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Innate immune memory in mammals

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ABSTRACT

Innate and adaptive immunity have evolved as sophisticated mechanisms of host defence against invading pathogens. Classically the properties attributed to innate immunity are its rapid pleiotropic response, and to adaptive immunity its specificity and ability to retain a long-term memory of past infections. It is now clear that innate immunity also contributes to raising a memory response upon pathogenic assault. In this review we will discuss the interaction between bacterial, viral, fungal and parasitic molecular patterns and innate immune cells in which a memory response is imposed, or has the potential to be imposed.

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1. Introduction

The first line of defence against invading pathogens is through the innate immune response. This ancestral mechanism is shared by all metazoans and is crucial for survival of multicellular organisms. In mammals pathogen surveillance involves multiple layers

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of regulation starting with germ-line encoded pattern recognition receptors (PRRs), including the family of Toll-like (TLRs), C-Type Lectin, RIG-I like and Nod-like receptors. These PRRs recognize microbe specific molecules called Pathogen Associated Molecular Patterns (PAMPs), which include bacterial carbohydrates and peptides, nucleic acids, and fungal glucans. The recognition of such molecular patterns triggers the synthesis of cytokines and chemokines, and the engulfment of pathogens by phagocytic cells, both of which are essential features for inducing a productive inflammatory response. Further recruitment of monocytes and neutrophils from the bloodstream, and activation of macrophages are subsequent steps in the host defence against invading microorganisms and are crucial for the control of infections.

Innate immunity, however, is not always sufficient to eliminate all infectious organisms, and higher organisms evolved an adaptive immune system to provide a more precise and adjustable means of defence. The main characteristic of adaptive immunity lymphocytes is to increase protection against reinfection with the same pathogen. Important features of these lymphocytes are their antigen specificity, obtained by rearranging receptor genes, their ability to clonally expand upon encounter of foreign antigen, and their differentiation into effector cells that can eliminate the infectious agent [1]. A subset of these proliferating lymphocytes differentiates into memory cells, ready to respond rapidly to the same pathogen if it is encountered again.

Although innate immune cells are the first responders and are more versatile due to the large surface receptors repertoire, they play a crucial part in the initiation and subsequent development of adaptive immune responses. Activation of antigen-presenting cells such as dendritic cells is a necessary first step for induction of adaptive immunity. Moreover innate immunity participates as well in the removal of pathogens that have been targeted by an adaptive immune response. Although both innate and adaptive systems are closely linked, in this review we will focus our discussion on responses that only involve innate immunity.

As highlighted above, immunological textbooks teach that the immune system is composed of two distinct branches. Innate immunity is defined as natural or non-specific in contrast to adaptive immunity, which is considered more complex and effective due to its specificity and the capacity to mount memory. However it is becoming clearer that this dichotomy between the two systems is not so simple. First of all, many cell types of the immune system play a role in both innate and adaptive arms such as γδ T-lymphocytes or innate lymphoid cells (ILCs) from the lymphoid lineage. Similarly, as mentioned above, macrophages, can be activated by T cell-expressed molecules, and participate in the removal of pathogens that are targeted by the adaptive immune arm. Moreover, recent research has documented the capacity of innate immune cells such as natural killer (NK) cells, monocytes and macrophages to recall a first encounter with a pathogen demonstrating that a non-specific innate immune compartment is capable of memory. Finally, numerous reports have shown that lower organisms, such as *Drosophila* [2], mealworm beetles [3] *Anopheles* [4] and plants [5] that are devoid of classical adaptive immune structures can still adapt upon primary challenge. These observations in lower organisms support the findings in mammals and will be covered in this issue [86,87].

In our opinion it is important to start by defining as precisely as possible the principles of innate immune memory. The first fundamental feature is the ability of innate immune cells to mount a differential immune response upon a secondary infection, whether it is a heightened or a tolerized response. These cells may be selected and stored in a niche, may proliferate or become long-lived, and/or may cross-talk with other cells of the innate immune compartment. The second feature is that innate immune memory is non-specific, except in certain cases (see the viral memory section), which is in sharp contrast to the sophisticated adaptive immune recall response. However classical "cross-protection", which involves both adaptive and innate cells should be excluded from the definition of innate immune memory. Finally, an important feature required to define memory is the resolution of the primo-infection (Fig. 1). This is a delicate matter as the resolution/completion of an inflammation is dependent on the cell type, the nature of the infection and most importantly the type of inflammatory marks (gene, histone enrichment, metabolism, cytokine etc...). However, in our opinion, the clearance of the primary inflammation is a *sine qua none* condition, and memory should only be considered as such if it modifies the homeostatic status of the cells (Fig. 1).

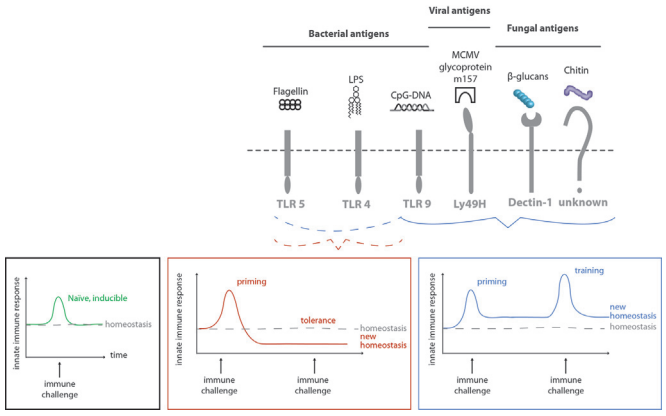

Fig. 1. Pathogenic antigens and their cellular receptors through which innate immune memory is induced and their consequence on cellular homeostasis.
The main receptor for CpG-DNA is TLR9, mainly present in dendritic and B cells. Flagellin and LPS are respectively TLR5 and TLR4 agonists, both of which are present on many different innate immune cells. Ly49H is the receptor on NK cells which specifically senses the m157 glycoprotein of MCMV. Fungal ß-glucans are sensed by the dectin 1 receptor, whereas the receptor for chitin has not yet been identified.
The definition of innate immune memory can be illustrated as followed: a primary infection will trigger innate immune responses. Upon resolution of the infection, the homeostatic state of the cells is modified and the immunological baseline reset into a heightened (trained immunity) or decreased-refractory (tolerance-immunoparalysis) immunity, which might translate into decreased or increased susceptibility to infections, respectively. The consequence of receptor activation on innate immune memory is indicated by a red accolade for tolerance and blue for heightened immunity.

In this review we will focus on the current knowledge of innate immune responses that have been demonstrated or have a potential for inducing memory. Detailed molecular mechanisms associated with innate immune memory will be covered in this issue [88].

2. Memory to bacteria

2.1. BCG

Historical studies done with *Mycobacterium bovis*, the bacillus strain used in the BCG vaccine, provided experimental evidence that infection with one pathogen alters the susceptibility to infection with unrelated organisms in a lasting manner. Indeed, animals injected with live *Mycobacterium bovis* acquired resistance to a variety of heterologous pathogens such as *Staphylococcus aureus* [6] *Herpesvirus* [7], *Salmonella* [8], *Listeria monocytogenes* [9], or *Candida albicans* [10]. Interestingly, BCG components or heat killed bacteria are sufficient to induce such cross reactivity to pathogens, lasting from 2 weeks to 2 months [6,11]. Although the molecular mechanisms of cross reactivity are unclear, studies hint to an important contribution of the innate immune response. Het-