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Cytoplasmic sensing of viral nucleic acids

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Viruses are the most abundant pathogens on earth. A fine-tuned framework of intervening pathways is in place in mammalian cells to orchestrate the cellular defence against these pathogens. Key for this system is sensor proteins that recognise specific features associated with nucleic acids of incoming viruses. Here we review the current knowledge on cytoplasmic sensors for viral nucleic acids. These sensors induce expression of cytokines, affect cellular functions required for virus replication and directly target viral nucleic acids through degradation or sequestration. Their ability to respond to a given nucleic acid is based on both the differential specificity of the individual proteins and the downstream signalling or adaptor proteins. The cooperation of these multiple proteins and pathways plays a key role in inducing successful immunity against virus infections.

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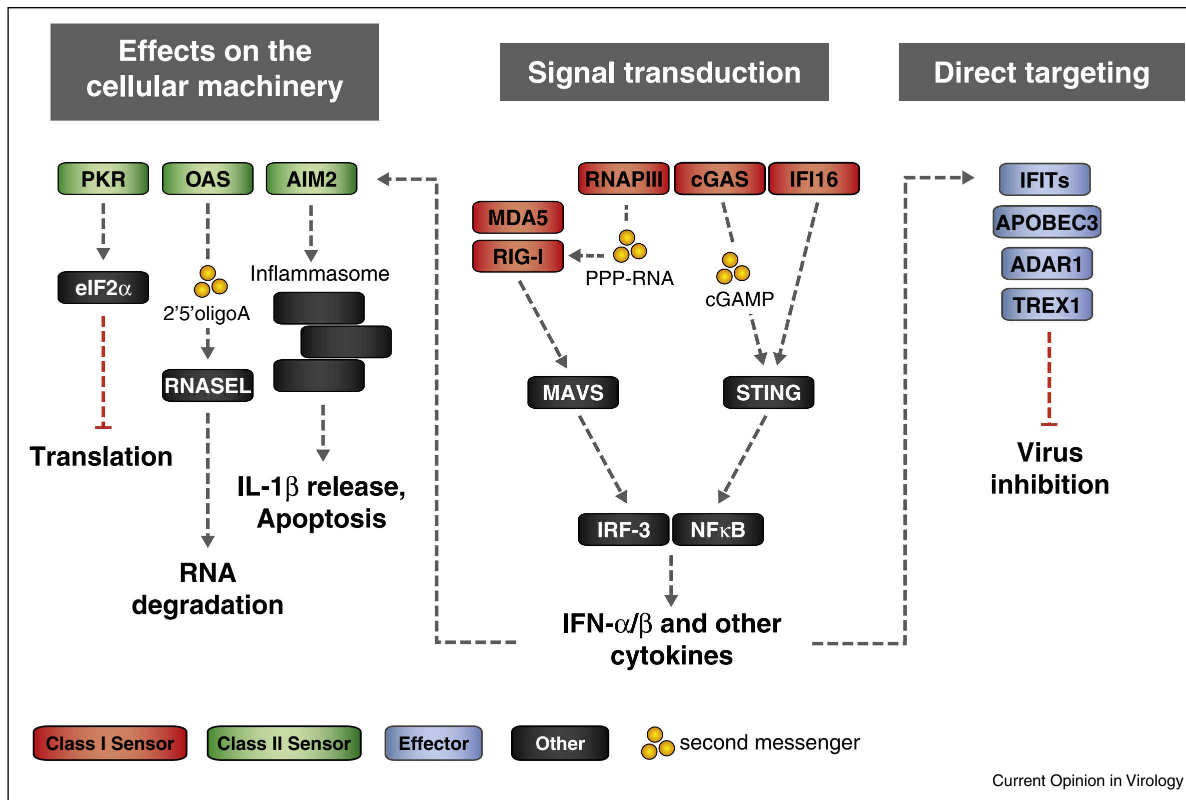
General properties of virus sensors

Almost all cells express germ-line encoded sensors with the ability to recognise virus infections and to initiate defence systems necessary to limit virus spread and pathogenicity. In technical terms, a sensor is 'a device that detects events or changes in quantities and provides a corresponding output without affecting the original trigger'. Sensors follow certain rules that include selective sensitivity to a specific measured property and insensitivity to other properties likely to be encountered. In analogy to technical terms, virus sensors convert a signal (virus infection) to an output that instructs the cell to take further actions. The magnitude of its activation is characterised by properties related to the exact nature and the quantity of the trigger. The targets of these sensors can be incoming virus particles [1], particular viral proteins [2] as well as general integrity of the cell [3]. However, the yet best understood sensors involved in antiviral defence are activated by viral nucleic acids [4]. Endosomal Toll-like receptors sample the extracellular milieu or cytoplasmic contents that are delivered into endosomes through autophagy. In this review we concentrate on intracellular nucleic acid sensors and effector proteins that evolved to mediate specialised tasks including, firstly, expression of cytokines such as type I interferons (IFN-α/β); secondly, modulation of cellular machineries required for virus replication and thirdly, direct inhibition of virus growth (Figure 1). Induction of cytokines utilises at least two distinct pathways either involving the adaptor proteins mitochondrial antiviral-signalling protein (MAVS) or stimulator of interferon genes (STING). Activation of either pathway regulates transcription of cytokines, which are key signals to shape adaptive immunity to induce an intracellular 'antiviral state' characterised by expression of antiviral defence proteins. Some of the latter proteins are activated by viral nucleic acids and in turn re-wire cellular machineries to limit virus spread. Other proteins directly bind viral nucleic acid and impair functionality through steric hindrance or degradation.

Differences between cellular and viral nucleic acids

To understand how viral nucleic acids are sensed by the innate immune system it is important to consider the different types of nucleic acids generated after virus infection. Viruses are intracellular pathogens that require cellular translation and host metabolism, but provide their own replication machinery. Independence of the host for multiplication of viral genomes allows high replication rates, which is often associated with pathogenicity [5]. 24–48 hours after infection approximately 25% of RNA can be of viral origin (P. Hubel and A. Meiler, unpublished). Viral nucleic acids accumulate in compartments typically devoid of cellular nucleic acids and often possess or lack modifications or physical properties that are not normally associated with cellular RNA or DNA (Figure 2). RNA polymerases commonly generate RNA with a 5′ triphosphate group (PPP-RNA). Cellular RNA polymerases co-transcriptionally modify newly synthesised RNA at the 5′ terminus. In case of mRNA an inverted guanine nucleotide cap is added and methylated at the N7-position as well as the 2′O position of the first ribose of the RNA strand (Cap1 mRNA) (Figure 2) [6]. These modifications are necessary to mark mRNA for further processing and export into the cytoplasm, where translation takes place. Other cellular RNAs are cleaved and have a 5′ monophosphate in case of transfer (t)RNA, most ribosomal (r)RNAs and small nucleolar (sno) RNAs [7]. Some small RNAs bear a terminally methylated 5′ triphosphate (U6 snRNA, 7SK RNA) or are further processed to a

Figure 1



Viral nucleic acid sensor and effector proteins and their primary antiviral properties. Engagement of a particular set of nucleic acid sensors (Class I sensors, red) results in signal transduction events, leading to expression of the type I interferons IFN-α/β and other cytokines. These in turn upregulate additional sensors (Class II sensors, green) with the ability to modulate the cellular machinery. In addition cytokines induce expression of effector proteins (blue) directly targeting viral nucleic acids. Transmission of signals in some pathways occurs through second messengers (yellow). Class II sensors include PKR, OAS and AIM2. PKR phosphorylates translation initiation factor eIF2α and consequently inhibits translation. Activated OAS synthesises the second messenger 2′5′ oligoA, which then binds to and activates the latent endoribonuclease RNASEL. Activation of the inflammasome, a large multimeric complex including pro-caspase-1, is mediated by the DNA sensor AIM2. Caspase-1 cleaves its substrates pro-IL-1b and IL-18 for extracellular release. For signal transduction, MDA5 and RIG-I (either activated directly or through binding of RNAPIII-synthesised PPP-RNA) engage the adaptor protein MAVS. cGAS and IFI16 transmit their signal to the adaptor STING. Both pathways culminate in phosphorylation and dimerization of IRF-3 as well as release of active NFκB into the nucleus, where they cooperate to form an enhanceosome to turn on transcription of cytokine genes.
Abbreviations: OAS, 2′5′ oligoadenylate synthetase; PKR, dsRNA-dependent protein kinase R; AIM2, absent in melanoma 2; eIF2α, eukaryotic initiation factor 2 alpha subunit; RNASEL, 2-5A-dependent ribonuclease L; MDA5, melanoma differentiation-associated protein 5; RIG-I, retinoic acid inducible gene I; RNAPIII, RNA polymerase III; cGAS, cyclic GMP–AMP synthase; IFI16, interferon gamma-inducible protein 16; MAVS, mitochondrial antiviral-signalling protein; STING, stimulator of interferon genes; IRF-3, interferon regulatory factor 3; NFκB, nuclear factor κ-light-chain enhancer of activated B cells; IFIT, interferon-induced protein with tetratricopeptide repeats; APOBEC3, apolipoprotein B mRNA-editing enzyme, catalytic polypeptide-like 3; ADAR1, RNA-specific adenosine deaminase 1; TREX1, three prime repair exonuclease 1; PPP-RNA, 5′ triphosphorylated RNA.

hypermethylated 2,2,7-trimethylguanosine cap (TMG) cap (snRNAs). In addition, more than 100 modifications on internal nucleotides of cellular RNAs have been described, some of which are critical to tame activation of the innate immune system. Total cellular RNA isolated from cells and transfected into indicator cells does not activate the innate immune system, whereas the products of most viral RNA polymerases are strong stimuli of antiviral responses [8]. Negative strand RNA viruses such as orthomyxo-viruses, paramyxo-viruses and bunya-viruses commonly generate full-length genomic PPP-RNA and short 5′ PPP subgenomic RNA, which have strong immunostimulatory potential [4]. To avoid the cellular defence system many viruses mimic cellular mRNA-like cap structures by encoding capping enzymes (e.g. Flaviviruses, Coronaviruses, Poxviruses, and Reo-viruses), 'steal' cap structures from cellular mRNAs for their transcripts (e.g. Orthomyxoviruses, Bunayviruses) or trim their genomic RNA to display only monophosphory-lated termini (Bunyaviruses, Bornaviruses) [9,10]. Picor-naviruses and Caliciviruses mask their RNA with a covalently 5′ genome-linked viral protein (VpG). In addition to the cap itself, 2′O methylation of the first ribose of mRNAs is an additional modification that is highly

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