ANTIVIRAL IMMUNE RESPONSES: -AN OVERVIEW-

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ABSTRACT

An effective immune response against viral infections depends on the activation of innate immunity, Tcell immunity and humoral immunity. But in some cases, infections persist and natural host immunity becomes insufficient.

This work summarizes the most relevant findings on the molecular mechanisms and signaling pathway of antiviral immunity responses and describes the specific mechanisms implicated in the case of some viruses causing a persistent infection: HSV-1 and HPV. Then we'll give examples of these persistent infections with their physiopathogenesis. The findings in molecular mechanisms of antiviral immunity may be exploited to develop new therapeutic modalities for treating persistent virus infections.

Keywords: Immune response; Persistent infections; Signaling pathways; Viral infections.

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INTRODUCTION

Viruses can cause acute and chronic infections. In acute virus infections the virus is cleared from the body in a short period. In some cases, an acute infection is followed by persistence of the virus in the host.(1)Herpes simplex virus is an example of a virus causing a persistent infection, due to the ability of the virus to hide in neurons. Often, these types of persistent infections do not cause any symptoms in healthy hosts. Chronic infections are a type of persistent infection usually caused by an inefficient immune response of the host, leading to long-lasting symptoms like some HPV infections. HPV is also frequently associated with cancers arising from mucosal epithelium. Viral persistence and even progression through precancerous lesion stages are prerequisites for HPV-associated cancer and reflect the inability of immune mechanisms to clear infections and eliminate abnormal cells in some individuals(2).

This work summarizes the most relevant findings on the molecular mechanisms of antiviral immunity and the specific mechanisms implicated in the case of some viruses causing a persistent infection: HSV-1 and HPV.

ANTIVIRAL INNATE IMMUNE RESPONSES

In case of viral infection, the innate immune response is initiated by detecting viral DNA and RNA with a set of pattern recognition receptors (PRRs) that are the TLRs family (toll-like receptor), the retinoic acid-inducible gene I (RIG-I)-like receptor (RLR) family, as well as cytosolic DNA sensors like cyclic GMP-AMP (cGAMP) synthase (cGAS), IFI16 and DDX41(3)(4). After recognition of viral nucleic acids, these PRRs trigger the production of pro-inflammatory cytokines, chemokines and type I interferons (IFNs), which induce antiviral proteins synthesis, infected cells death and activate the adaptive immune response.(5)(6)

TLR:

TLR3, TLR7, TLR8 and TLR9 detect endosomal nucleic acids derived from the enclosed microbes and infected apoptotic cells. While TLR9 detects unmethylated CpG DNA species, TLR3 and TLR7/8 recognize double-stranded RNA (dsRNA) and single-stranded RNA (ss RNA), respectively (7) . After ligand binding, TLRs form a signaling platform in which separate Toll/interleukin-1

receptor (TIR) domain containing adaptors are envolved. For example, TLR3 signals via TIR-domain-containing adaptor protein inducing interferon beta (TRIF), and TLR7/8/9 rely on myeloid differentiation factor-88 (MyD88) (8). For the TRIF-dependent pathway, the ubiquitin E3ligase TNF receptor-associated factor 3(TRAF3) is recruited and hence activates TANK-binding kinase-1 (TBK1) and Inhibitor-κB kinase ε (IKKε) (9). Activated TBK1 and IKKε then phosphorylate IFN regulatory factor (IRF) transcription factors IRF3 and IRF7 drive the expression of type I IFNs(10). For the MyD88-dependent pathway, TRAF6 is engaged to the MyD88 signal platform, leading to the activation of the kinase complex composed of IKKα and IKKβ. Activated IKK complex induces NF-κB activation, which induces the expression of pro-inflammatory cytokines such as TNF, IL-6 and IL-12 (8) (Fig. 1). In addition, Myd88 also facilitates IFN-α production by promoting IKKα-dependent IRF7 phosphorylation, which is particularly important for the antiviral activities of plasmacytoid dendritic cells (11)(12).

RLR:

In addition to the endosomal detection by TLRs, viral RNA in the cytosol is also recognized by RLRs, such as Retinoic acid-inducible geneI (RIG-I), melanoma differentiation-associated protein 5 (MDA5) and laboratory of genetics and physiology 2 (LGP2)(13). RLRs initiate antiviral immune responses in most cell types, which is in contrast withTLR3 and TLR7, which havemainly a phagocyte-restricted expression(14). By detecting the specific molecular characteristics of viral RNA pathogens such as 5triphosphate for RIG-I and long double-stranded segments for MDA5, these RLRs translocate to mitochondria and interact with the mitochondrial antiviral-signaling protein (MAVS) (15)(16). This interaction causes the aggregation of MAVS to form a huge prion-like protein complex for TRAF3 and TRAF6 engaging, which transmit signals to TBK1-IRF3 and IKKα/β- NF-κB pathways (5)(17)

Cytosolic DNA sensors:

Cytosolic viral DNA is mainly recognized by cyclic GMP-AMP (cGAMP) synthase (cGAS) that contains a nucleotidyl transferase (NTase) domain. After DNA binding, cGAS synthesizes a second messenger molecule, cyclic GMP-AMP (c GAMP), which then activates the stimulator of interferon genes (STING) (18)(19). STING is an endoplasmic reticulum adaptor protein that plays an essential role upstream of TBK1 in the cytosolic viral DNA sensing pathway (20).

Although some other proteins like IFI16, DDX41 and Mre11 are also reported to be receptors mediating DNA-induced IFN-β production in a STING-dependent manner, only cGAS, which enzymatically generates cGAMP as a second messenger that activates STING, provides a clear molecular mechanism for DNA-stimulated IFN-β production (21). **Fig.1**
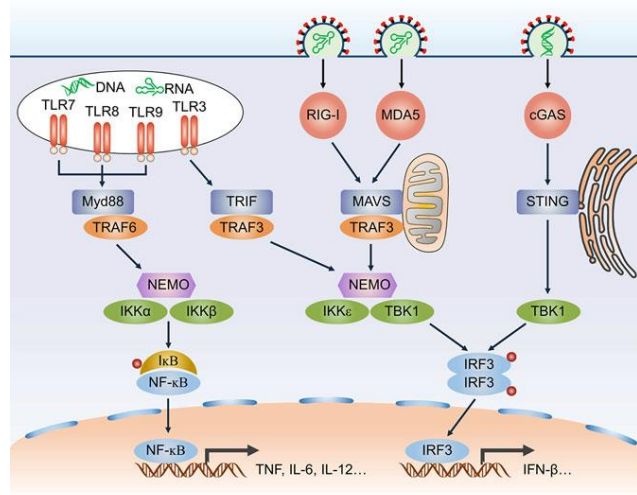

Fig 1. Interferon I signaling pathways (22)

However, a balanced production of IFNs and activation of antiviral responses is required. Posttranslational modifications (PTMs) are crucial for this immune homeostasis in antiviral responses.

PTMs such as phosphorylation have been extensively studied and others such as methylation, acetylation, SUMOylation, ADP-ribosylation and

glutamylation are being increasingly implicated in antiviral innate immunity(23)

Antiviral proteins:

By secretion of IFN, the response can be amplified and spread to surrounding uninfected cells through the JAK-STAT signaling pathway, and thereby activate hundreds of interferon stimulated genes (ISGs), most of which have deep antiviral effects, such as degradation of viral nucleic acids or inhibition of viral gene expression (24)

Defensins in viral infections:

Defensins have a direct antiviral activity in cell culture, with varied mechanisms for human viruses.In addition, defensins have potent immunomodulatory activity that can alter innate and adaptive immune responses to viral infection. But the major area of investigation that continues to lag is the link between the effects of defensins in cell culture models and viral pathogenesis in vivo(25)

Natural Killers in viral infections:

Natural Killers have a direct cytotoxicity, antibody dependant cytotoxicity (ADCC) and produce a wide range of cytokines and chemokines regulating both innate and acquired immune responses(26)

T cell antiviral immunity

The adaptive immune response is important in limiting and clearing viral infections. The humoral immune response consists of antibodies specific for the virus. But, if these antibodies are ineffective, viruses are able to infect host cells and can only be cleared by the cell immune response.
Once a virus infects a cell, the virus will use the protein-synthesis mechanisms of the host cell to synthesize its own proteins. During this process, some of the newly synthesized proteins will be degraded into peptide fragments and, if they have sufficient binding affinity, bind to MHC class I molecules. These MHC class I-peptide complexes will then be presented on the cell surface of an infected cell and activated CD8C T cells, specific for the peptide, can recognize the MHC class I-peptide complex and induce apoptosis of the infected cell by releasing cytotoxic granules. Activation of these CD8C T cells occurs in the draining lymph nodes,where antigen-presenting cells (APCs), such as dendritic cells (DCs), and naïve T cells encounter each other. In these lymph

nodes, DCs and CD4C T cells provide the co-stimulation necessary for proper activation of CD8C T cells. (**Fig.2**)
During the initial phase of a viral infection, the number of CD8 C T cells increases significantly. Priming of these naïve T cells will not only occur through the classical pathway directly leading to presentation of peptides on MHC class I molecules, but also through cross-presentation. Cross presentation enables the presentation of viral peptides, taken up from extracellular sources, on MHC class I molecules. Several cell types can cross-present antigens *in vivo,* including professional APCs such as macrophages and DCs. CD8C T cells, activated either through the classical or cross- presentation pathway, induce apoptosis of virus-infected cells by the release of cytotoxic granules and the production of TNF-alpha and IFN-gamma. The cytotoxic granules contain perforins, granzymes, and granulysin. Perforins aid in delivering contents of granules into the cytoplasm of the target cell. Granzymes, such as granzyme B, and granulys inactivate apoptosis of the target cell. TNF-alpha can interact with the TNFR-I receptor, which induces apoptosis of infected cells. IFN-gamma is an important cytokine in antiviral immune response. It can induce an antiviral state in uninfected cells and enhance the cytotoxic function of CD8C T cells. By the classical antigen presentation pathway or by the cross-presentation pathway, any virus can be presented on MHC class I and MHC class II and there for stimulate antiviral responses by both CD8C T cells and CD4C T cells, respectively, leading to a broad cellular response to infection. After infection, some of these activated Tcells will develop into memory T cells. So if a secondary infection occurs, these cells can rapidly mature into effector cells and respond to infection. Antigen-presenting cells that reside at the site of infection, can take up viral particles or remnants of virally infected cells from extracellular sources, and present them on MHC class II molecules. Subsequently, CD4C T cells recognizing peptides in the context of MHC class II will be activated. These activated CD4C T cells are capable of producing a wide range of cytokines and chemokines and can even have cytotoxic functions. Based on cytokine production, CD4C T cells can be divided into several subgroups: Th1, Th2, and Tregs are the most important.Th1 cells produce IFN-gamma. Th2 cells producemainlyIL-4, IL-5, and IL-13. The Treg cells produce IL-10 and TGF-b, and have mainly regulatory tasks such as dampening effector functions and limiting immunopathology. In addition to their effector functions, activatedCD4C T cells can provide help

to CD8C T cells by CD40- CD40L interaction, which induce regulation of ligands, such as CD 80 and CD 86 on DCs. These ligands interact with

CD28 on naïve T cells, providing a co-stimulatory signal to activate CD8CT cells. The mechanism by which CD4C T cells can help CD8C T cells.(27)
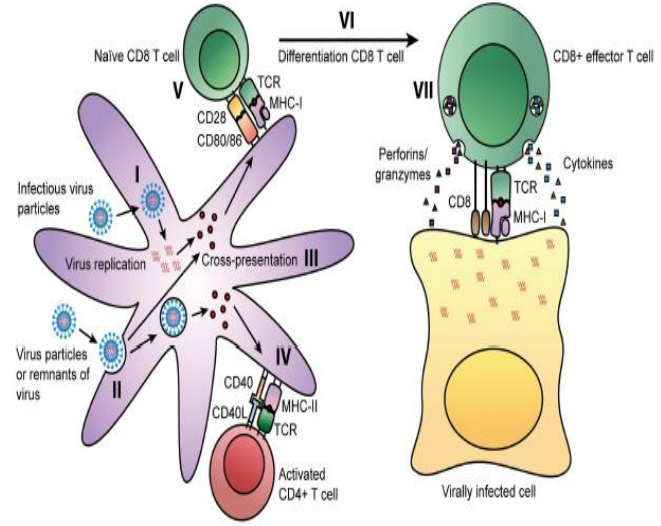

Fig2. Pathways of T cell mediated antiviral immunity (27)

Humoral antiviral immunity

Neutralizing antibodies (NAbs) prevent viral entry by binding to regions on the virus involved in the entry process to host cells. So, in the case of viral infections, broadly neutralizing antibodies (bNAbs) can recognize a wide variety of viral glycoproteins (GPs) on the surface of enveloped viruses or the protein shell of non enveloped viruses. bNAbs inhibit infection through blocking binding to cell surface receptors and inhibition of the viral fusion machinery for enveloped viruses or penetration for non enveloped viruses. In vitro studies with bNAbs are carried out using susceptible cells and viruses. In some cases, it is still unclear if binding to any site on a functional viral spike is sufficient to prevent infection or if neutralization requires binding to specific critical sites on the viral surface.In some special cases of neutralization, antibodies target host molecules that are displayed either on the surface of viral particles, such as human leukocyte antigen and ICAM-1 molecules or viral receptors on host cells. Only a fraction of memory B-cells contribute to the pool of bNAbs as a majority of antibodies are made toward denatured or internal proteins. B cells can also display regulatory functions to control excessive inflammation, mainly through interleukins secretion (28)

IMMUNITY AGAINST HSV-1

PRR and type I IFN signaling pathway:

The type I IFN signal pathway is activated upon recognition of viral components by pattern-recognition receptors (PRRs).
PRRs include several types of the Toll-like receptor (TLRs) family and certain DNA and RNA sensors. TLRs are the first to be discovered and identified PRRs that detect pathogen-associated molecular patterns. TLR3, TLR7, TLR8, and TLR9 locate on the endosomal membrane and detect nucleic acids. RIG-I-like receptors (RLRs), including retinoic acid-inducible gene I (RIG-I) and melanoma differentiation-associated gene 5 (MDA5) and other RNA receptors can detect distinct RNA structures, while cytoplasmic DNA is detected by recently discovered DNA sensors, including cyclic GMP-AMP synthase (cGAS), IFN-γ-inducible protein 16 (IFI16), DEAD box polypeptide 41 (DDX41), DNA-dependent activator of IRFs (DAI) and several proteins involved in the DNA damage response.
Moreover, viral infection also induces the formation of cytoplasmic granules known as stress granules (SGs). Evidence shows that there is a strong correlation among SG formation, type I IFN production and viral propagation, which suggests that SGs could induce innate responses and restrain viral infection (29)

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T cell immunity against HSV-1

HSV-1 can cause potentially blinding recurrent corneal herpetic disease. HSV-1 establishes latency within sensory neurons of trigeminal ganglia (TG). after the clearance of primary HSV-1 infection by T cell immunity, a pool of memory CD8+ T cells develops and recirculates between secondary lymphoid organs and peripheral tissues, whereas a different pool of memory CD8+ T cells develops and resides within peripheral tissues. TG-resident CD8+ T cells play a critical role in preventing HSV-1 reactivation from latently infected sensory neurons of TG and subsequent recurrent corneal herpetic disease(30)

Antibodies

Neutralizing antibodies can prevent HSV infection by blocking virus binding to a specific receptor or to more than one receptor; therefore, antibodies may only protect some cell types from HSV infection. For instance, antibody that blocks HSV binding to nectin-1 may neutralize HSV infection of neurons but not lymphocytes. In addition, antibodies also mediate other antiviral activities like ADCC(31)

EXAMPLE OF A HSV-1 PERSISTENT INFECTION: HERPES SIMPLEX ENCEPHALITIS

Herpes simplex encephalitis is an acute or subacute illness that causes both general and focal signs of cerebral dysfunction. It is a consequence of mutations in TLR3pathway genes (autosomic recessif (AR) or autosomic dominant (AD) transmission): UNC93B1 (AR), TRIF (AR et AD), TBK1 (AD), TRAF3 (AD) et IRF3 (AD)(32)(33) (**Fig.3**)

UNC93B1 is a gene that encodes a protein that is involved in innate and adaptive immune response by regulating toll-like receptor signaling. The encoded protein traffics nucleotide sensing toll-like receptors to the endolysosome from the endoplasmic reticulum) (34) .
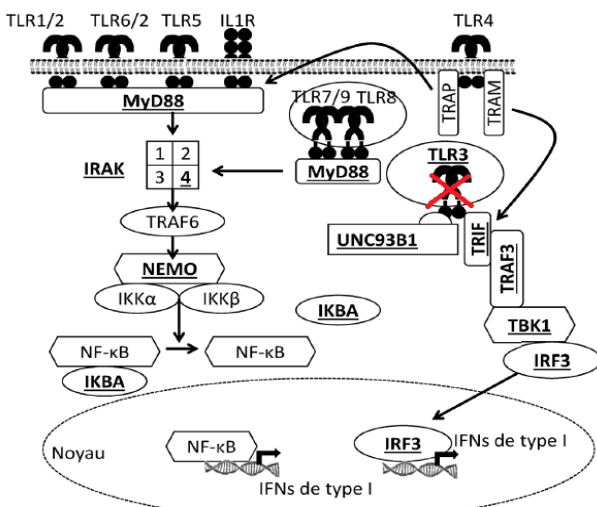

Fig.3: BlockingTLR 3 signaling pathway in Herpes simplex encephalitis

IMMUNITY AGAINST HPV

PRR and type I IFN signaling pathway:

PRRs are crucial in the induction of innate immune responses; viral nucleic acids can be detected by TLR3, TLR7, TLR8, and TLR9.
Keratinocytes (KC) also express the cytoplasmic dsRNA sensors protein kinase R (PKR), retinoic acid-inducible gene I (RIG-I), and melanoma differentiation-associated gene 5 (MDA5)(35) . Expression of dsRNA sensors is upregulated in KCby type I and II IFNs or poly(I·C).

PRR activation induces cytokine secretion both directly and through autocrine and paracrine cytokine signaling pathways. Cytokines and chemokines (chemotactic cytokines) can suppress viral gene expression, create an inflammatory microenvironment, and recruit both innate and adaptive immune cells. (IL-1alpha), IL-1beta, IL-6, IL-10, IL-12, CCL3, CCL5, CXCL8, tumor necrosis factor alpha (TNF-alpha), and IFN-gamma. IFN gamma expression in natural killers and activated T cells can be stimulated by IFN alpha, IL-12, and IL-18 produced by infected cells, activated dendritic cells (DC), or macrophages(2)

Defensins

Defensins can block HPV infection and influence adaptive immunity by recruiting immune cells. Greater expression of beta-defensins and alpha-defensin 5, has been reported in HPV-associated genital warts than in uninfected tissue(36)(37)

T Cell-mediated immunity

Activated KC amplify cell-mediated immune reactions. Resting KC express low surface levels of CD40 and ICAM-1, moderate levels of MHC-I, and high levels of IFN-gamma receptor (IFN-gammaR). Activation of KC by IFN-gamma secreted by NK cells or activated T lymphocytes (B) increases surface expression of MHC-I, MHC-II, CD40, and ICAM-1 and induces expression of CXCL9, CXCL10, and CXCL11, chemokines that attract activated Th1 cells (C). KC that present HPV antigens via MHC-II may interact with Th1 cells (D). Higher surface expression of ICAM-1 and CD40 improves adhesion and costimulation. Ligation of CD40 on KC by CD40 ligand on Th1 cells further increases ICAM-1 and stimulates further cytokine and chemokine expression to activate and recruit additional immune cells (E).(2) (**Fig. 4**)
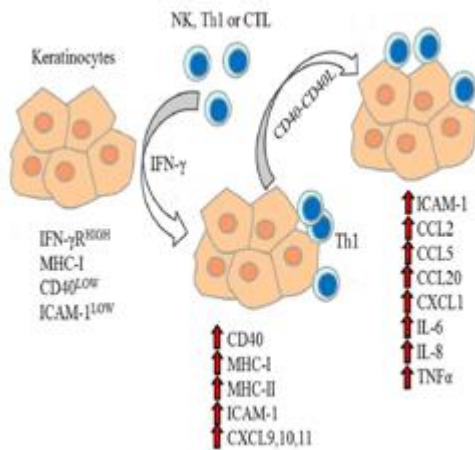

Fig.4 Amplification of cell mediated immune reactions by activated keratinocytes(2)

B cell mediated immunity

B cells play an important role in anti-tumor immunity associated with HPV. Indeed, in B cell-deficiency, the tumor growth is impaired due to a strong T cell dependent anti-tumor response. B cells expressing PD-L1, CD39 and Ly6A/E markers accumulate in the tumor draining lymph node which can directly impact T cell immunity (in an experimental model). B cells can also promote tumor immunity or display regulatory functions to control excessive inflammation, mainly through IL-10 secretion.(38).

The humoral immune response against HPV capsid proteins is not a protective response, but these antibodies can be used as markers to determine the stage of the infection and/or the stage of the cervical lesion (39).

EXAMPLES OF HPV PERSISTENT INFECTIONS:

WHIM syndrome

The wart, hypogammaglobulinemia, infection, and myelokathexis (WHIM) syndrome is associated with inherited gain-of-function mutations in the *CXCR4* gene that encodes a receptor for the CXCL12 chemokine (32). Binding of CXCL12 to CXCR4 triggers typical activation of Gαi protein-dependent pathways of a chemokine receptor that are regulated in a timely manner by β-arrestins, which preclude further G protein activation and also link CXCR4 to additional signaling pathways involved in cytoskeleton reorganization and anti-apoptotic signaling. In WHIM, the CXCL12/CXCR4 signaling pathways manifest by abnormally increased and prolonged G protein- and β-arrestin-dependent responses associated with an impaired desensitization of CXCR4. Such dysfunction are responsible for the characteristic panleukopenia.(40)

The tendency of patients with WHIM syndrome to develop human papilloma virus (HPV) infections seems to be disproportional, when compared to susceptibility to other viral infections. As wart keratinocytes up-regulate CXCR4 in both healthy skin and in WHIM patients, increased CXCL12signalling is observed in HPV infected dermis (41), which is a host factor in facilitating HPV infection and could explain this pathognomonic presentation. Recent studies suggested that plasmacytoid dendritic cells (pDCs) might have a protective role against HPV by secreting the antiviral cytokine interferon (IFN) α. This function was investigated in patients with WHIM syndrome who have a decrease in all subsets (myeloid and plasmacytoid) of dentritic cells in comparison to healthy persons. Sections of warts from WHIM patients did not have dermal pDCs infiltrates and did not express the antiviral proteins (that usually results from IFN-α secretion), suggesting that pDCs cannot migrate to the skin or

defend the host against HPV infection in these patients (42)

HPV and Cancers

Persistence of some HPV types causes ~5% of human cancers in immunosuppressed individuals. Interaction between viral and host proteins might lead to viral persistence and pathogenesis.
It was found that patients who are immunosuppressed as a consequence of mutations in the *CXCR4* gene encoding for the receptor of the CXCL12 chemokine have a cell hyperproliferation and stabilization of HPV viral oncoproteins expression at the expense of virus production. This identifies CXCR4 as an important gatekeeper of kératinocytes proliferation and as a new susceptibility factor in HPV pathogenesis and may be translated
into anti-viral and anti-cancer strategies(40)

CONCLUSION:

In summary, viral components can interfere at multiple steps of the host antiviral defense. The innate immunity signaling pathway is particularly relevant because it is in the first line toward the clearance of viruses infections.
 The findingsin molecular mechanisms of antiviral immunity may be exploited to develop new therapeutic modalities for treating persistent virus infections.

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