The immune system is one of the most dynamic in our bodies. The mechanisms that maintain immune homeostasis must contend with the constant churn of cell proliferation and death across a myriad of lineages at many different locations. These mechanisms must also cope with challenges such as responses to a variety of pathogens, drugs or cancer, and reestablish the status quo following clearance or adapt to chronic conditions by adjusting homeostatic set-points to limit tissue damage. This Special Feature provides in-depth reviews of how homeostatic mechanisms deal with these challenges in a range of contexts.

Garcillan et al. review the molecular mechanisms of B-cell homeostasis and the lessons learnt from pathologies arising from loss of B-cell homeostasis. Primary immunodeficiencies, systemic autoimmunity and B-cell leukemias all provide key insights into how B-cell homeostasis is fine-tuned at the various stages of B-cell differentiation. The challenge now is to realize the potential of this detailed knowledge into targeted therapies that can restore B-cell homeostasis and humoral immunity or, conversely, cripple the survival mechanisms hijacked in B-cell malignancies.

Dendritic cells (DC) orchestrate many aspects of the adaptive immune response to tailor a suitable defense to an invading pathogen, while limiting collateral damage. The complexity and logic of DC diversity is explored by Dress et al., focusing on the developmental and functional themes that provide the most important distinction. Many stimulating questions are posed: what is the nature of plasmacytoid DC—are they really a DC at all? How does the interplay between cell intrinsic and extrinsic homeostatic mechanisms control DC number and diversity?

Although closely related to T lymphocytes, natural killer (NK) cell development is unique in the sense that NK cells do not undergo positive or negative selection yet do not react against healthy self-tissue resulting in autoimmune diseases. In contrast, NK cells react strongly against transformed or infected self-tissue and are key effectors in tumor immunity. T-cell homeostasis is tightly regulated by cytokine levels and antigen receptor stimulation; however, the lack of antigen receptors on NK cells raises several questions about how NK cell numbers and activity are regulated during health and disease. Rautela et al. dive deep into how the pleitropic cytokine IL-15 controls NK cell homeostasis at a molecular level. This review specifically teases apart the transcriptional consequences of IL-15 signaling in NK cells in an attempt to understand how changes in IL-15 concentrations in response to pathogens and cancer might prime different NK cell responses.

The maintenance of immune homeostasis at barrier surfaces, such as the skin, presents a particular challenge. A constant barrage of stressors from microorganisms and other environmental challenges must be assimilated by innate and adaptive immune cells to orchestrate tolerance or response. Tikoo et al. lay out the key cellular and molecular controls involved in maintaining homeostasis at this site, including the role of resident memory populations, and how these can be perturbed in various skin pathologies. Melanoma is one of the first cancer types in which the efficacy of anti-CTLA-4 and anti-PD-1
therapies were first demonstrated. Da Gama Duarte et al.\textsuperscript{5} explore the various mechanisms that melanoma use to subvert immune tolerance and evade clearance. This review integrates new themes such as how host genetic factors, immune intrinsic mechanisms and extrinsic inputs from the microbiome influence the response elicited by checkpoint blockade. Furthermore, as the armamentarium of checkpoint inhibitors grows, a key question in the field will be the extent to which immune homeostasis can be reset to provoke antimelanoma responses, without inducing excessive adverse immune events.

Taken together, this Special Feature provides a detailed overview of our current knowledge of homeostatic mechanisms governing major immune subsets during health and disease. It is evident from each review that we understand a considerable amount about the fundamental pathways controlling steady-state immune cell homeostasis yet each review also raises an emerging challenge to the field and human health; that is, to effectively “drug” these homeostatic pathways to exploit desired immune functions in disease.

CONFLICT OF INTEREST

None declared.

REFERENCES