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Review

The innate immune response

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ABSTRACT

The innate immune response is of prime importance in the immediate recognition and elimination of invading micro-organisms. However, deregulation of this system is clearly associated with the pathogenesis of a wide range of inflammatory diseases. Innate immunity consists of a humoral and a cellular branch, which are closely interacting. An additional level of control is found at the level of neuronal reflexes that can fine-tune these immunological mechanisms.

1. Introduction: the innate immune response: an evolutionary old defense mechanism

The human immune system consists of two branches: the antigen-specific adaptive immune response and the innate immune response recognizing microbial associated molecular patterns (MAMP's). The adaptive immune response is relatively slow, is antigen specific and requires gene rearrangement. The molecules and the receptors of the innate immune response on the other hand are fixed present in the germ line DNA. Therefore, this system is quick as the system does not have to "learn"/adapt to a changing environment. This article will discuss a few important features of the innate immune system.

The development of the innate immune system predates the adaptive immune system by 500–700 million years [1]. Whereas the first indications of an antigen dependent adaptive response associated with T-lymphocytes are found in cyclostomata (e.g. lamprey) that evolved around 300 million years ago [2], innate immunity started already during the occurrence of multicellular organisms 1 billion years ago [1]. A special form of phagocytosis, endosymbiosis, is even much older. This latter process refers to engulfment by single cells of targets, endo-symbionts that could later evolve toward organelles such as mitochondria and chloroplasts [3]. The innate immune response is very complex and different mechanisms evolved at different times during evolution [1].

1.1. Intracellular responses

One of the oldest immune responses that is found in both plants and animals is RNA interference (RNAi) and other mechanisms recognizing intracellular nucleic acids from pathogens [1]. Another mechanism is mediated by antimicrobial peptides. These mechanisms can be operational in both uni- and multicellular mechanisms and do not need any form of circulatory system.

1.2. (Para) cellular responses

When multicellular organisms developed, the immune system adapted to this new situation by the evolution of immune mechanisms that could respond extracellularly: the humoral response mediated by single molecules and the cellular response mediated by effector cells. These two mechanisms have in common that a major part is mediated by proteins/receptors that recognize microbe associated molecular patterns or MAMP's. This pattern recognition response allows the identification of patterns that are present at multiple microbial products. A good example is the formyl-methionyl-leucyl-phenylalaline (fMLF) receptor that recognizes all proteins that start with the bacterial start sequence formyl-methionyl. The innate immune response evolved into a humoral part and a cellular part.

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1.3. The Humoral innate immune response consists of two groups of mechanisms: cascade systems such as the complement and coagulation systems and single antimicrobial molecules

The cascade systems are present in an inactive configuration are rapidly activated upon interaction with microbes. The single antimicrobial proteins are either present in the intercellular space or are produced by other cells or tissues during a stress or acute phase response [1]. The first indications of the evolution of the complement system has been found in sea urchins which dates the evolution of this important cascade system (see below) to around 450 million years ago [4].

1.4. The cellular innate immune response

When organisms became more complex, part of the cells differentiated into true immune cells. These cells acquired the propensity to eat or phagocytose targets such as bacteria. These phagocytes are found already in very simple multicellular organisms such as corals [5,6], which dates the evolution of these cells to 580 million years ago. Hereafter, the innate immune cells started to evolve into cells with different functions: neutrophils, eosinophils, monocytes, macrophages.

Starting 500 million years ago, a co-evolution of both innate and adaptive immune responses occurred, and a clear cross talk is now present in complex organisms such as vertebrates exemplified by the evolution of dendritic cells and immunoglobulins [7].

2. The humoral innate immune response

2.1. The complement system (see Fig. 1)

As mentioned earlier, the humoral arm of innate immunity consists of a large number of players including chemokines, cytokines, defensins and complement. All these mediator systems provide defense at the initial phase of contact with pathogens and are responsible to prevent potentially harmful infections. At the same time the innate system presents antigens in an appropriate fashion to innate immune cells, such as antigen presenting cells, which then subsequently induce the adaptive immune response. In this scenario the complement system is of major importance because it is involved in direct pathogen recognition and elimination via opsonization and phagocytosis of potentially harmful organisms. Complement activation plays a major role in chemotaxis and inflammation. Several functions of complement are essential to enhance the potency of our innate immune defense by induction of increased production of chemokines, cytokines and other innate defense molecules. When complement is activated by a pathogen, activated C3 namely C3b is deposited covalently on these pathogens. The deposition of C3b and its catabolic fragment C3d results in significantly increased recognition of antigens by follicular dendritic cells and B cells and induction of the humoral adaptive immune response [8] and production of antibodies and reactive T cells. In this regard it is known for a long time that for instance rats depleted of complement have a drastically reduced antibody response against novel antigens [9]. Another very interesting function of complement is the effect on clearance of soluble immune complexes and cell debris. The latter is of importance because it has been hypothesized [10] that large amounts of cell debris may induce an immune response against auto antigens and potentially induce autoimmunity.

The complement system consists of a large number of complement components which are found mainly in the circulation but also in all tissues. Under physiological conditions the complement system is activated to a very low degree but under conditions

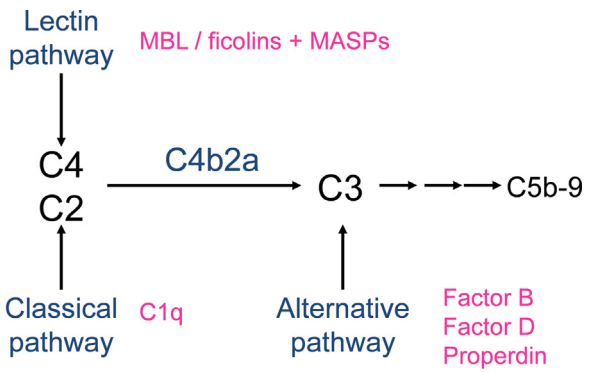

Fig. 1. The Complement system can be activated via three pathways: the classical, the alternative and lectin pathway. Activation of the classical and lectin pathway result in formation of the C3 convertase C4b2a leading to activation of C3 and further activation of the terminal effector pathway and generation of the membrane attack complex C5b-9. The alternative pathway is dependent on interaction of hydrolyzed C3 and the alternative pathway components factor B, D and properdin.

of infection the system can be activated fully by three different pathways. These three activation pathways of complement are referred to as the classical, the lectin and the alternative pathway. Each of these pathways has its own soluble pattern like recognition molecule(s). The classical pathway of complement is activated mainly by antigen–antibody complexes (immune complexes), by several bacteria and their products, by apoptotic and necrotic tissue and cells. Here C1q is the recognition molecule leading to further activation of the classical pathway that involves C4, C2 and generation of the classical C3 convertase C4b2a. A major role for the classical pathway is in the routing and elimination of soluble immune complexes. Following exposure to foreign antigen such as found in food large amounts of antibodies are generated and following re-exposure large amounts of immune complexes are formed in the circulation. These complexes can potentially be deposited at random in small vessel walls and cause immune-complex-mediated inflammation. Several studies have shown that immune complexes in the circulation can activate the classical pathway leading to deposition of C3b on their surface. C3b bearing immune complexes are recognized by C3b receptors (CR1, CD35) on erythrocytes and subsequently transported to the liver where they are ingested and degraded. In this scenario the immune complexes are kept away from host endothelium and prevented from deposition in small vessels.

A major insight was recently gained on the role of the classical pathway in the handling of apoptotic cells. Once apoptosis occurs there is a flip-flop of the cell membrane, nuclear fragmentation and exposure of phosphatidyl serine. It was demonstrated that apoptotic cells are major activators of the classical pathway and that the degree of opsonisation by complement and complement activation fragments. This potentially determines the rate of elimination of cell debris and exposure of the adaptive immune system to autoantigens (3). The classical pathway is a major driving force in induction of inflammation in autoimmune diseases such as Systemic Lupus Erythematosus (SLE). Next to complement activation there is significant autoreactivity against host complement components like C1q. These anti-C1q autoantibodies (C1qAb) were shown to induce glomerular inflammation in mice [11] explaining earlier findings of a strong association between the presence of C1qAb and renal involvement in patients with SLE [12].

The Lectin pathway is activated by complex carbohydrate stuctures and mediated via recognition molecules as Mannan binding lectin (MBL) and ficolins. This initial step leads to activation of mannan associated serine protease-2 (MASP-2) and subsequent activation of C4 and C2. This results in formation of the C3 convertase C4b2a, which is the same convertase generated via the classical