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Introduction

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Innate Immunity's Resurrection: How It Perceives Infection

In 1908, E. Metchnikoff and P. Ehrlich jointly received the Nobel Prize 'in recognition of their work in immunity'. Metchnikoff advocated the idea that phagocytes constituted a first line of innate defense by nonspecifically ingesting and digesting invading pathogens. In contrast, Ehrlich proposed the 'side chain theory' to explain how antibodies specific for diphtheria and tetanus exotoxins functioned. For decades, innate immunity was thus considered as 'non-specific', while the hallmark 'specificity' was confined to adaptive immunity – as mediated by T and B lymphocytes. Although microbes had long been recognized as the cause of infectious diseases, and Charles Janeway in 1989 had speculated that pathogen-associated molecular patterns alerted adaptive immunity by upregulating costimulatory signals on antigen-presenting dendritic cells, the fundamental question as to how innate immune cells perceive infections remained largely unknown. One guiding discovery and two seminal discoveries subsequently gave 'limited' specificity to innate immune cells. In 1985, Nüsslein Vollhard (Nobel Prize Laureate in 1995) and coworkers had shown that in fruit fly embryos the Toll gene controls the establishment of the dorsoventral axis. Using Toll mutants originally generated for embryological studies, Jules Hoffmann and Bruno Lemaitre then reported in 1996 that a functioning Toll gene was essential to control fungal infections in adult flies. The fact that the innate immune system of flies relies upon germ line-encoded and ligand-specific receptors to sense infection was a revelation to many immunologists. Later, the observation that inbred mouse strains C3H/HeJ and C57BL/10ScCr resisted otherwise lethal doses of lipopolysaccharide (LPS; endotoxin) prompted the speculation as to whether these inbred mice harbor a nonfunctional (mutated) receptor sensing LPS. Consequently, Bruce Beutler and colleagues used LPS-resistant C3H/HeJ mice and searched via 'positional cloning' for the postulated LPS receptor. In 1998, they discovered that LPS is sensed by Toll-like receptor 4 (TLR4); enforced cross-linking of TLR4 had previously been shown by C. Janeway and R. Medzhitow to cause NF-κB-dependent cytokine production. Beutler's milestone discovery was the first to link the TLR system with recognition of structurally defined molecules of utmost biological relevance.

By generating TLR gene knockout mice, Shizou Akira and his group made important contributions to the identification of TLR ligands and TLR signaling pathways that induce proinflammatory cytokines or type 1 interferons. Altogether, the pioneering work of Akira, Beutler, Hoffmann and Medzhitow brought about a shift in our understanding how the host perceives infection: Innate immune cells and many other cell types express evolutionary conserved germ line-encoded pattern recognition receptors (PRRs) able to sense pathogen-derived ligands. Upon recognition, such ligands specifically activate innate immune cells and function as powerful adjuvants to alert adaptive immunity. The Nobel Prize in Physiology/Medicine to J. Hoffmann, B. Beutler and R. Steinmann (for his pioneering work on dendritic cells) highlighted this paradigm shift in our understanding of innate immunity.

TLRs were the first PRRs (or immune sensing receptors) to be described. Numerous additional immune sensing receptors have now been described. TLRs and C-type lectin are membrane bound and either located on the cell surface or in the endosomal membrane. More immune sensing receptors are found in the cytoplasm. For example, retinoic acid-inducible gene I-like receptors (RIG-I like receptors including RIG-I and melanoma differentiation-associated protein 5) are members of the DExD/H box helicase superfamily. They function as cytosolic RNA sensors alerting innate immunity towards virus- and bacteria-derived RNA. Absent in melanoma 2 (AIM2)-like receptors represent a group of DNA-sensing receptors that comprises two members of the Pyrin and HIN domain-containing protein family: AIM2 and interferon-γ-inducible protein 16. While STING (stimulator of IFN genes) is mostly known as adaptor molecule, recent work highlighted its ability to bind bacterial DNA as well as cyclic di-GMP, a signaling molecule restricted to bacteria. Within the group of NLRs (nucleotide-binding domain leucine-rich repeat-containing receptors), the function of NLRP3 has been highlighted by the work of J. Tschopp. NALP3 was found to trigger 'inflammasome' formation upon ligand-driven oligomerization of cytosolic NLRP3 and ASC proteins. NLRP6 has recently been identified as a component of an inflammasome that activates IL-18 and negatively regulates colonic inflammation through alterations of the intestinal microbiota. ASC-dependent formation of inflammasomes is also a function of AIM2: the inflammasome then causes via caspase 11 and 1 the production/secretion of biologically active IL-1 family members.

Innate Immunity's Vibrancy: How Does It Promote Diseases?

In recent years, a second paradigm shift (the first concerns the germ line-encoded limited repertoire of innate immune cells) has appeared on the horizon. Innate PRRs appear to be 'promiscuous' in that they recognize not only exogenous, pathogen-derived ligands but also endogenous, host-derived molecules. In her 'danger theory', P. Massinger has collectively termed such endogenous 'danger' signals 'danger-associated molecular patterns' (DAMPs). DAMPS sensed by PRRs include liberated intracellular components (heat shock proteins, high-mobility box proteins, and extracellular host DNA), cleaved matrix hyaluronan proteins, misfolded proteins including amyloid-β, or CEPs (carboxyethyl pyrrole), the end products of lipid oxidation that are present in low-density lipoproteins. These discoveries added a second dimension: the degree to which innate immune responses cause or promote chronic autoinflammatory diseases. One striking example is the autoinflammatory disease gout: uric acid crystals activate the NALP3-driven inflammasome and IL-1β drives acute inflammation. Autoinflammatory responses have also been linked to atherosclerosis, certain aspects of the metabolic syndrome, as well as to type 2 diabetes.

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Innate Immunity and the Gut: How It Impacts Gut Microbiota Homeostasis

Defensins represent major determinants of gut homeostasis with its microbiota. While TLRs are unlikely to discriminate between commensals and pathogens, and NLRP6 expressed in gut epithelial cells control defensin production, IL-22 produced by gut-homing 'innate lymphoid cells' keeps commensal bacteria contained in their anatomical niches. Furthermore, the composition of gut microbiota appears to impact on the development of inflammatory Th17 (T) cells and that of regulatory T cells. If so, T cell functions appear to be imprinted not only in the thymus but also in the gut.

Concluding Remarks

Innate immunity's impact on protection against viral or bacterial pathogens is increasingly being understood on a molecular level. To combat intruders and driven by a limited repertoire of germ line-encoded PRRs, innate immune cells respond to infection with the balanced and well-controlled production of proinflammatory cytokines and type I interferon. The impact of innate immunity on autoinflammatory diseases, age-related chronic inflammatory disorders such as type 2 diabetes and atherosclerosis, and certain metabolic disorders for the large part is still puzzling and subject to intense investigation. Being engaged in unraveling the immunobiology of PRRs, we sensed that there is an urgent need for an information platform to discuss where this field of science stands now, and where it is likely to develop. The best platform envisaged was to organize a symposium in a remote place, in which an invited international Faculty of Scientists was to discuss their views on the state of the art in this field. The Else Kröner-Fresenius-Stiftung generously funded this symposium that focused on the role of innate immunity 'in protection against infection' and 'in promoting chronic autoinflammatory diseases'. The symposium, which took place in May 2012 at Schloss Elmau/Upper Bavaria, brought together leading experts, fostered scientific exchange, open and unsparing discussion, as well as future concepts. This meeting is the first of a series of biannual meetings which we plan in the context of the new DFG-funded Excellence Cluster ImmunoSensation: the Immune Sensory System with a scientific focus on these newly developing fields of immune sensing with connection to the metabolic, endocrine and nervous systems. This book represents a meeting report summarizing the current knowledge in this vibrant field of research at the starting point of this new excellence cluster.

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