity generates host defense without injury to the tissues and organs defended. We postulate that immunity changes tissues and organs in ways that confer protection against injury and this protection, which we call accommodation (29), is essential both to host defense and to prevention of autotoxicity.

We first recognized accommodation in studying the outcome of ABO-incompatible kidney transplants. Kidneys from blood group A or B survived even after antibodies against these blood group antigens returned to the circulation (Figure 1C) (30), (31), (32). Survival of grafts in the face of anti-HLA antibodies was subsequently described (33), although the significance of accommodation in this setting remains a point of controversy (34), (35). When considered in the context of the classical idea of *horror autotoxicus*, accommodation limits or prevents tissue injury when immunity occurs. For example, accommodation may explain why anti-DNA antibodies do not inevitably cause manifestations of systemic lupus erythematosus (36), (37).

We have suggested that accommodation may be a common, and possibly the most common, outcome of clinical transplantation (38). Many recipients of renal transplants produce donor-reactive antibodies (39). Since most transplants at any given time are functioning well, we postulate that the antibodies are absorbed to the graft, and that renal transplants acquire resistance to injury by those antibodies plus complement.

Accommodation may recruit pathways that not only protect cells from injury by complement or cytotoxic lymphocytes but also facilitate control of intracellular organisms. For example, Shan et al (40) recently reported that an agent that controls replication of the hepatitis c virus also heightens expression of heme oxygenase-1, a protein typically expressed by accommodated cells. Whether the cytoprotection characteristic of accommodation is integrally connected to host defense remains to be tested. On the other hand, accommodation may incur biological disadvantages in the form of changes in cell metabolism or loss of function (41). Long-term changes characterized as chronic rejection of transplanted organs might result from the pathways and products associated with accommodation, rather than a distinct immune response (29).

Integrating tolerance and accommodation

Accommodation and tolerance together explain avoidance of injury by the immune system more fully than either alone can. Tolerance chiefly reflects changes in the immune system, while accommodation refers to alterations of the target tissue. Tolerance avoids reactivity of the immune system with autologous cells; but this limitation is incomplete. Accommodation allows tissue to withstand vigorous immune responses but at a biological cost. If we define tolerance operationally, which is to say tissue injury does not occur, then one can not distinguish the impact of tolerance from the impact of accommodation. A more critical definition of tolerance, as proposed by Medawar, requires “specific non-responsiveness,” i.e. an adequate immunological stimulus has been delivered and no response is observed (25). Accommodation, by contrast, is a function or byproduct of immunity or inflammation.

Polack first described the absence of response to corneal allograft in rabbits treated with azathioprine as ‘tolerance’ (42), but the concept of tolerance today bears little resemblance to

inhibition of the immune system with antiproliferative agents. We originally postulated that mechanisms of accommodation might include changes in the properties of antibodies that limit impact on target cells, as in a change to a non-complement fixing isotype (43), (44). We should now consider this mechanism, to the extent that it limits inadvertent tissue injury, a manifestation of tolerance.

Tolerance and accommodation may together orchestrate immune responses. The effectors of immunity induce regulation and resistance to injury. For example, activation of complement on endothelial cells induces transcription of COX-2, the products of which suppress T lymphocytes, and confers resistance to a range of toxins (45), (46), (47). Binding of toll-like receptors suppresses further response to toll receptor agonists, a condition called “endotoxin tolerance” (48), (49). Expression of the immunoglobulin-like transcript (ILT) family of receptors on graft cells leads to the induction of anergic or tolerogenic responses by the recipient (50), (51), (52). These findings clearly show a role for the target tissue in modulating immune responses. Future therapeutic approaches will benefit from an expanded understanding of both accommodation and tolerance and a fuller appreciation of how the immune system and the targeted organ can coordinate host defense with avoidance of injury.

Concluding remarks

The orchestrated combination of structural and conditional tolerance and accommodation embodies the mechanism sought by Paul Ehrlich to explain the why immunity does not damage self. Accommodation protects against products of both innate and adaptive responses, and thus it allows those products to be generated for defense against invasive organisms and toxins. Future strategies for avoiding rejection of grafts should consider the relationships between these two evolutionary protections against self-injury. Some immunity against self or against a graft may prevent injury while controlling invasive organisms.

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A. Structural tolerance

B. Conditional tolerance

C. Accommodation

Figure 1.

A. Structural tolerance. The potential repertoire of the immune system (T and B cell receptors) is more diverse than the manifest repertoire, as autoreactive clones are deleted during development.

B. Conditional tolerance. The environment in which an antigen is recognized determines whether the naïve cell becomes anergic, or goes on to either an effector or tolerogenic phenotype. APC, antigen presenting cell.

C. Accommodation. Low-level injury (by complement, perforins, toxins, or other stimuli) causes cellular adaptations leading to survival in the face of higher-level insults.