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REVIEW

RNA polymerase III and antiviral innate immune response

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ABSTRACT

The innate immune system has numerous signal transduction pathways that lead to the production of type I interferons in response to exposure of cells to external stimuli. One of these pathways comprises RNA polymerase (Pol) III that senses common DNA viruses, such as cytomegalovirus, vaccinia, herpes simplex virus-1 and varicella zoster virus. This polymerase detects and transcribes viral genomic regions to generate AU-rich transcripts that bring to the induction of type I interferons. Remarkably, Pol III is also stimulated by foreign non-viral DNAs and expression of one of its subunits is induced by an RNA virus, the Sindbis virus. Moreover, a protein subunit of RNase P, which is known to associate with Pol III in initiation complexes, is induced by viral infection. Accordingly, alliance of the two tRNA enzymes in innate immunity merits a consideration.

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The innate immune system

The immune system has two divisions, the innate immune system and adaptive immune system, which together provide early and late immunity in vertebrates [1–5]. The innate immune system is a ubiquitous, primordial defense network found in vertebrates and invertebrates, including plants, insects and fungi [6]. In mammals, this system relies on macrophages, dendritic cells, neutrophils, epithelial and Natural killer cells in responding to invading pathogens and executing antigen presentation for mounting late immune response and memory by the adaptive immune system. These cells express pattern recognition receptors (PRRs) for identification of molecular features in pathogens, such as viruses and bacteria [7]. PRRs are sensors that identify two classes of molecules, pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) that represent loose components of damaged cells. In this respect, multiple context-dependent and direct molecular signatures are used to distinguish self from non-self nucleic acids of pathogenic contagions or autonomous pathologies. Common PAMPs of viral infections are viral genomic DNA and RNA that are recognized by two groups of PRRs, the Toll-like receptors (TLRs) and cytosolic PRRs [1,2,3,5,6,8–11].

TLRs are a family of receptors that sense viral and bacterial nucleic acids in endosomes of macrophages and dendritic cells and detect engulfed PAMPs in infected cells [4,9,12]. For instance, TLR3 detects dsRNA, TLR7/TLR8 recognize ssRNA, whereas TLR9 senses CpG DNA [6,13–17]. TLR3 distinguishes dsRNA that is larger than 40–50 nucleotides [18], whereas TLR9 elicits response to bacterial non-methylated CpG fragments that induce dimerization of the receptor and activation of signal transduction pathways leading to IFN production [19–21].

Cytosolic PRRs are diverse protein sensors that identify nucleic acids of viruses and bacteria in the cell cytoplasm [9,22,23]. These molecular sentinels include the retinoic acid-inducible gene (RIG)-like receptors, 2′-5′-oligoadenylate synthetase 1 (OAS1), cyclic GMP-AMP synthase (cGAS), stimulator of interferon genes (STING), additional absent in melanoma 2 (AIM2)-like receptors, DNA-dependent protein kinase (DNA-PK), as well as DEAH-box (DHX) and DEAD-box (DDX) RNA helicases [12,17,24–27]. The protein

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kinase RNA (PKR) is an IFN-stimulated gene and considered a PRR [28,29]. The PRR sensors are germline-encoded and conserved across evolution [30,31]. This is in contrast to somatic genetic rearrangements that produce new immunoglobulins and T-cell receptors of the adaptive immune system, endogenization of CRISPR in bacteria [32] or endogenization of retroviruses and bornaviruses in eukaryotes, including mammals [33–36]. Recent studies of insects also demonstrate the genetic acquisition of piDNAs, originating from RNA viruses, that confer protection against pathogens [37,38].

Recognition of viral DNA and RNA by cytosolic PRRs induces the production of type I IFNs via interrelated signal transduction pathways that integrate STING, TANK-binding kinase 1 (TBK1) and interferon response factor 3 (IRF3) for downstream induction of IFN-α and IFN-β [21,39,40]. Infected macrophages and dendritic cells primarily produce IFN-α, whereas fibroblasts and epithelial cells, nonimmune cells, mainly synthesize IFN-β [41]. Production of type I IFNs induces the expression of IFN-stimulated genes that finally block the dissemination of viral or bacterial infection in mammals. The aforementioned cells also respond to type I IFNs by mediating antigen presentation and producing cytokines and chemokines, e. g. tumor necrosis factors and interleukins known to act as major immune response mediators [28,42,43]. Type I IFNs also stimulate antibody production by B cells and augment the activation of T cells for adaptive immunity [41]. Viruses have evolved diverse counteracting strategies to mask their genomes, such as formation of replication complexes that shield naked viral RNA, seizing of self-identifiers of cellular RNAs (e. g. Cap-snatching) and targeting of cellular protein sensors for degradation [44–48].

Pol III, a sensor of foreign DNA

An additional but interesting cytosolic sensor of viral and bacterial DNA is RNA polymerase III (Pol III) (Figure 1) [21,49–52]. This polymerase is able to bind and transcribe AT-rich genomes of distinct viruses. The resulted 5 -pppRNA transcripts, ~70 nt in length, are recognized and bound by RIG-I that directs the signal to MAVS, TBK1 and IRF3 for downstream induction of IFN-α and IFN-β gene expression in infected cells [6,27,49,50,52–58] (Figure 1). Pol III detects the genomes of common DNA viruses, such as cytomegalovirus, vaccinia, herpes simplex virus-1 and varicella zoster virus [21,22,49,50,54,59–63]. The importance of Pol III in innate immunity is exemplified by the ability of the vaccinia virus to counteract the polymerase stimulation by its E3 protein, revealing a deep host-pathogen co-evolution [64,65]. However, the molecular mechanism by which the polymerase pinpoints its start point in viral genomes and initiates RNA synthesis remains largely unknown.

The discovery that Pol III acts as a sensor of diverse DNA viruses raises the question if it has a general role of recognizing foreign nucleic acids in invaded cells. Previous studies show that Pol III transcribes a synthetic poly(dA-dT) template in a promoter-independent manner [66,67] and the resulted poly(A-U) transcripts trigger type I IFN induction in transfected cells [17,50,68]. The high AT content of the DNA template is critical to transcription by Pol III, probably owing to the inclination of AT-rich boxes to serve as kick-start for RNA polymerization. By contrast, non-poly (dA-dT) dsDNAs elicit type I IFN induction, but via a Pol III–independent pathway [50]. Pol III also starts transcription from synthetic circularized DNA oligonucleotides, termed coligos, in cultured cell lines and in extracts [69,70]. Transcription of a coligo template begins at a single-stranded region and it seems to take place in the cytoplasm [69,70]. In fact, the ability of Pol III to initiate transcription from ssDNA promoters is well established [71]. Moreover, the presence of linearized or circular plasmids in transfected human cell lines elicits the activity of Pol III in transcription of tRNA genes (Figure 2) [39,72]. But whether these plasmids have functional AT-rich sequences utilized as startpoints for transcription remains elusive. Together, Pol III activity is stimulated to varying extents by tiny amount of foreign DNA, viral or otherwise.

Does Pol III sense RNA viruses?

As described above, many PRRs sense RNA and DNA viruses [73,74]. For instance, RIG-I senses

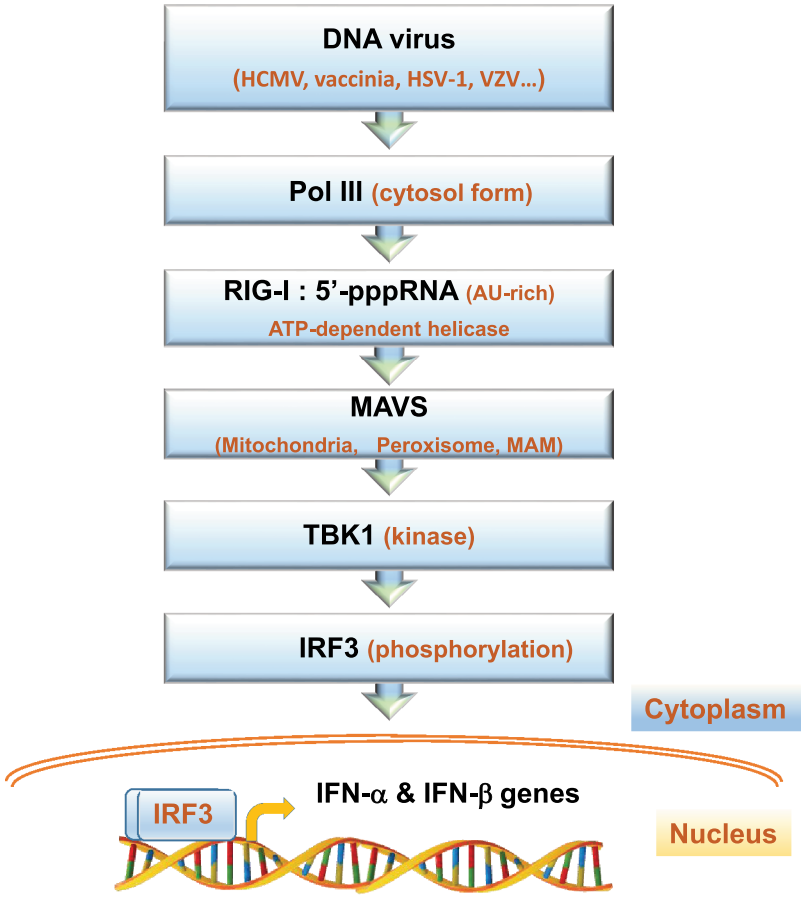

Figure 1. The signal transduction pathway of Pol III for induction of type I IFNs. The indicated DNA viruses with AT-rich genomes are sensed and transcribed by Pol III in the cell cytoplasm. The resulted AU-rich 5'pppRNA transcripts are then detected and bound by the RIG-I helicase. This ATP-dependent helicase requires the RING finger E3 ubiquitin ligases, Riplet and TRIM25 for K63 ubiquitination for full activation (not shown). RIG-I oligomers form a translocon complex with TRIM25 and the molecular chaperone 14-3-3ε [124] (not shown). This complex interacts with MAVS, a tail-anchored membrane protein, found on intracellular membranes, including peroxisomes and mitochondria, in addition to the mitochondrion-associated membrane (MAM), a domain of the endoplasmic reticulum. A phosphorylated and ubiquitinated form of MAVS then associates with the kinase TBK-1 and other factors to phosphorylate the IFN regulatory factor IRF3. The modified IRF3 enters the nucleus and binds its upstream regulatory element in the IFN-α and IFN-β genes for initiation of transcription (arrow).

the Sendai virus, a negative ssRNA virus that replicates in the cell cytoplasm, in addition to the vaccinia virus, a DNA virus with cytoplasmic replication cycle [27,40,49,73,75,76]. A recent study shows that infection of cultured cell lines by the Sindbis virus induces the expression of the POLR3E subunit of Pol III [72]. The finding raises the possibility that Pol III is involved in sensing a positive AU-rich ssRNA enveloped virus known to replicate its ~11.7 Kb genome in the cytoplasm (Figure 2). Preliminary results unveil that Pol III activity is central for the resistance of cells to infection by Sindbis virus, and possibly another RNA virus (Figure 2)(Mani D., unpublished data). Apparently, Pol III plays an antiviral role in cells infected with RNA viruses. This conclusion is supported by the discovery that a recessive substitution mutation in the human POLR3E gene is linked to systemic and concurrent infections with DNA and RNA viruses, including cytomegalovirus, metapneumovirus, respiratory syncytial virus, parvovirus, parainfluenza 3, and human herpesvirus 6 [72]. Fibroblasts with this rare mutation exhibit impaired induction of type I IFN and increased susceptibility to cytomegalovirus infection. The molecular mechanism underlying the mutation of POLR3E involves the assembly of malfunctioning initiation complexes of Pol III.

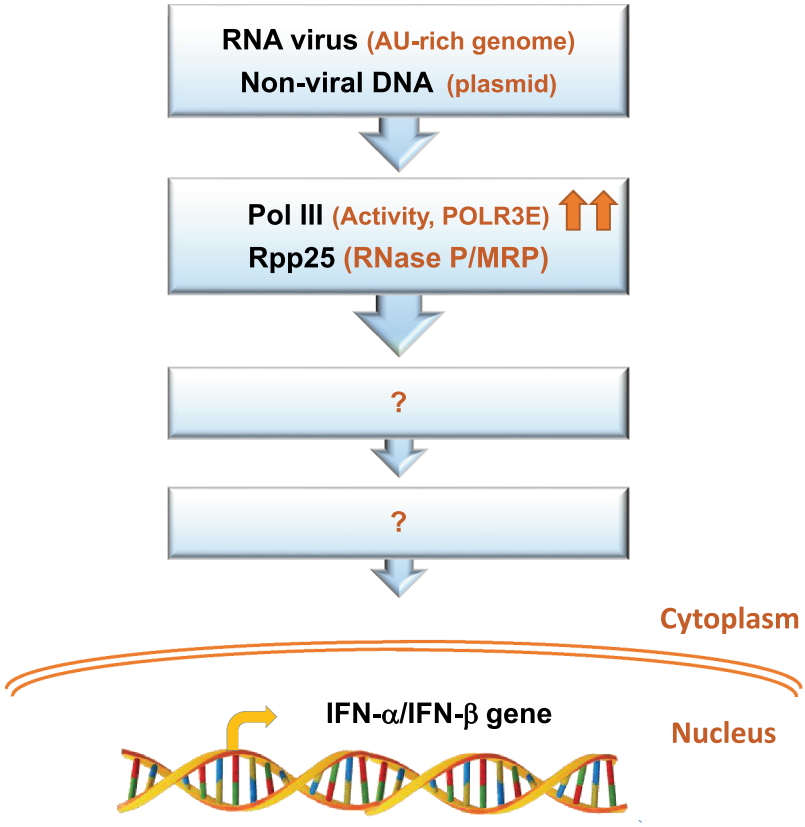

Figure 2. Potential foreign nucleic acids that induce human Pol III and RNase P in the innate immune system. The presence of RNA virus, whose genome is enriched with AU sequences, or non-viral DNA, such as plasmid, in the cell induces the expression of the POLR3E subunit of Pol III and its activity, as well as the expression of the protein subunit Rpp25 of RNase P/RNase MRP [72]. Arrows indicate increase in expression or activity. The downstream signal transduction pathways for induction of type I IFNs or else by these tRNA enzymes or their subunits remain unknown.

Hence, mutated POLR3E and Pol III are linked to an innate immune deficiency condition in human [72].

RNase P and its links to the immune system

RNase P is a ubiquitous endoribonuclease that removes the 5 leader of precursor tRNA [77–81]. In human cells, nuclear RNase P consists of H1 RNA and ten distinct protein subunits, termed Rpp14, Rpp20, Rpp21, Rpp25, Rpp29, Rpp30, Rpp38, Rpp40, Pop1 and Pop5 [82–86]. Cryo-electron microscopy reveals that H1 RNA, also known as RPPH1, is covered by its protein subunits arranged in three subcomplexes, Rpp20-Rpp25, Pop5-Rpp14-$(Rpp30)_2$-Rpp40, and Rpp21-Rpp29-Rpp38 and single polypeptide Pop1. These conserved proteins [87,88] form an interlocked clamp that stabilizes the catalytic RNA in a tertiary conformation fitted for binding and cleavage of precursor tRNA substrates [89].

RNase P shares protein subunits with RNase MRP [79,83,84,88,90], a mitochondrial and rRNA processing ribonucleoprotein [86,91–93]. The RMRP gene, which codes for the RNase MRP RNA, is found to be mutated in several immunodeficiency disorders, including cartridge hair hypoplasia, Omenn syndrome, anauxetic dysplasia, kyphomelic dysplasia and metaphyseal dysplasia without hypotrichosis [94–96]. Protein subunits of the two ribonucleoproteins are recognized as Th/To autoimmune antigens [82,85,97,98]. Considering the increasing overlap in the components and functions of the adaptive and innate immune systems and their contribution to initiation and progression of autoimmune diseases [99–103], it is conceivable that RNase P, RNase MRP and/or their RNA substrates and products [104] take part in the immune system (see below).

In fact, the specific subunit Rpp21 of RNase P is encoded by a gene positioned in the genetic locus of the major histocompatibility complex class I [105]. A form of this protein is fused to the ubiquitin ligase TRIM39 via transcription read-through and alternative splicing to generate TRIM39R [106]. The hybrid polypeptide regulates type I interferon induction in response to viral infection and is genetically linked to the Behcet's disease, a chronic inflammatory autoimmune condition characterized by eye inflammation, oral and genital sores and skin legions [107]. Of note, TRIM proteins, which possess E3 ubiquitin ligase activities, have various roles in the immune system, including antiviral innate immunity [108].

Human RNase P is evolutionary linked to viruses. Thus, screening of microbial genome databases for RNase P RNA-like genes reveals that the camelpox virus has a gene that codes for a transcript that folds into the universally conserved secondary structure of the RNase P RNA [109]. This viral gene is conserved in orthopoxviruses, including the vaccinia virus [110]. The vaccinia RNase P RNA-like transcript is detected in infected cells, but it is inactive in tRNA processing [110]. A recent study also shows that infection of cultured human cells with Sindbis virus leads to induction of the expression of the subunit Rpp25 of RNase P (Figure 2) [72]. Induction of Rpp25, which belongs to the Alba-like chromatin-binding proteins and binds the P3 domain of H1 RNA, is transient and concomitant with that of the subunit POLR3E [72].

Is RNase P linked to the sensor Pol III?

Human RNase P is implicated in transcription of small noncoding RNA genes by nuclear Pol III in cells and extracts [111–113]. Thus, targeted destruction of RNase P subunits by RNA interference inhibits transcription of tRNA and 5S rRNA genes [111,112]. This ribonucleoprotein coexists with Pol III in purified initiation complexes and inhibition of expression of its subunits demolishes the structure and function of these large complexes [112]. Of note, the coexistence of the two tRNA enzymes in initiation complexes contrasts the general view that processing of precursor tRNA occurs post-transcriptionally [114], an assessment inferred from genetic studies in the budding yeast and that show that knockout of RNase P subunits leads to accumulation of precursor tRNAs.

As a viral sensor, Pol III seems to act in the cytoplasm [49,50], whereas RNase P functions in transcription and processing of tRNA in the nucleus [105,115,116]. Nevertheless, we may speculate on possible relationship of RNase P to viral genome sensing by Pol III in the cytoplasm. Thus, it is known for a long time that a fraction of H1 RNA is localized in the cytoplasm, as local [117] and passerby to mitochondria [118–120]. Moreover, the yeast homologs of Rpp20, Rpp25 and Pop1 exist in the cytoplasm and facilitate the nuclear import of a related ribonucleoprotein, the telomerase [121–123]. Assuming that the human homologs of these three proteins are present in the cytoplasm, in which they are translated, an encounter with H1 RNA and/or Pol III is conceivable. Future studies will provide answer to whether individual subunits or new forms of RNase P act alone or together with Pol III in the innate immune system or else.

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