



# Editorial overview: Pillars of innate immunity: constantly learning and trying to remember

Nicolas Manel and James P Di Santo

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## Nicolas Manel



Immunity and Cancer Department, Institut Curie, PSL Research University, INSERM U932, 75005, Paris, France

Nicolas Manel, trained in the Sitbon lab in Montpellier and Littman lab at NYU, heads the Innate Immunity lab at Institut Curie-INSERM, Paris, France. His lab has identified cGAS and NONO as critical innate immune sensors of HIV, and revealed a Trojan horse mechanism of innate immune activation by viruses.

## James P Di Santo



Innate Immunity Unit, Institut Pasteur, Inserm U1223, Paris, France

James Di Santo (MD/PhD; Cornell Medical College and the Sloan Kettering Institute) trained with Alain Fisher (Paris) and Klaus Rajewsky (Cologne) and currently heads the Innate Immunity Unit at Institut Pasteur-INSERM in Paris. Research interests focus on the molecular dissection of NK cell and innate lymphoid cell development. More recently, his lab identified circulating ILC precursors suggesting that tissue ILC are largely generated *in situ*.

Textbooks teach us that the innate immune system provides the first line of defense against pathogens. We now understand that innate immunity involves a fully equipped and diverse set of cellular actors that are organized in a tightly orchestrated fashion. Innate defense involves layers of communication that operate at the molecular, cellular and organismal levels.

The founding principle that innate immune is endowed with the ability to recognize and respond to pathogens and damages in a non-clonal fashion remains at the center of this system. What we have learned in the recent years is that innate immunity is not a special feature of few immune cell types, but that all cells can engage directly or indirectly molecular and cellular components of the innate immune system. Cell–cell communication and cell-extrinsic mediators constitute a linchpin of innate immunity, making a clear distinction with intracellular stress-related pathways and intrinsic immune effects such as antiviral restriction factors. Innate immunity emerges as a system that can sense deviation from steady-state conditions, and triggers both local as well as systemic responses, mediated by effectors that modify the function of hematopoietic and non-hematopoietic cells.

A principal function of innate immunity is to mediate rapid and localized defense against viral infections. Two reviews explore new concepts in this area.

[Andreacos \*et al.\*](#) review the biology of lambda (type III) interferons [1]. Similar to type I interferons, lambda interferons are induced by infections and mediate antiviral effects. Recent work has revealed their critical role at barrier surfaces, and their ability distinct from type I interferons, to limit inflammation and prevent host damage while mediating anti-microbial defense. The review illustrates particularly well the common and unique characteristics of lambda interferons with type I interferons and IL-10.

[Wu \*et al.\*](#) review the mechanistic antiviral resistance of stem cells [2]. Stem cells are critical to maintain tissue structure and function. Because of this requirement for longevity throughout organismal life, viral infections represent a high risk for stem cells. Antiviral effectors belonging to the interferon-stimulated genes family are normally expressed transiently in somatic cells to temporarily reprogram cells in order to prevent, inhibit or sterilize infection. Here is reviewed the surprising finding that stem cells constitutively express these antiviral defenses, enabling a permanent level of antiviral protection. Of particular interest, the cost-versus-benefit selective advantage of constitutive versus inducible antiviral gene expression systems is discussed.

Innate immunity is not a jealous system and can similarly deal with internal problems. Two reviews explore the link between altered self DNA and cellular innate immune activation.

*Coquel et al.* review the identification of a novel link between cellular innate immunity and the DNA damage response pathway [3]. SAMHD1 deficiency results in a devastating auto-inflammatory interferonopathy [4]. Here, the authors review their findings showing that SAMHD1 normally interacts with MRE11 and acts at stalled replication forks to promote degradation of nascent DNA. In the absence of SAMHD1, DNA fragments are released in the cytosol leading to activation of a cellular innate immune response.

*Glück and Ablasser* review the role of innate sensing of DNA in cellular senescence [5]. Innate immune sensors of DNA play a key role in the sensing of DNA from invading pathogens. Recent work has highlighted the reciprocal ability of innate immune DNA sensors to respond to damaged self DNA. A fascinating consequence of sensing self-damaged DNA is the activation of senescence pathways. Traditionally viewed as an irreversible cell-cycle arrested state, senescence now represents an effector program that comprises inflammatory cytokine production, which overlap with cytokines produced by immune cells. In particular, the authors provide clarification as to the stages and types of senescence states that implicate innate immune DNA sensing by the cGAS-STING pathway, and propose a temporal model of senescence induction by distinct self DNA species.

Whether due to infection or damages, life versus death is the ultimate biological decision, and innate immunity has its word to say at it — as have two reviews here.

*Ugolini and Sander* review the mechanisms that enable the innate immune system to distinguish live versus dead organisms [5]. Viability-associated molecular patterns (vitaPAMP) inform the innate immune system on the presence of live organism, resulting in the induction of robust immune responses. RNA is a fragile molecule, and microbial RNA is now considered a vitaPAMP. Interestingly, the mechanisms that sense this vitaPAMP are distinct in mice and humans. The putative existence of additional vitaPAMPs is discussed, as well as their functional impact on immune responses, which has immediate consequences on vaccine research.

*Scaturro and Pichlmair* review a new form of cell death termed oxceptosis [6]. Cell death is a universal response to pathogens, and its modalities define the development of the immune response. The authors review their new findings that identify a mechanism of reactive oxygen species (ROS)-mediated cell death. Surprisingly, the same proteins that respond to low levels of ROS to

promote cell protection switch to a cell-death inducing mode at high levels of ROS. Oxceptosis promotes a non-inflammatory apoptosis-like but caspase-independent cell-death, that likely operates in parallel to other cell death pathways during infections.

The impact of infection or inflammation on ‘long-term’ conditioning of the innate immune system is a question of great interest. Exposure to cytomegalovirus remodels both innate and adaptive immunity in humans with lifelong consequences for immune reactivity [7]. That innate immune response ‘history’ may impact on subsequent immunity during the lifetime of an individual is a concept with important implications for immune defense (innate priming for cross-protection against unrelated pathogens for example) but also for disease (e.g. auto-immunity). While immune memory has been classically associated with adaptive B and T cells that bear clonal antigen receptors, innate ‘memory-like’ responses have been reported for natural killer cells and innate lymphoid cells (ILCs), while ‘training’ has been described for monocyte/macrophages following pathogen encounter. After activation, innate immune responses are downmodulated to avoid excess tissue damage; the molecular and cellular mechanisms of the ‘return to baseline’ (and to what level this constitutes ‘memory’) remain poorly understood.

The existence of ILCs as innate counterparts of ‘helper’ and ‘killer’ T cells provides the means for continuity between innate and adaptive phases of the immune response. Two reviews examine the developmental pathways for ILC generation and the functional stability of these novel innate effector populations.

*Scoville et al.* summarize current models of ILC development in mouse and man [8]. While many common features are apparent, including the strong conservation of transcription factor-driven effector functions that are reminiscent of T cell differentiation, some notable and unique features of human NK/ILC development are discussed. In particular, it appears that cell fate decisions that specify NK and ILC subsets may occur later in humans than in mice, providing the opportunity to fine-tune innate immune system differentiation depending on environmental cues.

*Germain and Huang* ask the question whether innate lymphoid cells have ‘hard-wired’ effector functions or whether they are able to adapt to their local microenvironments [9]. T helper cells exhibit ‘plasticity’ and can modify their signature effector functions in response to environmental cues. Accumulating evidence in both mouse and human models suggest that ILC plasticity exists, although the regulatory mechanisms and functional relevance remain unclear. Germain and Huang show that activated ILC2 can migrate to distant tissue sites and can exert new functions in response to novel

local triggers, suggesting strong parallels with adaptive T cell immunity.

Metabolism is the basis for life and accordingly intersects with innate immunity at several critical levels. Four reviews explore how metabolism is intricately linked to signaling and function in immune immunity.

**Dang and Cyster** review the new link they have established between the loss of sterol metabolic homeostasis and the activation of inflammation [10]. Cholesterol and isoprenoid are essential components of cells. Recent work reviewed here demonstrated that alterations in the metabolic pathways of these lipids can promote innate immune inflammation: isoprenoid post-translational modifications of Rho GTPases underlies the inflammatory phenotype of Pvrin deficiency; cholesterol crystals activate the NLRP3 inflammasome; deficiency in a Ch25h, a cholesterol hydrolase, induces inflammasome activation. Notably, the authors make the fascinating proposition that intracellular innate immune sensors of DNA could be part of a homeostasis altering molecular pathway (HAMP) sensing system, that would detect and respond indirectly to alteration in cholesterol metabolism.

**Garaude** reviews the interplay between cellular innate immune activation and programming of the mitochondrial metabolism [11]. Through innate immune sensors, microbes rewire mitochondrial proteins complexes, providing a specific metabolite program to cells. These in turn impact the development of the cellular innate immune response and anti-microbial mechanisms. This review illuminates how a large body of knowledge and assays related to mitochondrial biochemistry is only starting to permeate into immunology, opening fascinating avenues of research for future work.

**Domínguez-Andrés and Netea** review the metabolic basis of trained immunity, which is a form of immune memory, remanence or conditioning that does not require genetic diversification and clonal amplification [12]. The energetic metabolism, namely glycolysis TCA and OXPHOX, the lipid metabolism and amino acid metabolism have been implicated trained immunity. Pertaining to a different timescale than acute immune activation, trained immunity provides another interesting example of mitochondrial reprogramming and lipid homeostasis modulation during immune activation.

**Dalmas** extends the concept of metabolic regulation by the innate immunity to the organismal level [13]. Pancreatic islet  $\beta$  cells produce insulin that controls cellular glucose utilization and sets the tone of systemic metabolic homeostasis. Remarkably, innate immune cells, including macrophages and ILCs, are components of an elaborate cross-talk that control  $\beta$  cell function. The capacity of the innate immune system to modulate islet endocrine

function may ultimately lead to novel therapies that can impact on a variety of metabolic syndromes.

The tissue microenvironment constantly changes and how the dynamics of this process regulate innate immunity is of considerable interest. Three reviews address different aspects of this important ‘cross-talk’ between innate immune cells and the tissue microenvironment.

**Chen and Stappenbeck** cover the emerging field of microbiome regulation of innate immune reactivity [14]. Our mucosal surfaces are exposed to the microbial world and an elaborate system of host-derived physical, chemical and immune-mediated mechanisms are active at barrier sites to restrict pathogen entry. The diverse commensal communities that inhabit these sites impact on local and systemic immune functions. The molecular nature of this microbiome-host ‘cross-talk’ is rapidly coming into focus.

**Barrow and Colonna** [15] address the role of ILC sensing of the everchanging tissue microenvironment on innate immune reactivity. Tissue sentinels of hematopoietic (dendritic cells, macrophages) as well as non-hematopoietic (epithelial cells, stromal cells, etc.) origin are well-known for their capacity to recognize pathogens and initiate immune responses. In this review, innate lymphocytes such as NK cells and ILCs are shown to possess a myriad of receptors that sense environmental changes, thereby providing an additional layer of innate immune reactivity.

**Klose and Artis** [16] summarize recent advances in our understanding of neuronal regulation of ILC function. Several factors elaborated by the rich neural plexus present at mucosal sites have been shown to influence tissue ILC function. The ability of neuronal signals to modify innate immunity at local and perhaps the systemic level may provide a novel means to fine-tune innate immunity in a variety of clinical settings.

Overall, these complementary reviews illustrate the breadth of biological mechanisms and principles that innate immunity employs to promote host defense. As we are learning about these new findings, it is tempting to propose that they reveal ‘pillars of innate immunity’ (see cover) that constitute fertile ground for future research.

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