Cytokines in the balance

Cytokines have context-dependent roles that dictate their normal physiological function; however, dysregulation or chronic activation of cytokine pathways can alter tissue balance away from a return to homeostatic quiescence toward disease-associated immunopathology.

Cytokines are the chemical mediators that regulate immune cell homeostasis and coordinate signal-dependent immune responses. Cytokine signaling circuits include multiple regulatory checkpoints, which often involve feedback inhibition; this process allows tissues to return to a relatively quiescent non-inflammatory state of immunotolerance. Whereas proinflammatory cytokines alert the immune system to the presence of potential infection or danger, dysregulated cytokine production can lead to immunopathology, including autoinflammatory and autoimmune disease, and, in some cases, can promote cancer. This month, *Nature Immunology* presents four specially commissioned Reviews (<https://www.nature.com/collections/cytokines>) that discuss the signaling networks and regulation elicited by type I and type II interferons and the cytokines IL-7, IL-17 and TSLP (thymic stromal lymphopoietin).

Many patients diagnosed with autoimmune or autoinflammatory syndromes have interferon-dependent gene-expression signatures that contribute to the chronicity of these disease states. Barrat, Crow and Ivashkiv review how interferon signaling, induced by viral infection or aberrant handling of self nucleic acids, induces acute activation of the expression of interferon-stimulated genes via the activation of STAT and IRF transcription factors that act together with the transcription factor NF- κ B, and also discuss the extensive genome-wide epigenetic changes that are imposed after exposure to interferons. Indeed, even tonic signaling by the interferons IFN- β and IFN- γ promotes an epigenetic immune memory by 'bookmarking' chromatin in tissues, which sensitizes cells to subsequent environmental cues and influences the robustness and duration of ensuing immune responses. Type I interferons increase the abundance of the activating histone mark H3K4me3 at promoter sites, and IFN- γ signaling enhances histone acetylation at both enhancers and promoters of genes encoding inflammatory mediators. Such epigenetic remodeling allows dynamic interactions among transcription factors, dictated by cellular identity and context, to facilitate the expression of even non-interferon-stimulated genes. These epigenetic changes induced

by interferons seem to be stable over time, which allows induced transcription to persist beyond the immediate window of interferon signaling. It may be possible to delineate disease-associated epigenomic signatures elicited by interferons to identify biomarkers that can be used to predict disease activity and more-effective intervention strategies.

IL-7 is best known as a pro-survival homeostatic cytokine that is essential for the development and maintenance of B lymphocytes and T lymphocytes in lymphoid tissues and is now also known to be required for innate lymphoid cells. However, as Barata, Durum and Seddon discuss, dysregulated expression or function of the cytokine receptor IL-7R α in lymphoid progenitor cells can drive leukemic transformation and survival, particularly in T cell or B cell acute lymphoblastic leukemia. Aberrant IL-7–IL-7R signaling also is evident in solid non-hematological tumors, such as breast and prostate cancers, whereby high IL-7 expression is associated with poorer prognoses. Various clinical trials are now underway in which IL-7R inhibitors are being used for the therapeutic treatment of acute lymphoblastic leukemia and other tumors.

The physiological roles of the IL-17 cytokine family have been more difficult to elucidate. IL-17 normally acts at mucosal sites to promote barrier function and wound repair by inducing metabolic adaptations that result in tissue re-epithelization, and to elicit immune defenses against fungi and extracellular bacteria. However, IL-17 has also been associated with autoimmunity and certain types of cancer. Li and colleagues review the IL-17R signaling network, which centers on the multifunctional adaptor Act1. Act1 is an E3 ubiquitin ligase capable of recruiting multiple adaptors of the TRAF family and has also now been shown to have nuclear functions and RNA-binding activity. The IL-17R–Act1–TRAF6 axis promotes proinflammatory and mitogenic responses via gene expression dependent on NF- κ B and kinases of the MAPK family; this expression can be negatively regulated by competing interactions of other TRAF members for binding to Act1. Notably, Act1 acts as a post-transcriptional regulator to enhance mRNA stability and to promote the translation of IL-17-responsive gene products. The

complexity of IL-17 signaling is further increased by synergistic interactions with other cytokine and growth-factor receptors that are co-expressed on IL-17R $^{+}$ cells. Elucidating these synergistic signaling networks will aid in the identification of potential therapeutic targets that can impede the pathophysiological effects of IL-17 but retain normal barrier protection.

TSLP is produced by epithelial cells at barrier mucosal sites, where it is best known for promoting type 2 immune responses by acting on multiple immune cell types, including dendritic cells, T cells, group 2 innate lymphoid cells and mast cells. Corren and Ziegler discuss the role of TSLP in type 2 inflammatory diseases, including atopic dermatitis, food allergy and asthma, as well as promising results from clinical trials in which TSLP is targeted by monoclonal-antibody therapy for these conditions. Similar to the complexity of IL-17 signaling, TSLP-mediated responses are influenced by cellular context and the presence of other cytokines, such as IL-33, and by the Notch signaling pathway. Studies have now revealed a role for TSLP in cancer, notably in breast, pancreatic and colon tumors. In these scenarios, IL-1 produced by the tumor cells can induce TSLP expression by cancer-associated fibroblasts, which in turn promotes a type 2 immunosuppressive environment within the tumor. Additionally, TSLP acts directly on tumor cells that express its receptor, TSLPR, to increase expression of pro-survival members of the Bcl-2 family. Thus, targeting TSLP might provide anti-tumor benefits.

The understanding of cytokine signaling has expanded to recognize synergistic cross-talk pathways that allow dynamic tissue-specific and context-dependent immune responses. However, with that complexity comes the danger of dysregulation that tips cytokine responses away from a return to tissue homeostasis. With the identification of these contextual drivers underlying pathophysiological cytokine responses, new therapeutic interventions are now being developed and tested in the clinic to alleviate the detrimental immunopathology in afflicted patients. □

Published online: 19 November 2019
<https://doi.org/10.1038/s41590-019-0557-0>