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Cytokines

Editorial overview

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To paraphrase the title of an old Broadway play, a funny thing happened on the way to . . . preparing this issue of *Current Opinion in Immunology*, entitled 'Recent Developments in Cytokine Regulation'. We brought together scientists interested in diverse aspects of cytokine biology to summarize their area of expertise and hoped that a thematic cohesion would emerge from the reviews. In reading through the articles of this issue, it became clear that virtually all the authors were grappling with recurring themes at the heart of cytokine regulation — the complexity of the cytokine response, the crosstalk between response pathways and the diversity of biological effects elicited by individual cytokines.

Cytokines are essential for the activation, differentiation and control of the immune system. The era of simpler times, when a cytokine interacted with a single receptor, is long gone. Many cytokines, alone or in combination with other cytokines, have multiple functions and can often act on many different cell types with distinct developmental or functional consequences. The explosion of new information in cytokine regulation, daunting to some, yet we believe offers new opportunities to alter signaling pathways with more precision, which will provide more targeted regulation of the immune response, and hopefully, with clear outcomes in the clinic.

The interferon paradigm

The interferons (IFN) have long been recognized and defined by their ability to induce resistance to viral infection. Three distinct types of IFN have now been characterized (type I, type II and type III), based on their structural features, receptor usage and biological activities. The type I IFN have served as an important model to understand transcriptional and signaling events that orchestrate the early host response to virus infection. In this issue, Belgnaoui *et al.* summarize recent findings related to initial sensing of RNA virus infection by the RIG-I like receptors, with a focus on the mitochondrial antiviral signaling adapter MAVS and its role as a signaling platform that orchestrates interferon signaling. Complex posttranslational modifications and extensive protein–protein interactions, as well as distinct sub-cellular localizations of MAVS contribute to the induction of antiviral and inflammatory pathways; additionally, new data argue that MAVS also coordinates apoptotic and metabolic functions.

At the heart of sensing virus infection is the recognition of viral nucleic acids. Double-stranded RNA (dsRNA) has often been used to trigger antiviral innate immunity, IFN production as well as IFN actions. Among the best studied IFN inducible gene products are the protein kinase regulated by RNA (PKR) and the adenosine deaminase acting on RNA (ADAR1). Pfaller *et al.* describe the key role played by PKR in the antiviral actions of IFN, mediated through dsRNA-dependent activation

and subsequent phosphorylation of protein synthesis initiation factor eIF2 α , thereby altering the translational pattern in cells. A distinct biochemical function is attributed to ADAR1, which catalyzes the deamination of adenosine in RNA with double-stranded character, leading to the destabilization of RNA duplex structures and genetic recoding. In contrast to the antiviral and pro-apoptotic functions associated with PKR, ADAR1 can stimulate virus activity and it protects the infected cell, as ADAR functions to suppress dsRNA-mediated antiviral responses including activation of PKR and interferon regulatory factor 3.

For decades, type I IFN were considered indispensable mediators for innate antiviral protection. The interferon (IFN) family expanded recently with the discovery of type III IFNs or IFN λ , also known as IL-28/29. Kotenko describes the rapid developments concerning IFN λ — different antiviral potency, patterns of induction and differential tissue expression of corresponding receptor subunits — all of which indicate that type I and type III IFNs do not merely duplicate each other but rather possess unique biological properties beyond innate antiviral immunity.

Inflammasome cross-regulation

The inflammasome-forming NOD-like receptors represent a protein complex mediating the activation of caspase-1 and the cleavage of pro-IL-1 β and pro-IL-18 into their active, secreted forms. Barker *et al.* argue that components of the inflammasome cascade may also possess novel functions that influence inflammasome-independent pathways of cytokine production, in part through transcriptional induction of non-inflammasome cytokines through the activation of NF- κ B and MAP kinase signaling pathways. This level of cross-regulation between inflammatory cytokine cascades may contribute to an increased capacity of the cell to respond appropriately to diverse pathogens.

Interleukin families

Originally discovered in 1976 as a T-cell growth factor in supernatants of activated T-cells, Interleukin-2 (IL-2) is a well-characterized cytokine that drives T-cell growth, augments NK cytolytic activity, induces the differentiation of regulatory T-cells, and mediates activation-induced cell death. Among the other family members are IL-4, IL-7, IL-9, IL-15, and IL-21. Liao *et al.* provide an update on the complex roles of IL-2 in broadly modulating T helper cell differentiation. IL-2 modulates expression of receptors for other cytokines and transcription factors, thereby either promoting or inhibiting cytokine cascades that correlate with each Th differentiation state. Thus depending on the cytokine milieu, IL-2 can prime and maintain Th1 and Th2 differentiation as well as expand these populations. In contrast, IL-2 inhibits Th17 differentiation but can also lead to Th17 cell expansion.

Interleukin-10 and IL-22 are crucial regulators of inflammation during immune responses. While IL-10 functions to prevent excessive inflammation by acting on immune cells, IL-22 elicits innate responses from tissue epithelia and promotes wound healing. Interleukin-10 (IL-10) and IL-22 are broadly expressed cytokines among Th cells, and expression of IL-10 and IL-22 are largely independent of a particular T-cell differentiation program. Rutz and Ouyang discuss common and distinct aspects of the molecular regulation of these cytokines, that might explain their broad but distinct expression among Th cell subsets.

The newest and least understood cytokine family — the IL-17/IL-17 receptor family — is highlighted by Sarah Gaffen. Composed of ligands IL-17A-IL-17F and receptors IL-17RA-IL-17RE, these cytokines have many unique structural and functional features. With the discovery of the ‘Th17’ subset in 2005, many long-standing discrepancies associated with the Th1/Th2 model have been reconciled. Although much of the research has focused on IL-17A and IL-17F and their cognate receptors, far less is known about the rest of the family. This review discusses the recent surge in information on IL-17 cytokines, with an emphasis on IL-17A biology.

TNF superfamily

Attempting to harness an explosion of information regarding molecules that regulate TNF-R1 signaling, the review by John Silke, followed by the review by Ware and Sedy highlights different molecular aspects of the TNF superfamily. Regulation of NF- κ B signal transduction by ubiquitination following TNF activation has evolved from a relatively simple pathway to a complicated regulatory cascade. This article addresses the role of ubiquitin in the activation of NF- κ B by TNF with a focus on interpreting *in vivo* results. Many of the concepts concerning the regulatory roles of ubiquitin in signal transduction have emerged from studies of TNF-R1 signaling and newer concepts — for example the role of linear ubiquitin chains in regulating signaling — may also be applicable to the TNF family in general.

Ware and Sedy further expand on the TNF superfamily with a review of the herpesvirus entry mediator (HVEM; TNFRSF14) network that activates both proinflammatory or inhibitory signaling pathways, particularly important for regulating T cell responses. HVEM is rather unique with two groups of structurally distinct ligands, TNF related cytokines, LIGHT and LT α , and the Ig superfamily members, BTLA and CD160. These two groups of ligands however only partially explain the proinflammatory or inhibitory signaling by HVEM. Recent evidence indicates that the signal generated by HVEM depends on the context of its ligands expressed in *trans* or in *cis*. HVEM engagement by all of its ligands in *trans* initiates bidirectional signaling. In contrast, naïve

T-cells coexpress BTLA and HVEM forming a *cis*-complex that interferes with the activation of HVEM by extraneous ligands in the surrounding microenvironment. The HVEM network thus emerges as a key survival system for effector and memory T-cells in mucosal tissues.

The cytokine conundrum

Despite the myriad of cytokines and cytokine receptors, relatively few signaling molecules transduce these diverse cytokine signals. With a prescient title that goes to the core of this issue — interpreting mixed signals: the cell's cytokine conundrum — Delgoffe *et al.* discuss the

potential mechanisms used by cytokines to mediate distinct cellular outcomes from a small number of signaling molecules. Using the examples of STAT1 and STAT3, this review illustrates that a single molecule can orchestrate diverse cellular events, mediated in large part through receptor, signaling and/or epigenetic modulation.

Altogether the reviews assembled in this issue of *Current Opinion in Immunology* provide an overview of some of the critical emerging themes in cytokine regulation, and further highlight important outstanding questions that will require further fundamental investigation.