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EDITORIAL

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Nobel Prize laureates pave the way for therapeutic advances in sepsis

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In 1908, Mechnikov and Ehrlich received the Nobel Prize respectively for the identification of phagocyte cells that engulf and devour intruders, and for developing a theory that explained how antibodies released in the blood tackle invaders. On 3 October 2011, the Nobel Prize in Physiology or Medicine 2011 was awarded to three researchers for adding milestones on the way opened by Mechnikov and Ehrlich. One half of the Nobel Prize was shared by Jules A. Hoffmann (Institut de Biologie Moléculaire et Cellulaire, Strasbourg, France) and Bruce A. Beutler (Scripps Research Institute, La Jolla, CA, USA) for their discoveries of novel mechanisms of activation of the innate immune response, and the other half by Ralph M. Steinman (Rockefeller University, New York, NY, USA) for his discovery of the dendritic cell and its role in adaptive immunity. Their discoveries established the modern concepts of host defence to infections that constitute real breakthroughs in the quest for novel therapeutic targets in sepsis.

Infection by a pathogenic microorganism triggers a coordinated activation of innate and adaptive immune responses that aims to control microbial growth and protect the host. The innate immune response is the first line of defence against microorganisms and is shared by all multicellular organisms, including mammals, insects and plants. It produces an almost immediate, non-specific, inflammatory response that aims to eradicate invading microorganisms and to prevent tissue damage. In contrast, the adaptive immune response is specific for a given pathogen and is related to the antigen-dependent proliferation of T and B lymphocyte clones. In contrast to innate immunity, the adaptive immune response is present only in vertebrates, and requires a few days to become fully activated. It also carries the immunological memory that quickens and strengthens the response to subsequent infections by identical pathogens. Until recently, we had little insight into how the immune system senses and identifies infective microorganisms to trigger the innate immune response, and the link between innate and adaptive immunity remained enigmatic.

Accurate recognition of microbial-associated molecular patterns by pattern-recognition receptors is the cornerstone of the innate immune response. Since fruit flies do not have an adaptive immune system, their host defence to infections relies solely on innate immune response. Jules Hoffmann was awarded for the discovery of the role of the Toll receptor in *Drosophila* defence against infections. The Toll receptor is a transmembrane receptor that was initially involved in the establishment of the dorsal–ventral polarity of the *Drosophila* embryo by Christiane Nüsslein-Volhard (Nobel Prize 1995). Using flies with mutations in genes of the Toll signalling pathway, J. Hoffmann's team was able to demonstrate that

Toll controlled the expression of antimicrobial peptide genes and that deficient Toll signalling dramatically reduced survival after fungal infection [1]. Toll was also subsequently involved in *Drosophila* antibacterial defence [2].

These results were extended to mammals after the discovery of homologous receptors named Toll-like receptors (TLR) in humans and in mice. Bruce Beutler, also known for the discovery of tumour necrosis factor-α (TNF-α) [3–5], was awarded for the identification of TLR4 as the receptor of the Gram-negative bacterial product lipopolysaccharide (LPS). Injection of LPS in mice leads to endotoxinic shock that recapitulates the main features of septic shock. While searching for the LPS receptor involved in endotoxinic shock, Beutler and colleagues observed that some mice, which displayed resistance to the LPS challenge, carried constitutive mutations in a gene similar to the *Drosophila* Toll gene. This gene coded for a receptor now known as TLR4 that turned out to be a central part of the LPS receptor complex [6]. This is probably one of the most striking examples of the power of "forward genetics", an approach that allows one to find genes immediately once they have been mapped and to identify mutations that cause phenotype, thereby establishing cause and effect relationships often with revolutionary consequences.

These discoveries have triggered intense research in the field of innate immunity—as illustrated by almost 16,000 publications retrieved when entering the search term "Toll-like receptors" in PubMed. To this day, 10 TLRs have been identified in humans and 13 in mice. Genetically engineered mice deficient for TLRs or for downstream signalling molecules have allowed the specific role of each TLR to be deciphered not only in the innate immune response but also in the inflammatory process. Undoubtedly, the discovery of TLRs has revolutionized our understanding of the pathophysiology of sepsis and inflammation. Beyond their critical role in antimicrobial host defence, TLRs and their associated signalling pathways appear to contribute to almost all inflammatory processes and they are now considered as targets likely to result in therapeutic advances in the near future.

Beyond innate immunity, effective clearance of invading microorganisms relies on the coordinated activation of adaptive immune responses. Nobel laureate Ralph Steinman greatly contributed to advance our understanding of the interplay between the innate and adaptive components of the immune response. In 1973, he described dendritic cells as a minority population of splenic cells acting as the main antigen-presenting cells, with the unique capacity to activate T cells and orient adaptive immune response [7–9]. Dendritic cells are able to sense and engulf pathogens, to process the antigen and to present it to the T cell receptor, resulting in T lymphocytes activation. To this end, dendritic cells undergo a maturation process leading to overexpression of the type II major histocompatibility complex and coactivation molecules, as well as the production of cytokines able to induce various T cell responses. The maturation process depends on microbial or inflammatory stimuli sensed by pattern-recognition receptors including TLRs. Thus, signals arising from the innate immune response are integrated by dendritic cells to initiate and to direct T cell responses. Dendritic cells have been involved in the pathophysiology of multiple infectious and non-infectious disorders. Their discovery has prompted the development of improved anti-infective vaccines, and anti-tumoral vaccination is currently in the advanced phase of clinical development. Unfortunately, Ralph Steinman will not see the important consequences of his pioneering work as he passed away 3 days before the announcement of his Nobel Prize.

Thanks to the efforts of J. Hoffmann, B. Beutler and R. Steinman, improved understanding of how the immune system deals with pathogens and with endogenous molecules provides major insights into the prevention or treatment of infectious diseases. For all the physicians that have had the chance to hear one of these outstanding scientists expose their work in critical care congresses and symposia, it is clear that their fundamental discoveries will translate into novel treatments at the bedside in the near future. The comprehension of the molecular and cellular mechanisms of severe sepsis and septic shock has already generated new therapeutic approaches in experimental models as well as in clinical trials. It is thus time to acknowledge the considerable contribution of these three outstanding scientists and their research teams to the advancement our knowledge, and pay them a vibrant tribute in the journal for their major achievements.

Conflict of interest None.

References

1. Lemaitre B, Nicolas E, Michaut L, Reichhart JM, Hoffmann JA (1996) The dorsoventral regulatory gene cassette spatzle/Toll/cactus controls the potent antifungal response in Drosophila adults. Cell 86:973–983
2. Michel T, Reichhart JM, Hoffmann JA, Royet J (2001) Drosophila Toll is activated by Gram-positive bacteria through a circulating peptidoglycan recognition protein. Nature 414:756–759
3. Beutler B, Greenwald D, Hulmes JD, Chang M, Pan YC, Mathison J, Ulevitch R, Cerami A (1985) Identity of tumour necrosis factor and the macrophage-secreted factor cachectin. Nature 316:552–554

4. Beutler B, Mahoney J, Le Trang N, Pekala P, Cerami A (1985) Purification of cachectin, a lipoprotein lipase-suppressing hormone secreted by endotoxin-induced RAW 264.7 cells. J Exp Med 161:984–995
5. Beutler B, Milsark IW, Cerami AC (1985) Passive immunization against cachectin/tumor necrosis factor protects mice from lethal effect of endotoxin. Science 229:869–871
6. Poltorak A, He X, Smirnova I, Liu MY, Van Huffel C, Du X, Birdwell D, Alejos E, Silva M, Galanos C, Freudenberg M, Ricciardi-Castagnoli P, Layton B, Beutler B (1998) Defective LPS signaling in C3H/HeJ and C57BL/10ScCr mice: mutations in Tlr4 gene. Science 282:2085–2088
7. Steinman RM, Cohn ZA (1973) Identification of a novel cell type in peripheral lymphoid organs of mice. I. Morphology, quantitation, tissue distribution. J Exp Med 137:1142–1162
8. Steinman RM, Cohn ZA (1974) Identification of a novel cell type in peripheral lymphoid organs of mice. II. Functional properties in vitro. J Exp Med 139:380–397
9. Steinman RM, Lustig DS, Cohn ZA (1974) Identification of a novel cell type in peripheral lymphoid organs of mice. 3. Functional properties in vivo. J Exp Med 139:1431–1445