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Survey

Unmasking immune sensing of retroviruses: Interplay between innate sensors and host effectors

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ABSTRACT

Retroviruses can selectively trigger an array of innate immune responses through various PRR. The identification and the characterization of the molecular basis of retroviral DNA sensing by the DNA sensors IFI16 and cGAS has been one of the most exciting developments in viral immunology in recent years. DNA sensing by these cytosolic sensors not only leads to the initiation of the type I interferon (IFN) antiviral response and the induction of the inflammatory response, but also triggers cell death mechanisms including pyroptosis and apoptosis in retrovirus-infected cells, thereby providing important insights into the pathophysiology of chronic retroviral infection. Host restriction factors such as SAMHD1 and Trex1 play important roles in regulating innate immune sensing, and have led to the idea that innate immune defense and host restriction actually converge at different levels to determine the outcome of retroviral infection. In this review, we discuss the sensing of retroviruses by cytosolic DNA sensors, the relevance of host factors during retroviral infection, and the interplay between host factors and the innate antiviral response in different cell types, within the context of two human pathogenic retroviruses – human immunodeficiency virus (HIV-1) and human T cell-leukemia virus type I (HTLV-1).

Contents

Abbreviations: AIM2, absent in melanoma 2; AP-1, activating protein-1; APOBEC, apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like; AZT, azidothymidine; CCCR5, C-C chemokine receptor type 5; CDK1, cyclin-dependent kinase 1; CXCR4, C-X-C chemokine receptor type 4; cGAMP, cyclic guanosine monophosphate–adenosine monophosphate; cGAS, cyclic GMP-AMP synthase; CypA, cyclophilin A; CPSF6, cleavage and polyadenylation specificity factor subunit 6; DAI, DNA-dependent activator of IFN-regulatory factors; DC, dendritic cells; DDX41, DEAD (Asp-Glu-Ala-Asp) box polypeptide 41; DNA, deoxyribonucleic acid; DNA-PK, DNA-dependent protein kinase; dNTP, deoxynucleotide triphosphate; dNTPase, deoxynucleotide triphosphate triphosphohydrolase; dsDNA, double-stranded DNA; EIAV, equine infectious anemia virus; gp, glycoprotein; HBV, hepatitis B virus; HIV-1, human immunodeficiency virus-1; HTLV-1, human T-cell leukemia virus-1; IFI16, gamma-interferon-inducible protein 16; IFN, interferon; IL, interleukin; IRF, interferon regulatory factor; ISG, interferon-stimulated gene; MEF, mouse embryonic fibroblast; MLV, murine leukemia virus; MMTV, mouse mammary tumor virus; Mo-DC, monocyte-derived dendritic cell; mRNA, messenger RNA; Myd88, myeloid differentiation primary response gene 88; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NLRP3, NACHT, LRR and PYD domains-containing protein 3; pDC, plasmacytoid dendritic cells; PRR, pattern recognition receptor; RIG-I, retinoic acid-inducible gene 1; RNA, ribonucleic acid; RNase H, ribonuclease H; RT, reverse transcription; RTI, reverse transcriptase intermediate; SAMHD1, SAM domain and HD domain-containing protein 1; SIV, simian immunodeficiency virus; SLFN11, schlafen family member 11; ssDNA, single-stranded DNA; STAT1, signal transducers and activators of transcription 1; STING, stimulator of interferon genes; TBK1, TANK-binding kinase 1; TLR, toll-like receptor; TRAF, TNF receptor associated factor; TREX1, three prime repair exonuclease 1; TRIM, tripartite motif; tRNA, transfer RNA.

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1. Introduction

The past twenty years has witnessed a revolution in the understanding of innate immune response and the early events of host–pathogen interactions that dictate the ensuing cellular adaptive immune response to microbial pathogens [1]. The initial interactions of the immune response to pathogenic insult begins with the interaction between the microbial pattern-associated molecular patterns (PAMP) and different classes of pattern recognition receptors (PRR) that encompass a dizzying collection of innate receptors. Identification of cell surface and endosome-associated Toll-like receptors (TLR), characterization of cytosolic receptors of the RIG-I-like receptor (RLR) family, characterization of the NOD-like receptors – coupled with the ongoing elucidation of the signaling adapters, kinases and transcriptional factors that control anti-microbial innate immunity – have expanded our knowledge of innate immune responses in general, and specifically improved the understanding of the intrinsic response to virus infection [2–4]. Since the discovery of the RIG-I cytosolic sensor ten years ago by Fujita and colleagues [5], many of the mechanistic details associated with the sensing of foreign viral RNA infection have been determined [6,7]. Likewise, new information concerning the sensing of DNA virus infection has progressed rapidly in the past five years with the description of the AIM-like receptors (ALR) [8–10] and other sensors that distinguish self and non-self DNA [11–13]. Many of these topics are covered extensively in this volume of CGFR by leading experts in their respective areas. Mechanistic questions as to how retroviruses interface with the innate immune response has lagged significantly, and the PRR involved in the detection of evolutionarily conserved, retrovirus-derived structures have not been fully articulated.

Exciting work in the past years has demonstrated convincingly that retroviruses can selectively trigger an array of innate immune responses through various PRR. The identification and the characterization of the molecular basis of retroviral DNA sensing by the DNA sensors IFI16 and cGAS has been one of the most exciting developments in viral immunology in the last two years [14–16]. DNA sensing by these cytosolic sensors not only leads to the initiation of the type I interferon (IFN) antiviral response and the induction of the inflammatory response, but also triggers cell death mechanisms including pyroptosis and apoptosis in retrovirus-infected cells, thereby providing important insights into the pathophysiology of chronic retroviral infection.

Detection and restriction of retroviral infection by the host is not simply a matter of immune sensing. Indeed, among the hundreds of interferon stimulated genes (ISGs), host restriction factors constitute a specific, IFN-inducible arm of the innate antiviral response that is employed by the host to limit viral infection [17,18]. Host restriction activities range from the induction of hypermutations in the viral genome, to proteasomal degradation of viral capsid, and blockade of virus secretory mechanisms, altogether acting to inhibit the early cellular events of infections (reviewed in [19,20]). Emerging evidence has also suggested that host factors play an important role in regulating innate immune sensing, and recent studies have led to the idea that innate immune defense and host restriction actually converge at different levels to determine the outcome of retroviral infection.

In this review, we discuss the sensing of retroviruses by cytosolic DNA sensors, the relevance of host factors during retroviral infection, and the interplay between host factors and the innate antiviral response in different cell types. In particular, we describe these developments within the context of two human retroviruses that establish persistent infections in humans and are responsible for a significant burden of morbidity and mortality worldwide – human immunodeficiency virus (HIV-1) and human T cell-leukemia virus type I (HTLV-1).

2. A condensed view of the retroviral lifecycle

Reverse transcription – the reverse flow of genetic information from RNA to DNA – is a hallmark of the replicative cycle of all retroviruses. More than 40 years after this stunning discovery by Temin and Baltimore [21,22], it has become apparent that the replicative intermediates central to the process of reverse transcription are also of paramount importance for the initial recognition of retroviral infection by the host innate immune system. Below and in Fig. 1, we provide a brief overview of the retroviral lifecycle.

Replication of retroviruses takes place in several distinct stages. The initial step in retroviral infection involves specific interactions between viral envelope glycoproteins and cell surface receptors on the host cell. HIV-1 entry in T cells and macrophages requires interactions between gp120 with CD4 and gp41 with CCR5 or CXCR4 (reviewed in [23]). In contrast, HTLV-1 infectivity involves interaction with 3 different molecules – heparin sulfate proteoglycans, glucose transporter type 1, and neuropilin 1 (reviewed in [24]). These interactions between the virus envelope and the target cell membrane result in fusion and subsequent penetration of the virus into the cell, where the virus is uncoated and the viral core particle is released into the cytoplasm.

Viral DNA synthesis is thought to begin within the viral core, in the cytoplasm of the infected cell and may continue even when the replicative nucleoprotein complex enters the nucleus. Within the reverse transcription complex, the viral diploid genomic single-stranded RNA (ssRNA) of minus strand polarity is reverse transcribed by reverse transcriptase, leading to the generation of double-stranded DNA (dsDNA) in several distinct steps (reviewed in [25]) that are outlined in Fig. 1 (adapted from [25]). The enzymatic reactions during reverse transcription are facilitated by the two distinct enzymatic activities of the reverse transcriptase (RT): a DNA polymerase that elongates the primer by incorporating the appropriate deoxyribonucleotide triphosphates (dNTP) into the RNA or DNA template; and a ribonuclease H activity that specifically degrades the RNA strand of the RNA:DNA duplex. Following its synthesis in the cytoplasm, the viral reverse transcription product migrates to the nucleus, where it integrates into the cellular genome as a proviral template. Isolation of the replicative nucleoprotein complex from the cytoplasm of HIV-1-infected cells revealed that the complex contained linear viral DNA and integrase, but no other viral proteins [26]. Viral integrase prepares the blunt-ended linear DNA molecule for integration by cleaving the 3′end, thereby liberating the sites of attachment of the provirus to host DNA, and subsequently catalyzing the integration of the provirus into host DNA [27]. Only a fraction of the proviral DNA integrates, leaving behind in the cytoplasm a fraction of viral DNA containing closed

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