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Regulating damage from sterile inflammation: a tale of two tolerances

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Abstract

The severity of immunopathology from non-infectious inflammation is mainly understood and managed by targeting immune cells. The role of target tissues in determining damage severity has been largely overlooked. We discuss here the concept of ‘tissue tolerance’ for tissue-intrinsic programs that ameliorate organ damage in the setting of sterile immune-pathology.

The immune system has evolved to protect the organism from infectious non-self through mechanisms that mediate host ‘resistance’ against infections to reduce pathogen burden^{1,2}. Additionally, ‘disease tolerance’ describes the pathogen-independent response to infection, functionally serving to mediate tissue damage caused either by pathogens or by the immune response against them^{1,2}. Disease tolerance improves host fitness in the presence of similar pathogen burdens, and is distinct from resistance to an infection, that aims at reducing the pathogen burden^{1,2}. This concept of disease tolerance and its impact is illustrated in Figure 1A where arrow AB demonstrates the contribution of resistance and the arrow AC demonstrates the contribution of tolerance to disease severity. Arrow AD models how both resistance and tolerance can cooperatively improve health.

In the context of sterile, non-infectious inflammation another form of tolerance, ‘immune tolerance’ regulates the immune response to self and non-infectious non-self antigens. Immunologists, long familiar with this concept, continue to make significant strides in understanding immune tolerance mechanisms. Efforts to understand and mitigate tissue damage caused by sterile and infectious inflammation have primarily focused on the modulation of immune responses. While enhancing ‘disease tolerance’ in the context of infections in plants and more recently in mammals has shown impact in mitigating tissue damage^{1,2}, whether a similar processes, considered under different terminology in the discussion of disease tolerance³, play a role in mitigating damage from sterile or non-infectious immunopathology such as in autoimmunity, allo-graft rejection and graft-versus-host disease (GVHD), has not been systematically explored and remains poorly understood.

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Herein we suggest that a similar concept could be applied to tissue damage from non-infectious immune damage, as shown in Figure 1B. When viewed through this lens, current therapeutic approaches largely focus on moving along from point A to B in Figure 1B by enforcing 'immune tolerance' to reduce the burden of immune effector cells. Several disparate lines of experimental observations nonetheless do suggest that target tissue intrinsic features and responses contribute to disease severity during sterile immunopathology. Dampening the immune activation response may not always be sufficient to protect against immunopathology from autoimmune or allogeneic reactions.

For example despite massive immunosuppression, we may be unable to completely mitigate immunopathology such as those illustrated by end-stage or steroid refractory GVHD⁴. Furthermore, patients with a genetic immunodeficiency can also show autoimmune symptomology⁵. Specifically, *PRKDC* encodes for DNA-dependent protein kinase catalytic subunit (DNA-PKcs), a kinase that is crucial for DNA double-strand break repair and that forms part of a protein complex required for AIRE-dependent expression of peripheral antigens in medullary thymic epithelial cells (mTECs). Patients with mutations in *PRKDC* present with reduced T and B cells (Combined Immune Deficiency) yet demonstrate features of autoimmunity⁵. The mutation is present in all cells and whether this makes tissues in specific organs uniquely susceptible to damage despite the reducing autoimmune T/B cell load is not known. However, it does offer an illustration of how tissue pathology can present as a movement from point D to A (Figure 1), suggesting factor(s) other than immune effector cell number may contribute to disease severity. Experimental data show that TLR signaling by the intestinal epithelial cells (IECs) protects them from non-infectious (DSS) colitis without reducing the leukocyte burden⁶. The protection was associated with increase in cytoprotective growth factors such as IL-6, heat-shock protein (hsp) 25 and hsp72, demonstrating that tissue intrinsic signaling and generation of cytoprotective factors control target organ damage⁶. Recent observations showed that enhanced uptake and metabolism of butyrate by the IECs increased their survival and expression of junctional proteins and mitigated gastrointestinal GVHD without significantly altering the burden of alloreactive T cells⁷. Similarly, restoration of IL-22 or R-spondin in the intestinal tract mitigated GVHD damage by protecting intestinal stem cells and promoting intestinal regeneration without directly affecting alloreactive T cells^{8,9}. Likewise, pathways responding to protein stress appear to mitigate the consequences of autoimmune responses: the unfolded protein response-associated protein kinase RNA-like ER kinase (PERK) in target cells was protective in models of multiple sclerosis³ and XBP1 protects against diabetic disease progression³. In accommodated allo-graft organs, rejection is mitigated without manipulation of immune cell activity¹⁰. Accommodation has been defined as a process wherein transplanted allo-graft do not succumb to humoral injury despite no change in antigen or the antibody load or functions¹⁰. In Figure 1, an accommodated organ might be represented by line 2 as compared to unaccommodated grafts, which might be represented by line 1. Additionally, graft-intrinsic factors, may contribute to graft survival while leaving immune elicitor and response unchanged, shifting the graft from point A in Figure 1 to point C. For example, in liver transplant, A20, through its protection against ischemic reperfusion injury and promotion of hepatocyte proliferation, contributes to liver graft survival¹¹. Furthermore, genetic polymorphisms of glutathione S-transferase T1 in donor renal

allografts was associated with significantly higher rates of acute rejection¹². In each of these models, the immune effector burden remained the same, but the ability of the target organs to ‘tolerate’ the immune effector burden appears to be critical for disease severity. Collectively these data point to tissue intrinsic repair (Figure 2A) and regeneration pathways (Figure 2B) that protect against disease severity without altering the burden of effector immune cells^{3,5–10}.

In light of these studies and the work on resistance and tolerance during infection, we define ‘tissue tolerance’ as properties that shift a tissue’s response to inflammatory immune attack from line 1 to line 2 in Figure 1B. The manifestation of various tissues’ intrinsic ability to ‘tolerate’ or withstand damage from inflammatory immune activity could include mechanisms that facilitate their regeneration, repair, or expand their homeostatic range (Figure 1B). Tissue tolerance mechanisms could include features that overlap or in some cases indistinguishable from cellular stress responses, tissue regeneration and repair³. Thus could include, but not be limited to metabolic, apoptotic, autophagic, redox, or cell renewal pathways. Importantly, as damage inducing mechanisms vary in different pathologies, tissues and disease stages, the mechanisms of ‘tissue tolerance’ are likely to be context specific. The involved pathways may conversely be broadly conserved or uniquely developed and might share overlap with disease tolerance pathways³. For instance, like disease tolerance, tissue tolerance pathways may manifest as mechanisms to counteract these stressors². Direct experimental evidence linking tissue tolerance and disease tolerance is currently lacking. However, accommodated organs were found to show increased expression of the kinases PI3K/AKT and the transcription factor Nrf2¹², two proteins which have been implicated in disease tolerance^{1,3}.

Thus considering tolerance(s) as involving both tissues as well as immune cells may lead to novel ways of not only understanding sterile immune-pathologies but may also allow for development of more effective therapies, just has been with the consideration of disease tolerance for infectious immunopathology^{1,2}. Specifically, it becomes possible to consider therapies that may increase tissue tolerance to protect against organ damage. Thus this also has potential for broadening the development of potential treatment repertoire that could be adjuncts to strategies aimed at promoting immune tolerance or suppression. Therefore we propose that including ‘tissue tolerance’ along with immune tolerance in the conceptual repertoire for mitigating tissue damage will allow for better understanding and treatment of non-infectious immunopathology.

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Figure 1. Tolerance is the relationship between immune stimulus and health of the tissue being studied

(A) In disease tolerance, inciting stimulus is measured by pathogen burden. Line 1 represents a tissue with low disease tolerance whereas Line 2 represents a tissue with high tolerance. Point A is used as a reference state. Moving from A to B results from increased resistance, reducing the pathogen burden alone. Moving from A to C results from increased tolerance; pathogen burden is unaffected but tissue health is improved. Moving from A to D represents a scenario where both resistance and tolerance are employed. Homeostatic stability and disease severity are represented by the width of the appropriate cross-section of each respective wedge. (B) In tissue tolerance, inciting stimulus is measured through the activity of immune effectors. Like in (A), Lines 1 and 2 represent low and high tolerance tissues, respectively. With Point A as a reference state, moving from A to B results from immune tolerance mechanisms modifying immune effector function alone. Moving from A to C represents a case of tissue tolerance where immune effector activity remains the same but tissue health improves. Moving from A to D plots how both immune tolerance and tissue

tolerance might work to improve tissue health. Homeostatic stability and disease severity are represented as in (A).

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Figure 2. Mechanisms of tissue tolerance

(A) Tissue-intrinsic pathways serve to protect parenchymal tissue from inflammatory immune attack by tissue cell-autonomous methods. (B) Tissue-extrinsic pathways protect parenchymal tissue from inflammatory immune attack by repairing damage, either in parallel with immune insult or after inflammation terminates.