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UNDERSTANDING THE DISEASE

Understanding host–pathogen interaction

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Introduction

A strong response to pathogens is mandatory for survival of the host. However, the local defence mechanisms may be detrimental when overwhelmed and/or spread systemically.

Recognition of pathogens by the host induces inflammatory response

Specific receptors called pattern recognition receptors (PRR) sense the interface between epithelium and organs in a way that rapidly induces a strong inflammatory response to kill the pathogens (Fig. 1) [1]. PRRs recognize conserved structures on pathogens called pathogen-associated molecular patterns (PAMPs). Five classes of PRR including Toll-like receptors (TLRs), nucleotide oligomerization domain-like receptors (NLRs), RIG-I-like receptors, C-type lectin receptors, and absence in melanoma 2 (AIM2)-like receptors have been described [2]. These PRRs share common properties explaining their high efficiency: (1) Expression on epithelial, endothelial, innate and adaptive immune cells; (2) PRR activation induces recruitment and activation of leukocytes to kill pathogens; (3) a stereotypical transcriptional program engages signal transduction pathways that activate key transcription factors including NF-κB, activator protein1 (AP-1), interferon regulatory factors (IRFs) and nuclear factor of activated T cells (NFAT) [3]. It is fascinating to consider that these five families of receptors allow the host to recognize and sense the vast majority of pathogens.

The inflammatory response secondary to infection induces local tissue damage, and the subsequent cell injuries play an important role in the response of the host against the pathogen. These "danger signals" are called danger associated molecular patterns (DAMP) or alarmins. The endogenous products of injured cells become extracellular DAMPs (HMGB1, S100 proteins, extracellular RNA, DNA and histones) and, like PAMP issued from pathogens, they activate PRR as well as the formation of cell surface signalosomes [4]. Activation of signalosomes mediates the onset of apoptosis. This intrinsic process of removing or recycling damaged proteins or organelles that induce apoptosis clearly evokes autophagy. When autophagy is altered an overwhelmed, an inflammatory response may occur inducing organ dysfunction. Inflammasomes may also mediate pyroptosis, a particular form of programmed cell death that releases cellular debris extracellularly, thereby increasing the inflammatory process [5]. In conclusion, an infection may induce organ dysfunction through an excessive inflammatory response by two mechanisms: (1) direct recognition of the pathogen by the host (interaction PAMP–PRR) and/or (2) alteration of the apoptosis mechanisms (interaction DAMP–PRR).

Alterations of homeostasis induce immunosuppression

The strong inflammatory response described above may be accompanied by an impairment of the immune response in the context of severe infections, sepsis and septic shock. Several patterns of immunosuppression were described including monocyte deactivation, decreased capacity for antigen presentation (low HLA-DR II expression on blood monocytes) and apoptosis of immune effector cells (lymphocytes, dendritic cells). The number of immunosuppressive cells like Treg or myeloid-derived suppressor cells is also increased. The main consequences of this immunosuppression are a higher rate of secondary nosocomial infections and viral

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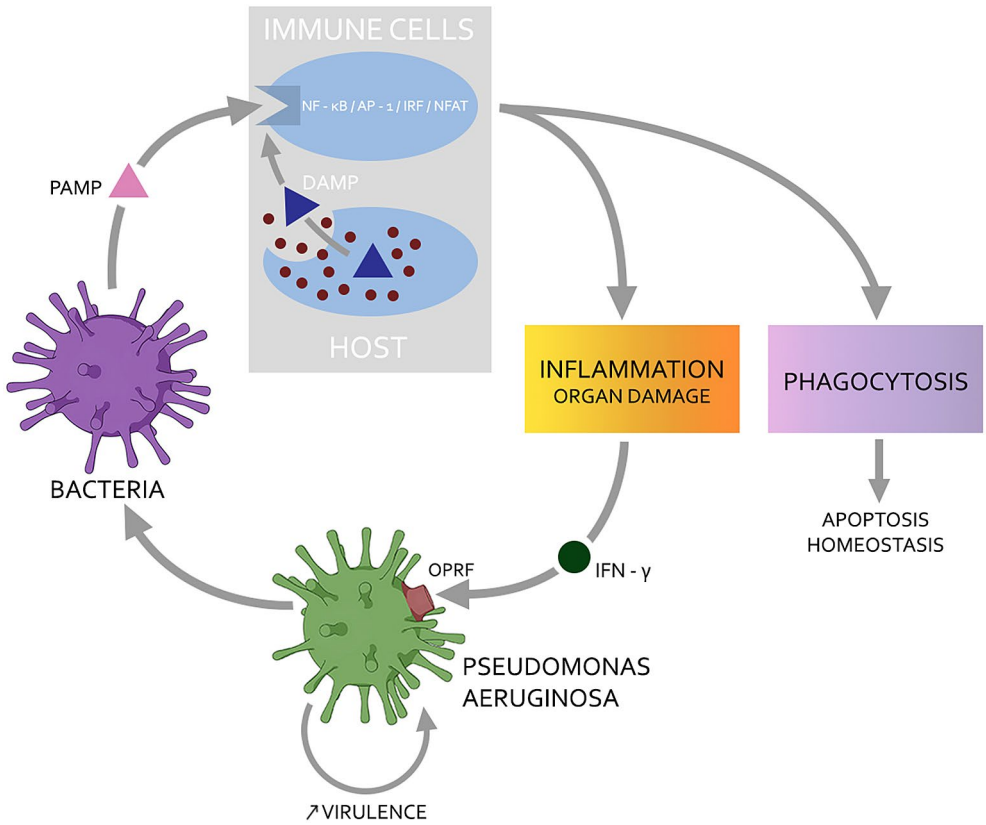

Fig. 1 Pathogen associated molecular patterns (*PAMPs*) from bacteria bind to pattern recognition receptors (*PRRs*) and activate pathways leading to the engagement of key transcription factors including NF-κB, activator protein1 (*AP1*), interferon regulatory factors (*IRFs*), and nuclear factor of activated T cells (*NFAT*). Immune cells will also release danger associated molecular patterns (*DAMPs*) from the intracellular compartment into the extracellular milieu; these DAMPs like PAMPs will be recognized by PRRs. PAMPs and DAMPs induce the release of inflammatory mediators including cytokines. Two scenarios can occur: (1) after bacterial phagocytosis, the immune cells may undergo apoptosis leading to homeostasis; (2) excessive inflammation may overwhelm host regulatory pathways leading to organ failure. Finally, some cytokines, e.g. IFN-γ, that are released during the inflammatory process may be recognized by bacteria (*Pseudomonas aeruginosa*) through specific receptors (OPRF) allowing the bacteria to increase its virulence

reactivation along with worsened long-term outcomes for the infected host [6–8].

Opportunistic pathogens sense the host response

The response of the host against the pathogen is now largely studied and described, whereas the response of the pathogen to evade the defence mechanisms of the host remains largely unknown. Opportunistic infection was generally believed to be a passive phenomenon. In this scenario, the invading pathogen simply takes advantage of the stressed host to proliferate. However, it is now well recognized that bacteria themselves can sense the host immune activation through specific receptors. The prototypical opportunistic bacteria involved in these escaping phenomenon are *Pseudomonas aeruginosa* (PA). In PA, a cell-to-cell communication based on signal molecules (named quorum sensing) can control the production of extracellular virulence factors [9]. More interestingly, these bacteria can sense the response of the host in tissues (mediators released in the microenvironment) either to become more virulent when the host defences are impaired or to produce biofilms for protection against harsh environmental condition (vigorous host response). The quorum sensing machinery can therefore confer a selective advantage on PA. In this setting, Wu et al. demonstrated that interferon-γ, a major actor of the host defence, binds to a membrane receptor (OprF) on PA (Fig. 1). This phenomenon proves important since binding of IFN-γ to OprF induces the expression of a virulence trait PA-I lectin [10]. In other words, the more the host activates its immune system, the more virulent PA becomes. Among the large arsenal of virulence factors, the type III exoenzyme system has been correlated with poor outcome [11]. This secretion

system is composed of a needle complex (T3SS) allowing the injection of three effectors (Exoenzymes S, T, Y) directly into the host cell's cytoplasm, and thereby enabling the bacteria to directly interfere with intracellular signalling [12]. In particular, ExoT (expressed by more than 95 % of clinical PA strains) [13] and ExoS both target Rho-like GTPases and induce an actin-cytoskeleton rearrangement disturbing the host cellular metabolism and activation.

From individual responses to personalized medicine

Beyond a better comprehension of the host–pathogen interactions, it remains important to consider the extreme heterogeneity of the response of the host after a given infection. In this setting, identifying a set of biomarkers that predict the type of host immune response for a given individual to a particular pathogen will enable the clinician to tailor immunomodulatory therapy to ensure the best outcome; this is the basis of the concept of "personalized medicine". This emerging concept was recently highlighted in the context of severe community-acquired pneumonia. In that study [14], the transcriptome was analysed in blood leukocytes. A specific immunosuppressive response was associated with increased mortality, and a set of seven genes was able to identify this deleterious host response. Interestingly, these genes may be incorporated into a "point of care" test that could be easily performed at the patient's bedside. This approach is a first step toward precision medicine providing investigators with a rational approach for using immunomodulatory therapy to modify patient immunity. One of the main targets might be the factors that regulate the immunomodulatory properties of the antigen-presenting cells that are dedicated to sensing both PAMP and DAMP and initiate T cell immunity [15].

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Compliance with ethical standards

Conflicts of interest

All authors declare that they have no conflict of interest to declare.

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