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Review article

Innate and intrinsic antiviral immunity in skin

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ABSTRACT

As the body's most exposed interface with the environment, the skin is constantly challenged by potentially pathogenic microbes, including viruses. To sense the invading viruses, various types of cells resident in the skin express many different pattern-recognition receptors (PRRs) such as C-type lectin receptors (CLRs), Toll-like receptors (TLRs), nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs), retinoic acid-inducible gene I (RIG-I)-like receptors (RLRs) and cytosolic DNA sensors, that can detect the pathogen-associated molecular patterns (PAMPs) of the viruses. The detection of viral PAMPs initiates two major innate immune signaling cascades: the first involves the activation of the downstream transcription factors, such as interferon regulatory factors (IRFs), nuclear factor kappa B (NF-κB) and activator protein 1 (AP-1), which cooperate to induce the transcription of type I interferons and pro-inflammatory cytokines. The second signaling pathway involves the caspase-1-mediated processing of IL-1β and IL-18 through the formation of an inflammasome complex. Cutaneous innate immunity including the production of the innate cytokines constitutes the first line of host defence that limits the virus dissemination from the skin, and also plays an important role in the activation of adaptive immune response, which represents the second line of defence. More recently, the third immunity "intrinsic immunity" has emerged, that provides an immediate and direct antiviral defense mediated by host intrinsic restriction factors. This review focuses on the recent advances regarding the antiviral immune systems, highlighting the innate and intrinsic immunity against the viral infections in the skin, and describes how viral components are recognized by cutaneous immune systems.

Contents

Abbreviations: AIDS, Acquired immune deficiency syndrome; AIM2, Absent in melanoma 2; AMPs, Antimicrobial peptides; APCs, Antigen presenting cells; AP-1, Activator protein 1; APOBEC3, Apolipoprotein B mRNA-editing, enzyme-catalytic, polypeptide-like 3; ASC, Apoptosis-associated speck-like protein containing a caspase recruitment domain; BMDC, Bone marrow-derived DC; CARD, Caspase activation and recruitment domain; CCR5, CC chemokine receptor 5; cGAS, Cyclic GMP-AMP synthase; CMV, Cytomegalovirus; CLEC, C-type lectin-like receptor; CLR, C-type lectin receptor; DAI, DNA-dependent activator of IFN-regulatory factors; DAMP, Danger-associated molecular pattern; DC, Dendritic cell; DCIR, DC immunoreceptor; DC-SIGN, DC-specific intercellular adhesion molecule-3-grabbing non-integrin; DNA-PKcs, DNA-dependentprotein kinase; ds, Double-stranded; EBV, Epstein Barr virus; EBER, snonpolyadenylated, noncoding RNA that forms stem-loop structure by intermolecular base-pairing; ER, Endoplasmic reticulum; GM-CSF, Granulocyte macrophage colony-stimulating factor; HBD, Human β defensin; HIV, Human immunodeficiency virus; HMGB1, High mobility group box-1; HNP, Human neutrophil peptides; HPV, Human papilloma virus; HSV, Herpes simplex virus; IFN, Interferon; IL, Interleukin; IRF, Interferon regulatory factor; KSHV, Kaposi's sarcoma-associated herpesvirus; LARG, Leukaemia-associated Rho guanine nucleotide exchange factor; LCs, Langerhans cells; LTR, Long terminal repeat; MAP, Mitogen-activated protein; MAVS, Mitochondrial antiviral signaling protein; MDA5, Melanoma differentiation-associated gene 5; MDP, Muramyl dipeptide; MyD88, Myeloid differentiation protein 88; NF-κB, Nuclear factor-κB; NLR, NOD-like receptor; NLRP3, NACHT, LRR and PYD domain-containing protein 3; NO, Nitric oxide; NOD, Nucleotide-binding oligomerization domain; PAMP, Pathogen-associated molecular pattern; PBMC, Peripheral blood mononuclear cells; pDC, Plasmacytoid dendritic cells; PKR, Protein kinase R; PRR, Pathogen recognition receptor; RLR, RIG-like receptor; RIG-I, Retinoic acid inducible gene I; ROS, Reactive oxygen species; RT, Reverse transcriptase; SAMHD1, SAM domain and HD domain-containing protein 1; si, Short hairpin; ss, Single-stranded; STDs, Sexually transmitted diseases; STAT, Signal transducer and activator of transcription; STING, Stimulator of IFN genes; SYK, Spleen tyrosin kinase; TBK1, TANK-binding kinase 1; TLR, Toll-like receptor; TNF-α, Tumor necrosis factor α; TRAF, TNF receptor-associated factor; TREX1, Three primerepair exonuclease 1; TRIF, Toll/IL-1 receptor domain-containing adaptor inducing IFN; TRIM5α, Tripartite motif 5α; VSV, Vesicular stomatitis virus; VV, Vaccinia virus; VZV, Varicella zoster virus; WNV, West Nile virus.

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1. Introduction

The skin plays a central role in host defence against a broad array of potentially pathogenic microbes, including viruses. Cutaneous innate immunity constitutes the first line of host defence that limits the virus dissemination from the local sites of infection, and also plays an important role in the activation of adaptive immune response, which represents the second line of defence. Over the past decade, remarkable progress has been made towards understanding the innate immune responses, especially to viral detection. More recently, the host's third immunity “intrinsic immunity” has emerged. Unlike the innate and adaptive immune systems, intrinsic immunity provides an immediate and direct antiviral defense mediated by intrinsic restriction factors, which are mostly preexistent in certain cell types.

There are many viral skin infections, which range from the common to the rare, from the intractable to the self-healing and from those causing just local infection in the skin to those with associated systemic diseases (Table 1). To counter viral invasion, the cells resident in the skin, including keratinocytes, Langerhans cells (LCs), dermal dendritic cells (DCs), macrophages, mast cells, and fibroblasts, express many different pattern-recognition receptors (PRRs) that can detect the pathogen-associated molecular patterns (PAMPs) of the invading viruses, which in turn activate antiviral innate immune responses.

This review focuses on the recent advances regarding the host antiviral immune systems, highlighting the innate and intrinsic immunity against the viruses which are transmitted via the skin or associated with cutaneous symptoms, and describes how viral components are recognized by cutaneous immune systems.

2. Antiviral innate immunity in skin

The conserved microbial components known as PAMPs are recognized by host PRRs. Viral recognition by the innate immune system is more challenging than recognition of other pathogen classes, because any given viral protein is unlikely to be shared among diverse viruses [1,2]. However, remarkable progress has been made over the past few years towards understanding the contribution of PRRs, such as C-type lectins (CLRs), Toll-like receptors (TLRs), NOD-like receptors (NLRs), RIG-I like receptors (RLRs) and other cytosolic PRRs, to viral detection.

In various viral infections in the skin, the detection of viral PAMPs via PRRs initiates two distinct innate immune signaling cascades: the first involves the activation of the transcription factors interferon regulatory factor 3 (IRF3) and/or IRF7, nuclear factor kappa B (NF-κB) and activator protein 1 (AP-1), which cooperate to induce the transcription of type I interferons (IFNs, e.g. IFN-α and IFN-β), chemokines and pro-inflammatory cytokines (Fig. 1 and Fig. 3). Through the secretion of type I IFNs, the response can be amplified and spread to surrounding uninfected skin cells and thereby activate hundreds of IFN-stimulated genes (ISGs), most of which encode products with profound antiviral effects, such as the degradation of viral nucleic acids or inhibition of viral gene expression [3,4]. The second signaling pathway results in the formation of an inflammasome complex, which activates caspase-1, a protease which processes pro-interleukin (IL) 1-β and pro-IL-18 to generate active cytokines ready for secretion (Fig. 2). In general, TLRs and RLRs are involved in the expression of type I IFNs or proinflammatory cytokines and chemokines, whereas viral detection by NLRs leads to caspase-1-mediated processing of IL-1β. The importance of viral recognition via these PRRs and subsequent cytokines production in the skin is illustrated by the

Table 1
Representative viruses transmitted via skin or associated with cutaneous symptoms.

dsDNA viruses	
Poxviridae	Molluscum contagiosum virus
Herpesviridae	α: human Herpesvirus 1, 2, 3 (HSV-1, HSV-2, VZV)
	β: human Herpesvirus 5, 6, 7 (HCMV, HHV-6, HHV-7)
	γ: human Herpesvirus 4, 8 (EBV, KSHV)
Papillomaviridae	Human papillomavirus (HPV) 1, 2, 3, 4, 5, 6, 7, 8, 10, 11, 57, 60
Smallpox	Vaccinia virus (VV)
ssDNA viruses	
Parvoviridae	Human parvovirus B19
DNA and RNA reverse transcribing virus	
Retroviridae	Human T-lymphotropic virus 1 (HTLV-1)
Lentivirus	Human immunodeficiency virus 1 (HIV-1)
Negative stranded ssRNA viruses	
Rhabdoviridae	Rabies virus
Paramyxoviridae	Measles virus
Positive stranded ssRNA viruses	
Picornaviridae	Human enterovirus A, Coxsackie virus A
Flaviviridae	Dengue virus (DV), Japanese encephalitis virus (JEV), West Nile virus (WNV)
Togaviridae	Rubella virus