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Review

The cells that mediate innate immune memory and their functional significance in inflammatory and infectious diseases

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ABSTRACT

Immunological memory mediated by antigen-specific T and B cells is the foundation of adaptive immunity and is fundamental to the heightened and rapid protective immune response induced by vaccination or following re-infection with the same pathogen. While the innate immune system has classically been considered to be non-specific and devoid of memory, it now appears that it can be trained following exposure to microbes or their products and that this may confer a form of memory on innate immune cells. The evidence for immunological memory outside of T and B cells has been best established for natural killer (NK) cells, where it has been known for decades that NK cells have heighten responses following immunological re-challenge. Furthermore, recent studies have demonstrated that monocyte/macrophages, and probably dendritic cells, can be re-programmed through epigenetic modification, following exposure to pathogens or their products, resulting in heighted responses following a second stimulation. Unlike antigen-specific memory of the adaptive immune system, the second stimulation does not have to be with the same pathogen or antigen. Indirect evidence for this comes from reports on the non-specific beneficial effect of certain live vaccines, such as Bacillus Calmette Guerin (BCG) against unrelated childhood infectious diseases. It also appears that certain pathogen or pathogen-derived molecules can prime immune cells, especially macrophages, to secrete more anti-inflammatory and less pro-inflammatory cyokines, thus opening up the possibility of exploiting innate immune training as a new therapeutic approach for inflammatory diseases.

Contents

Abbreviations: NK cell, natural killer cell; LPS, lipopolysaccharide; TLR, Toll-like receptor; TCR, T cell receptor; BCR, B cell receptor; DCs, dendritic cells; BCG, Bacillus Calmette Guerin; PRR, pathogen recognition receptor; NLR, Nod-like receptor; PAMPs, pattern-associated molecular patterns; DAMPs, danger-associated molecular patterns; CMV, cytomegalovirus; MCMC, murine CMV; HCMC, human CMV; CHS, contact hypersensitivity; DTH, delayed type hypersensitivity; VSV, vesicular stomatitis virus; ILCs, innate lymphoid cells.

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1. Introduction

Some of the first evidence the innate immune system can have memory or undergo some form of training emerged over a half a century ago when Youmans and Youmans demonstrated that injection of mice with lipopolysaccharide (LPS) enhanced their resistance to infection with *Mycobacterium tuberculosis* when challenge 7–14 days later [1]. The cells and receptor(s) targeted by LPS were not identified for several decades [2]; we now know that LPS is a powerful activator of innate immune response through binding to and signalling downstream of toll-like receptor (TLR)4, that is expressed highly, though not exclusively, on myeloid cells [3]. The term 'trained immunity' has been used to describe the modulated immune response observed following reactivation of cells the innate immune system, a trait that is generally associated with cells and functions of the adaptive immune system.

Immunological memory mediated by antigen-specific activation of lymphocytes through T cell receptors (TCR) and B cell receptor (BCR) is a defining feature of the adaptive immune system. Indeed, this is still thought to be primary mechanism that explains the heightened antigen-specific immune responses to a secondary exposure to antigen following booster immunization or re-infection and is still considered to the fundamental basis of long term protective immunity against pathogens induced by previous infection or vaccination (Fig. 1). The dogma that adaptive lymphocytes have memory, whereas innate immune cells do not, has been challenged following the discovery that cells of the innate immune system, especially monocytes/macrophages, can be 'trained' so that they mount a heightened immune response following a second encounter with a pathogen-derived molecule (Fig. 1). Trained innate immunity can be beneficial to the host, for example upon subsequent infection or during tumouregensis, but may also be detrimental by enhancing the immune responses that precipitate or mediate autoimmune or inflammatory disease.

2. Monocytes/macrophages and dendritic cells (DCs)

It has been known for some time that immunization with certain attenuated bacterial or viral vaccine can confer non-specific protective immunity to unrelated pathogens. Some of the strongest evidence for this has come from the study of Bacillus Calmette Guerin (BCG), the attenuated bacteria used to vaccinate against tuberculosis. Immunization with BCG has been shown to confer non-specific protection against un-related pathogens [4] and intravesical immunotherapy with BCG is used as first line therapy against bladder cancer [5]. Although the protective mechanism has not been defined, it is thought to involve non-specific activation or training of innate immune responses, especially NK cells, but also myeloid cells [6]. A number of recent studies have provided convincing evidence that myeloid cells of the macrophage linage can be undergo training following exposure to certain PAMPs and that this can confer a type of immunological memory on these cells [7,8].

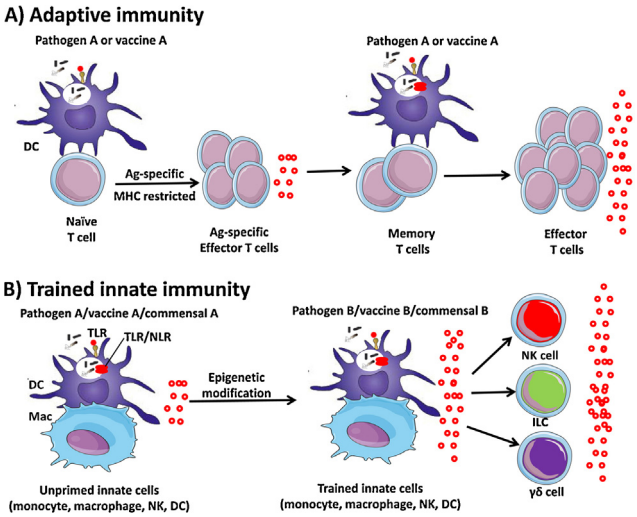

Fig. 1. Adaptive memory *versus* innate training. (A) Naive T cells are activated by specific antigen (Ag) following binding of the T-cell receptor to MHC-peptide complexes on dendritic cells (DC). The activated Ag-specific T cells ($CD4^+$ or $CD8^+$) differentiate into effector T cells that secrete cytokines, such as IFN-γ, IL-17, IL-4. A proportion of these cells survive as memory T cells, which can be rapidly activated following re-exposure of the host to the same pathogen. The activated T cells proliferate and secrete cytokines, including IFN-γ and IL-17, which help to eliminate the pathogen. (B) Innate immune cells, including DCs and macrophages, are activated by pathogen-associated molecular patterns (PAMPs) that bind to toll-like receptors (TLR) and Nod-like receptors (NLR). This priming can induce epigenetic modifications, which influences the subsequent responses when the cells are exposed to PAMPs for a second time from the same or different pathogen. The innate immune cells are trained to respond more effectively to the second stimulus, secreting high concentrations of inflammatory cytokines, including IL-1, IL-12, IL-18, and IL-23, which promote IL-17 and IFN-γ production by innate lymphocytes, including γδ T cells, innate lymphoid cells (ILCs), and NK T cells, that exert protective effector function against the second pathogen.

2.1. Specificity of monocyte/macrophages and DCs

While B cells and MHC-restricted T cells have exquisite specificity for antigen through their BCR and TCR, most innate immune cells do not display such specificity, but do express pathogen recognition receptors (PRRs), including TLR, Nod-like receptors (NLR) and nucleic acid sensors that allow them to be activated by pattern-associated molecular patterns (PAMPs) and endogenous danger signals from dead and dying cells (danger-associated molecular patterns: DAMPs) [9,10]. Natural Killer (NK) cells also express specialized receptor families for MHC class I recognition [11]. While these NK receptors and PRRs are not gene re-arranging antigen receptors, and their diversity does not approach that of BCR and TCR on lymphocytes, it is increasingly being recognized that these families are quite extensive and confer a level of specificity on the innate immune system. Unlike T and B cells, which undergo clonal expansion following activation through TCR or BCR, macrophages and DCs do not clonally expand following activation through PRRs, but can undergo epigenetic modification following exposure to PAMPs or DAMPs making them more sensitive to subsequently exposure to the same or unrelated signals [8]. Furthermore, activation though PRRs stimulates signalling pathways in macrophages and DCs that