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Innate immunity

Editorial overview

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Sasha Tarakhovsky is Professor of Immunology at The Rockefeller University. His laboratory studies the epigenetic control of immune cell responses, with a focus on determining the role of histone-like sequences ('histone mimics') within non-histone proteins in gene regulation and receptor-mediated signaling. The laboratory also applies the concept of 'histone mimicry' to the development of new anti-inflammatory pharmacological approaches.

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Guido Kroemer's research team focuses on the regulation of cellular catabolism in cancer therapy, anticancer immune responses, degenerative pathologies and aging. He studies the relationship between metabolism, organellar stress and cell death, as well as the connection between cellular stress/death and inflammatory and innate immune responses.

One of the requisites of life is the continuous homeostatic adaptation to changing external conditions, be it the abundance of nutrients, chemical clues (pH, osmolarity, different ion concentrations, growth factors), physical parameters (temperature, pressure, damage by light or radiation) or the presence of infectious microorganisms. Although the expression 'innate immunity' mostly refers to our defense against microbial pathogens, it appears that the frontier between innate immune responses and other adaptive responses to environmental or internal stress are fluctuating and that vice versa many of the general stress responses (to nutrient stress or changes in the physical and chemical environment) are also employed to control pathogens. This convergence goes beyond the well-recognized fact that the same pattern recognition receptors (PRRs) can respond to microbial pathogen-associated molecular patterns (PAMPs) and to (endogenous) danger-associated molecular patterns (DAMPs). Thus, 'innate immunity' does not only recognize PAMPs and DAMPs, it also recognizes any major deviation from homeostasis including the disruption of central cellular processes such as energy metabolism, redox control and protein synthesis.

What are the essentials of innate immunity? Usually, an innate immune response starts as a pathogen or a danger elicits a cellular stress response, which can occur secondary to the stimulation of one of the known PRRs and/or involve a more general response including changes in organellar physiology, ranging from altered intracellular Ca^{2+} fluxes, the unfolded stress response (UPR) in the endoplasmic reticulum, the uncoupling of the respiratory chain with enhanced production of reactive oxygen species, the permeabilization of mitochondrial membranes, the programming of gene transcription, to the activation of autophagy. In this context, autophagy likely constitutes (one of) the most primitive innate response(s), as it sequesters and destroys intracellular pathogens and damaged organelles. Autophagy can be elicited by multiple types of cellular stress, as well as by any kind of PRR. Molecules that are involved in the intracellular recognition of infectious pathogens can target invading microbes or viruses directly to elimination by autophagy. Beyond these 'autophagic adaptors', which indeed constitute a novel class of intracellular PRRs, there is extensive overlap between gene products that are known to affect the innate immune response and gene products that regulate or execute the autophagic response. Autophagy can also regulate inflammasome activation. One model suggests that basal autophagy avoids spurious inflammasome activation and hence prevent the unwarranted production of interleukin-1 β , while induced autophagy would stimulate the secretion of IL-1 β through a contribution to unconventional secretion.

The vast spectrum of responses to pathogens (and danger) is conserved — in principle, though not in the molecular details — between all eukaryotes. Even bacteria have (co-) evolved in the context of a continuous, ferocious

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competition with their pathogens, developing strategies to rapidly change their molecular phenotype (and even to produce interfering RNAs) by genetic and epigenetic mechanisms, thereby avoiding infection by or replication of bacteriophages. In plants, the cell-autonomous response to pathogens (and danger) is elicited via specific PRRs, which are highly diversified as in animals, yet restricted to on particular subtype of PRRs, the LRRs. In plants, this cell-autonomous response is circumscribed to a local level (due to the absence of mobile inflammatory cells), often culminating in the sacrifice of infected cells by programmed cell death mechanisms. The phylogenetic conservation of cell-autonomous innate immune responses justifies their experimental exploration of model animals like *Caenorhabditis elegans* (that also lacks mobile cells dedicated specifically to innate immune responses, yet cannot afford the loss of a single somatic cell) and *Drosophila melanogaster* (whose use in the study of innate immunity has been highlighted in 2011 by the attribution of the Nobel Prize to Jules Hoffmann). Thus, there is a fascinating difference between eukaryotic organisms that possess mobile immune cells (flies and mammals) or lack them (plants and nematodes), as well as between organisms that can afford the suppression of pathogen-infected or damaged cells (plants and mammals) and organisms that are essentially composed by post-mitotic cells (such as nematodes) with respect to the organization of innate immune responses.

Notwithstanding these differences in the overall organization of the system, there are common patterns in the innate immune response and common biological problems. For example, it is a general conundrum in biology how a limited number of molecules (such as PRRs) can give rise to a highly sophisticated, graduated and diversified range of responses. What determines the capacity of mammalian cells to react to external clues in a fashion that reflects the 'history' of the cell — its differentiation within a lineage, its activation state, its exposure to previous stress — as well as its context, be it determined by interactions with other (immune) cells or the concentrations of soluble factors including chemokines and cytokines. This extraordinary capacity to integrate past experience and present context into the response to pathogens is likely of the utmost importance for optimal fine-tuning the system. For instance, it may explain 'priming', that is an improved response to a pathogen upon secondary exposure, knowing that 'priming' can be observed in organisms that lack an adaptive immune system.

Several mechanisms exemplify the capacity of mammalian cells to integrate past and presence into their response to pathogens. First, many immunoreceptors (T, B and NK receptors, dectin, etc.), all of which use a conserved ITAM-molecule for their signaling, can engage in direct or indirect molecular interactions with dozens of distinct heterologous

receptors (that lack ITAM motifs). This ensemble of interactions may condition the response to immune-relevant ligands, explaining the extraordinary capacity of immune cells to integrate distinct signals that condition their response. Second, many PRRs elicit a cellular stress response via signaling molecules that are tethered or functionally connected to mitochondria, thus assuring the co-ordination of the response with mitochondrial metabolism. This design of the system also accounts for the interplay of PRR-mediated signals with those resulting in the activation of inflammatory or apoptotic caspases, knowing that these latter signals depend on the partial or complete permeabilization of mitochondrial membranes. Third, individual transcription factors (such as NF- κ B) may experience multiple post-translation modifications and co-regulatory interaction to transactivate target genes, whose expression is pre-programmed at an earlier stage of development (presumably during lineage commitment) at the epigenetic level altering the chromatin structure of each promoter.

The major gap that remains to be filled by studies of innate immune responses is an understanding of functional diversity of innate cells within a particular lineage, for example, macrophages or neutrophils. It is not known at this point whether phenomenon such as LPS tolerance or stepwise activation of discrete transcriptional programs take place within each triggered cell, or reflect population heterogeneity. It will be essential to determine whether the innate immune cells possess some sort of randomizing mechanism that establishes population and hence, functional heterogeneity of the innate cells at levels that may approach the heterogeneity of adaptive immune systems. One of the potential mechanisms may involve random assortment of distinct innate receptors on individual innate cells. By analogy to the adaptive immune responses, such a process may establish a clonal-like pattern of innate response that can optimize the efficiency of population response to the variety of innate triggers. Future studies of individual innate cell phenotypes will be essential in order to understand the existence and scope of innate cell diversification within well-defined lineages.

The same molecules and processes that participate in innate immune response *stricto sensu* (against invading pathogens) also play a major role in the response to endogenous pathological stimuli including excessive nutrients or misfolded proteins. For this reason, the comprehension of innate immunity will help elucidating the mechanisms of major diseases, in particular obesity, metabolic syndrome, diabetes and its co-morbidities, and the so-called auto-inflammatory diseases. For these reasons, we can anticipate that the in-depth elucidation of innate immunity will have vast implications for biomedical research and practice.