IMMUNOLOGY

Immunity as a continuum of archetypes

Numerous tissue-accommodation functions of immunity offer insights into disease

By **Adriana M. Mujal**[1] *and* **Matthew F. Krummel**[2,3]

The immune system has long been recognized for its importance in eliminating pathogens. Recently, it has become appreciated for additional distinct roles in normal tissue biology, contributing to tissue development and maintenance. Further, it is being revealed as a major force in diseases as diverse as fibrosis, type 2 diabetes, and Alzheimer's disease, as well as cancer. The immune system is exquisitely selective; more than a billion different adaptive immune lymphocytes (T cells and B cells) survey the body. These can individually be sensitized to antigens—for example, by vaccination—leading to their expansion and to a rapid and protective immune response that destroys antigen-bearing cells upon reexposure. Alternatively, the system can become "tolerant" when antigen-specific T cells and/or B cells are deleted or inactivated. Historically, activation versus inaction (tolerance) have dominated views of the immune system. These, however, should be considered the extremes of a continuum of "archetypal" response states that collections of immune cells can take, many of which serve to accommodate dynamic tissue function.

Individual lymphocytes demonstrate a broad range of differentiation programs. For example, activated CD4$^+$ T helper (T_H) cells adopt distinct differentiation states, producing cytokines that are tailored to the nature of the immunogenic insult such as interleukin-17 (IL-17) secreted by T_H17 cells or IL-4 released by T_H2 cells. A recent report shows additional flexibility in T cells that recognize commensal bacteria; under homeostatic conditions, they adopt a type 17 phenotype to provide protection, but when local injury occurs, they can rapidly produce type 2–specific cytokines for tissue repair (*1*). T cells can also differentiate into regulatory T cells (T_{regs}) that, through cytokine secretion and cellular interactions, actively oppose destruction by other T cells. Unlike the binary conceptions of tolerance versus destructive immunity, adoption of these fates is characterized by continuously active, and variable, responses to immunological stimuli.

Like T cells, other immune cell types appear to be heterogeneous. For example, innate myeloid cells, such as macrophages and dendritic cells, also demonstrate multiple epigenetic differentiation states and capacities. How these differentiated cells function together to support and maintain tissue function upon developmental change, aging, damage, or exposure to foreign organisms is only just beginning to be understood. These emerging roles for the immune system are distinct from pathogen protection, and it is timely to establish a shared language for defining such collections of immune cells and the processes by which they engage in nondestructive responses that foster tissue homeostasis. These programs, with specific transcriptional states and cellular circuits, could be considered as representing a continuum between strict forms of tolerance and destruction that might collectively be called accommodation (see the figure). This categorization is intended to recognize that the exquisite sensitivity and differentiation plasticity of innate and adaptive immune cells broadly support host viability in the face of physiological changes. The immune system should thus be considered an adjudicator with a palette of archetypal responses.

> ***"...the exquisite sensitivity and differentiation plasticity of innate and adaptive immune cells broadly support host viability in the face of physiological changes."***

Immune accommodation archetypes at mucosal interfaces such as in the gut assist in the retention of commensal species with ongoing protection from pathogens (*2*). These consist of coordinated interactions of specific myeloid and lymphocyte subsets. Myeloid cell maturation and/or migration to the lymph node can be restricted by microbial signals, which limits effector T cell priming (*3*). In parallel, uptake and presentation of commensal-derived antigens by these myeloid cells selectively induces commensal-specific T_{regs} that protect the tissue from inflammation and support commensal symbiosis, as well as T_H17 cells that prevent microbes from breaching epithelial barriers (*2*). B cells, through production of commensal-specific immunoglobulin A antibodies, provide additional ways for the immune system to monitor and promote commensalism. These cell types together represent a local archetype.

Immune quarantine of pathogen, rather than destruction, represents another accommodation archetype. In the context of chronic viral infection, cytolytic T cells specialized in recognizing and killing nonself and infected cells exhibit exhaustion, an epigenetically enforced state characterized by decreased cytotoxic activity (*4*). Presumably in cases of chronic infections, exhaustion undercuts the destructive potential of T cell responses, limiting immunopathological consequences of widespread elimination of infected host cells. In humans, once infections with herpes simplex virus or hepatitis C virus become persistent, an equilibrium may exist for many years, and it can be surmised that elimination of virally infected cells (e.g., neurons or hepatocytes) would substantially impair fitness (*5*). Currently, the cell types that function with exhausted T cells to establish this accommodation archetype are not well characterized but likely include monocytes or a specific macrophage subset (*6*). Unlike tolerance, the immune system is actively responding, and an immune response elicited by exhausted T cells given sufficient stimulus—for example, should a pathogen emerge from latency—presumably can limit its further dissemination.

Perhaps the best-developed exemplar for an immune response that is neither focused on destruction nor tolerance, but rather on achieving tissue homeostasis, is in wound healing and tissue repair. In early wounds, infiltration of inflammatory neutrophils and monocytes provides wound sterilization. In late wound-healing responses, a second archetype of nondestructive immunity emerges, which includes high numbers of macrophages that produce essential tissue and vascular growth factors and anti-inflammatory cytokines (*7*). These processes also involve various lymphocyte

[1]*Immunology Program, Memorial Sloan Kettering Cancer Center, New York, NY 10065, USA.* [2]*Department of Pathology, University of California, San Francisco, CA 94143-0511, USA.* [3]*ImmunoX Initiative, University of California, San Francisco, CA 94143-0511, USA. Email: matthew.krummel@ucsf.edu*

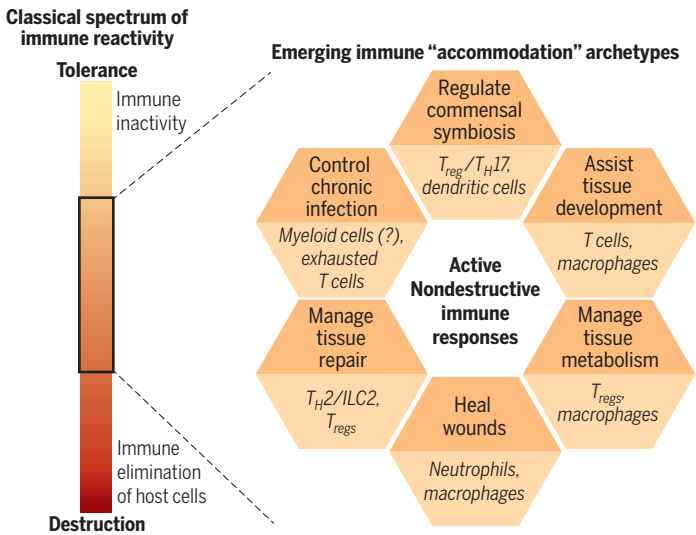
populations, including innate lymphoid cells (ILCs) that secrete cytokines such as IL-4 and IL-13, which in turn promote macrophages to carry out repair (*7*). Whereas optimal wound healing restores tissue structure and physiological function, dysfunctional and/or chronic wound healing results in fibrosis and scarring from the overproliferation and/or hyperactivity of fibroblasts, which can be driven by different macrophages and/or T_H2 cells (*7*). It is thus apparent that mobilizing the appropriate immune response archetype is critical in health as well as in disease.

Another emerging immune accommodation archetype is steady-state tissue remodeling. In the brain, the immune system plays an active and important role in neuronal function. Microglia—the tissue-resident macrophages of the brain—express the surface protein TREM2 (triggering receptor expressed on myeloid cells 2) and secrete complement factors such as C1q, which mediate synapse pruning and remodel neural connectivity (*8*). In breast epithelium, macrophages regulate ductal branching morphogenesis during development, notably in a manner that also depends on cross-talk with specific T cell populations (*9*). Failure to correctly assemble these tissue-remodeling archetypes can impair tissue processes. For example, in some familial forms of Alzheimer's disease, characterized by genetic defects in *TREM2*, microglia dysfunction results in chronic inflammation that compromises brain function (*8*).

Metabolic disorders such as type 2 diabetes also highlight the importance of accommodation at highly metabolically active sites. In adipose (fat) tissue of lean mice, high numbers of T_{regs} expressing PPARγ (peroxisome proliferator–activated receptor γ) act to maintain a noninflammatory state that supports metabolic activity and insulin sensitivity (*10*). This likely occurs because T_{regs} interact with adipose tissue macrophages and limit their production of proinflammatory cytokines that otherwise impair adipocyte function. Obesity, associated with insulin resistance and type 2 diabetes, represents a failure of this system; in obese mice, adipose tissue–associated T_{regs} are reduced in number and exhibitaltered gene expression profiles that may influence their residency and tissue-specific activity (*10*).

Accommodation archetypes

Traditional perspectives often reduce immune responses to tolerance and destruction. Emerging data show that the immune system has a larger palette of modular archetypes that accommodate healthy tissue. These archetypes can contribute to disease when dysregulated and/or dysfunctional.



The importance of thinking about the immune system as a continuum of accommodation archetypes is that it affects our understanding of many diseases, including cancer. Characterization of the tumor immune microenvironment has revealed a high density of immune cells that support tumor growth, such as T_{regs}, macrophages, neutrophils, and exhausted T cells, which likely resemble the archetypes discussed above. Higher resolution of immune cell infiltration and transcriptional patterns are needed, however, to better identify archetype patterns in diseased tissue and test their association with prognosis or therapeutic responsiveness. Analysis of The Cancer Genome Atlas gene expression data has identified cohorts of patients, across cancer types, that exhibit "wound healing" gene signatures (*11*), but more archetypes are likely present in other tumors. Recent data highlight variable components of tissue-repair archetypes in cancers; for example, tumor-associated macrophages (TAMs) and T_{regs} produce the growth factors EGF (epidermal growth factor) and VEGF (vascular endothelial growth factor) (*12*), and amphiregulin (*13*), possibly replicating a late tissue-repair archetype, whereas TAMs in some tumors can also express large amounts of both C1qa and TREM2 (*14*), indicative of a remodeling archetype.

Tumors also illustrate contrasting immune archetypes, including some that license destructive immunity. In particular, conventional type 1 dendritic cells (cDC1s) can activate antitumor T cells in the tumor immune microenvironment and tumor-draining lymph nodes through cross-presentation of tumor antigens and IL-12 production (*14*). cDC1 infiltration is driven in part by another member of this archetype, natural killer cells, and their density in a melanoma tumor immune microenvironment is a strong prognostic for overall survival and responsiveness to immune checkpoint blockade—a type of immunotherapy that targets inhibitory regulators of T cells (*14*, *15*). The presence of this destructive archetype, even at low levels, in progressing tumors suggests that a tissue may be a battleground between competing archetypes. Broadening patient responsiveness to immunotherapies may require therapeutic enhancement or repression of components of specific archetypes in a given tumor immune microenvironment to favor destruction over accommodation.

Direct profiling of immune states from a variety of tissues in health and disease, using high-dimensional methods such as flow cytometry and single-cell RNA sequencing, will begin to delineate immune archetypes that are replicated or hijacked. Expanding upon the binary conception of destruction versus tolerance to include accommodation archetypes will improve the understanding and treatment of many diseases. ■

REFERENCES AND NOTES

1. O. J. Harrison *et al.*, *Science* **363**, eaat6280 (2019).
2. Y. Belkaid, O. J. Harrison, *Immunity* **46**, 562 (2017).
3. G. E. Diehl *et al.*, *Nature* **494**, 116 (2013).
4. M. Philip *et al.*, *Nature* **545**, 452 (2017).
5. B. T. Rouse, S. Sehrawat, *Nat. Rev. Immunol.* **10**, 514 (2010).
6. B. A. Norris *et al.*, *Immunity* **38**, 309 (2013).
7. T. A. Wynn, K. M. Vannella, *Immunity* **44**, 450 (2016).
8. F. L. Yeh, D. V. Hansen, M. Sheng, *Trends Mol. Med.* **23**, 512 (2017).
9. V. Plaks *et al.*, *Dev. Cell* **34**, 493 (2015).
10. D. Cipolletta, P. Cohen, B. M. Spiegelman, C. Benoist, D. Mathis, *Proc. Natl. Acad. Sci. U.S.A.* **112**, 482 (2015).
11. V. Thorsson *et al.*, *Immunity* **48**, 812 (2018).
12. C. Engblom, C. Pfirschke, M. J. Pittet, *Nat. Rev. Cancer* **16**, 447 (2016).
13. J. A. Green *et al.*, *J. Exp. Med.* **214**, 3565 (2017).
14. M. L. Broz *et al.*, *Cancer Cell* **26**, 638 (2014).
15. K. C. Barry *et al.*, *Nat. Med.* **27**, 450 (2018).

ACKNOWLEDGMENTS

We thank colleagues at UCSF for helpful discussion and feedback. This work was supported by NIH grants U54 CA163123, R21CA191428, and R01 CA197363. M.F.K. is a founder and board member of, and shareholder in, Pionyr Immunotherapeutics, which develops immunotherapies.

10.1126/science.aau8694

GRAPHIC: N. CARY/*SCIENCE*

Immunity as a continuum of archetypes

Adriana M. Mujal and Matthew F. Krummel

Science **364** (6435), 28-29.
DOI: 10.1126/science.aau8694