Review paper

Innate and adaptive immunity in viral infections*

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Abstract

The defense against viruses requires collaboration of both arms of immunity, innate and adaptive one. Factors of the former may sense viruses early on the principle self/non self and mount fast reaction of the host. Early recognition of intracellular viral invasion is mainly done by pattern recognition receptors (PRRs). It results in the induction of complex inflammatory process composed of proinflammatory agents, collectively named inflammasome. Its formation has a pivotal role in the formation of adaptive response. Infected cells may be also eliminated by natural killer (NK) cells, able to recognize such cells as non-self.

Adaptive immunity, both humoral and cellular, is formed later than innate one. Antibodies have a neutralizing effect on viruses, while they are still outside target cells. Cytotoxic T lymphocytes (CTLs) may recognize infected cells and kill them by apoptosis. They are, however, usually too few, to totally eliminate viral infection. Resistance to the progression of HIV/AIDS infection in some individuals is due to the presence of particular HLA alleles, which influence the induction of CTLs directed versus dominant epitope (p24 Gag) of virus. Besides, most viruses possess various escape mechanisms from immune response. Thus, efficient battle with viral infections still remains a formidable challenge.

Key words: *cytokines, pattern recognition receptors, inflammasome, NK cells, antibodies, CTLs.*

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General features of viral infections

Viruses as obligatory parasites hidden in cell interior or even incorporated in the cell genome pose a major challenge to the host immune system. Their size allows them to penetrate virtually all regions of the body. The speed of viral replication exceeds markedly any defense possibilities of specific immune response. Moreover, most of viruses possess several means allowing them to evade recognition and to escape from effector mechanisms of the host. They include molecular mimicry i.e. total or partial homology of viral epitopes with those of the host. Moreover, several viruses produce various molecules preventing their recognition or resulting in the inactivation of potential antiviral agents. For example, pox viruses produce soluble interferon receptors, what results in the abolition of interferon antiviral activity. Herpes viruses secrete homologues of some cytokines such as vIL-10 (interleukin 10), and vIL-6. The same viruses produce chemokine homologues resulting in the disrupting of chemokine network essential for cell migration toward the site of infection. Antigenic variation due to mutations and various inaccuracies on genetic level seen in HIV, HCV, influenza viruses and other viral infections results in the failure of the recognition by preformed antibody and T cells, of newly synthesized viral antigens [1].

Nevertheless, in spite of their potency, the speed of spreading and enormous number of viral bodies, viruses did not conquered neither the animal kingdom nor human beings. It was because in the long course of evolution all

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living creatures, both, invertebrates and vertebrates evolved various strategies of antiviral defense, initially based on the mechanisms of innate immunity and later including means of adaptive one or both, as it is evidenced in higher animals and man.

Pivotal factors of innate immunity relevant for antiviral defenses

Innate immunity is a evolutionally conserved way of protection, that is present already in the most primitive *eukariota*. It is evident already after birth and manifested almost immediately following microbial invasion. Agents of innate immunity may be subdivided on humoral, cellular ones and various cell receptors. Out of humoral agents, interferons (IFNs) belonging the cytokine family, are definitely the most important in antiviral defense. They are subdivided on IFN type I and type II, but direct antiviral activity is limited to the former. Type I IFNs are produced by various cells, when appropriately stimulated. They bind to IFN responding cells via IFN receptors. Following cell entry IFNs activate several genes which encode antiviral proteins, some of them possessing enzymatic function. The latter include protein kinase that blocks viral protein synthesis and 2'5'oligoadenylate synthetase degrading viral mRNA. Moreover IFN induces in infected cell the synthesis of several proteins, including Mx ones, which inhibit viral transcription of RNA viruses [2].

An important role in antimicrobial defense is played by proinflammatory cytokines. Apart from their direct action, they activate granulocytes and macrophages that leads to the release of toxic oxygen and nitrogen intermediates. Some cytokines, such as IL-1β and IL-18 are produced by monocytes/macrophages as inactive precursors and require enzymatic cleavage to become bioactive ones. They have crucial impact on various aspects of inflammatory activity (Fig. 1). The cleavage of precursors is usually done by intracellular enzyme caspase I, from cysteine protease family. Activation of caspase is regulated by protein complexes called inflammasomes [3]. The latter are formed intracellularly from NLR segments. NLR – NOD-like receptors belong to pattern recognition receptor (PRRs) family and present in a cell interior of most of cells. Stimulation of inflammasomes leads to the transformation of procaspase into active form able to cleave the inactive precursors of IL-1β and IL-18 into bioactive cytokines. Inflammasomes may be stimulated by both external agents such as bacterial ligands, viral RNAs and internal ones such danger-associated molecular patterns (DAMPs) such as apoptotic remnants or other products of metabolism [4]. There are known at least four inflammasomes that differ in the structure and activating ligands. One of the best known inflammasomes is NLRP3 (also known as NALP3) that has been found to mediate immunity against influenza A virus. It is composed of NLR protein (NLRP3) the adaptor molecule apoptosis – associated speck-like protein (ASC) and pro-caspase-I. Influenza A virus, following the entry to a cell is recognized by at least three distinct mechanisms. In plasmocytoid dendritic cells (pDC) ssRNA of virus released in acidified endosomes is recognized by Toll-like receptor 7 (TLR-7). Another pattern recognition receptor (PRR) cytosolic RIG-1 senses influenza virus through recognition of 5'-triphosphates on viral genomic ssRNA [5, 6]. The third mechanism involves Toll-like receptor 3 (TLR-3) able to recognize double-stranded RNA (dsRNA) in the endosomes. The activation of NLRP3 inflammasome is a complex process with the engagement of at least two signals. The first one, following the recognition of virus by TLRs, mainly TLR7, is triggered by viral genomic RNA. It leads to the activation of genes that encode pro-IL-1β, pro-IL-18 and NLRP3. The second signal for inflammasome activation is multifactorial and includes the participation of several agents such efflux of ions K^+, H^+), lysosomal activation, activity of cathepsin B, ROS (reactive oxygen species) and other still unknown ones [7, 8] (Fig. 2).

From the study in mice it seems evident that inflammasome activation is required to generate adaptive immune responses. Virally infected caspase-1–/– mice, but not NLRP3–/– ones were not able to activate virus specific CD4 and CD8 T cells, and to secrete nasal IgA or serum IgG immunoglobulins. It appears that NLRP3 is crucial for the inflammasome activation in cells of the immune system such as macrophages and dendritic cells. NLRP3 deficiency apparently does not impact the induction of specific immunity by other cells of the immune system [9].

Natural killer cells – this topic has been recently discussed by us in relation to hepatitis C infection [10]. In the early phase of most viral infections the number and activity of NK cells is dramatically increased. It holds true for

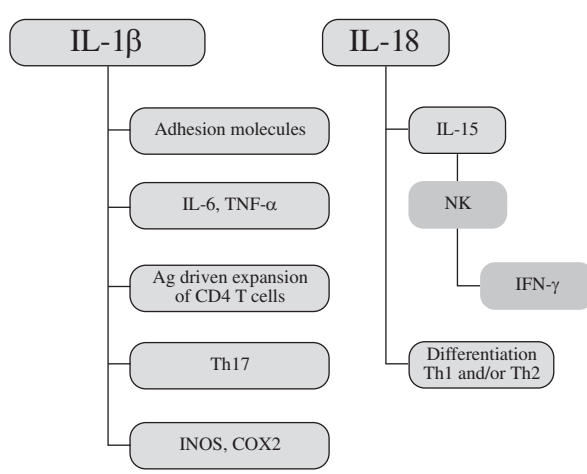

Fig. 1. Pathogenic significance of IL-1β and IL-18 in innate immunity

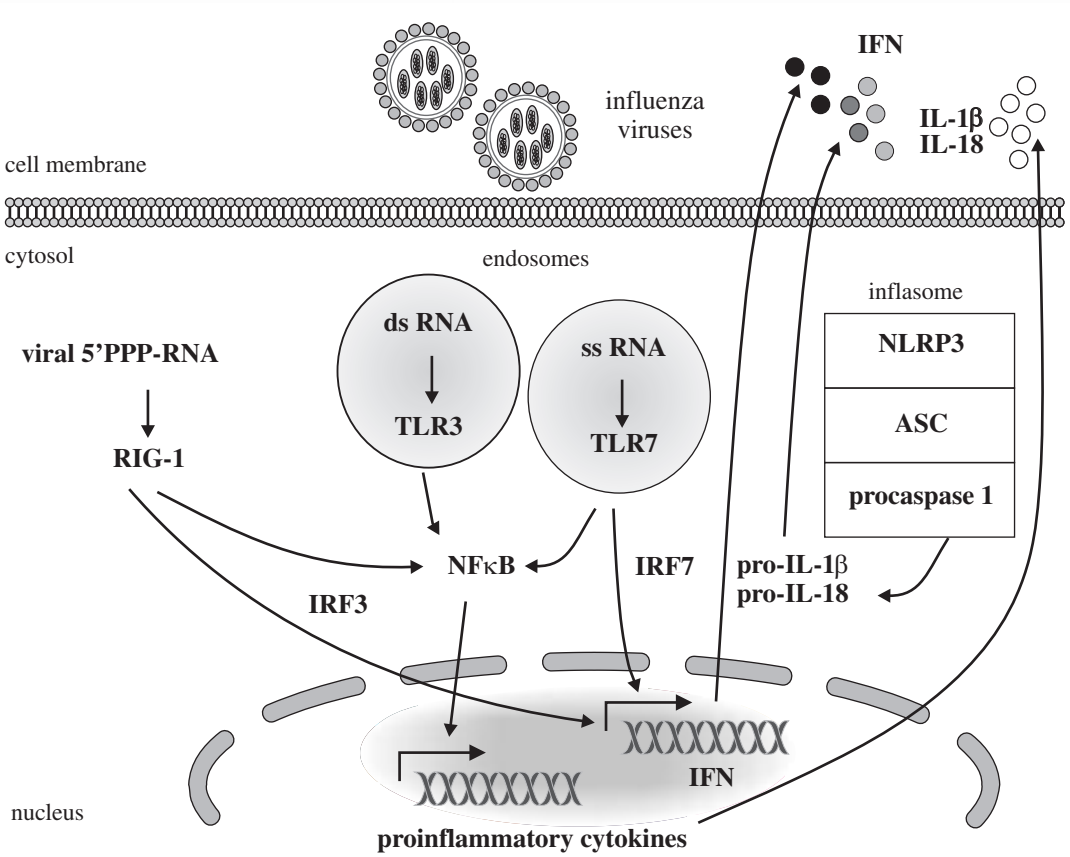

Fig. 2. Recognition of pathogen and the role of inflammasome in the case of influenza A virus infection (according to Pang and Ivasaki [6] modified)

HIV infection, in which functional NK cells are apparently derived from pluripotent stem cells [11]. An increase of NK cells in the blood of patients in early stage of infection is not associated with their rise in lymph nodes. Moreover, lymph node NK cells expressed decreased inhibitory receptors and had elevated TRAIL [12]. It might explain, why lymph nodes become HIV reservoir. In the course of HIV infection patients show gradual loss of NK cells, correlated with disease progression. Apart from CD56+ bright and CD56+ dim cell subsets, there is an increased percentage of CD56– negative and Siglec-7 (neg) NK cells, lacking CD94 molecules, expressing low cytotoxic potential and poor IFN-γ production [13]. These unsatisfactory features may be partly corrected by HAART therapy [14, 15]. Relatively little is known about the role of NK cells in other viral infections. In experiments on purified human fibroblasts infected with human cytomegaly virus (HCMV) it has been shown that NK cell protease from granzyme M inhibits CMV replication by cleavage of viral phosphoprotein 71 [16]. Novel aspect of NK cell function appears their recently found ability to transfer specific immunity to naïve host. Moreover, NK cells seem to possess memory resembling that of T cells. This phenomenon has been evidenced in murine cytomegaly (mCMV). It was found that Ly49H receptors of NK cells recognize m157 glycoprotein of mCMV. Following infection with mCMV Ly49H+ NK cells become expanded and inhibit mCMV spreading. They can be also adoptively transferred to another naïve recipient and again undergo expansion following mCMV infection [17]. Recently such NK cells bearing memory have been shown in mice in other viral infections such as influenza and vesicular stomatitis virus [18]. There is no so far, whatsoever, information about memory NK cells in humans [19]. Nevertheless, the difference between innate and adaptive immunity became less sharp, at least in the case of viral infections.

Adaptive immunity in viral infections

Adaptive immunity is definitely the most efficient self-made means to clear viral invasion due to its specificity. Both, humoral and cell-mediated arms of this immunity are relevant, but operate in distinct stages following virus entry.

Antibodies of any class if present, may neutralize viral particles until they enter target cells. It may happen both, on mucosal surfaces and in the blood. Antibody reactivity may trespass species barrier, because it was shown that antibodies against swine influenza virus may neutralize human influenza A/H1N1 [20]. Antibodies may act in concert with complement, leading to destruction of viral bodies, but in general, the role of the latter is relatively low in viral infections. Possible cause of this phenomenon is due to the various viral mechanisms aimed to evade the initiated complement cascade. For example, herpes simplex viruses (HSV) produce two surface glycoproteins gE and g1, that bind to Fc fragment of IgG antibody. Such bridging excludes the attachment of early complement components to Ig what results in the prevention of generation of complement cascade [21]. Apart from eliminating free viral particles, antibodies may recognize viral antigens expressed on the surface of infected cells and destroy them in the association with complement. This is relatively rare, because the most of eukaryotic cell types are resistant to complement action. More likely is ADCC reaction in which antibody coated infected cells are recognized by virtue of Fc fragment–Fc receptor expressed by a number of cells such as NK cells macrophages, granulocytes and other, what result in the target cell cytotoxicity. The role of passively acquired neutralizing antibodies has been questioned because it was found that they do not protect of infants from HIV-1 infection [22]. Moreover, in adult patients cross-reactive neutralizing antibodies were associated with lower CD4(+) counts, but did not protect from HIV-1 disease progression [23]. On the other hand autologous patient NK cells effectively degranulated granzyme B, activated by HIV-specific antibodies directed toward envelope proteins [24]. Thus, humoral immunity in HIV/AIDS remains elusive so far.

Specific cell-mediated immunity appears to be the most relevant in the control of viral infections. Viruses after reaching their targets are hidden in cells and it is now evident that such cells have to be sensed and destroyed. It can only be done by T cell receptor (TCR) able to recognize the viral peptide exposed on the surface of infected cell. Both main T cell subsets $CD4^+$ and $CD8^+$ are engaged in antiviral response, but they use distinct armamentarium. $CD4^+$ cells secrete mainly cytokines with antiviral effect, while $CD8^+$ ones are considered main effectors, using such means as perforins, granzymes, some cytokines or Fas-Fas L system. In spite of great potential of cell-mediated adaptive immunity, its real efficiency in the control of the majority of viral infections is relatively poor. There are several reasons for this. It has been calculated that the number of cytotoxic virally sensitized $CD8^+$ T cells (CTL) in HCV infection is in the range 1-2% [25]. In early AIDS/HIV the disease is smoldering for some time, but later the destruction of $CD4^+$ T cells leads to its rapid progression, presumably due to the lack of help for CTL. In several viral infections the time factor plays crucial role. The speed of viral proliferation significantly exceeds the induction and proliferation of virus – sensitized CTLs. Moreover, viruses produce several factors aimed to dampen specific T cell immunity. In influenza A infection adaptive immunity is significantly influenced by the number, quality and activation of dendritic cells (DC) in lung parenchyma. Following direct infection and/or phagocytic engulfment of cell-free virions migrant DC ($CD103^+$, $CD11b^+$) acquire viral antigens and transport them to draining lymph nodes. There takes place the antigen presentation to $CD8^+$ T cells by DC. At the same time pDC produce type I IFN following capture of viral antigen. Apart from beneficial role linked to antiviral IFN activity, they were found to be detrimental to enhance mortality of specific $CD8^+$ T cells in lethal influenza infection [26]. $CD8^+$ T cells destroy virus-infected cells in a specific manner via TCR engagement [27]. The destruction involves also infected alveolar type II pneumocytes, constitutively expressing MHC class II antigens. Besides, T cells, both $CD8^+$ and $CD4^+$ produce proinflammatory cytokines, attracting neutrophils, monocytes, all together leading to pulmonary injury during influenza infection. This is only partly inhibited by anti-inflammatory cytokine such as IL-10, produced mainly by $CD8^+$ T cells [17]. Thus, it appears that in the case of influenza it is hard to find the balance between beneficial and detrimental effects of adaptive immunity.

In HIV/AIDS infection the role of adaptive immunity is still far from clear. The robust $CD8^+$ CTL response is able significantly reduce viral load in early stage, but appearance of mutant variants leads to chronic stage and later overt AIDS. In experiments in SIV-infected macaques it was found that that significant reduction of viral load was achieved at effector CTL – target cell ratio > 100 [28]. In human HIV/AIDS CTL response is in most cases insufficient to inhibit progression of disease. In some individuals, however, so called "elite suppressors" are able to maintain $CD4^+$ T cells at reasonable level and keep viremia at extremely low values. It was noted that some HLA class I specificities are over-represented in those people namely HLA B*27 and HLA B*57 [29]. It was shown, that $CD8^+$ T cell reactivity of the individuals possessing above mentioned alleles is directed versus immunodominant HIV epitope p24 Gag (aminoacid residues 262-272), so called KK10 [30, 31]. This prevents virus replication and provides significant immune control provided, that there will be not the mutation within KK10 or blocking access of CTLs to this epitope, so called "anchor mutation". In patients devoid of protective alleles prevalence of mutations appears the highest in conserved residues of Gag, Nef and Pol of HIV. The explanation of the above mentioned findings has been elusive, because other HIV-infected individuals lacking the above listed alleles were found to be "elite suppressors" or non-progressors [32].

By and large, these data suggest that precise determination of aminoacid content of viral epitopes and recognizing them HLA-I alleles is probably the only way for the induction of efficient immune response to this virus.

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