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Functions of DNA damage machinery in the innate immune response to DNA virus infection

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DNA is potently immunostimulatory, and self-DNA is packaged in the nucleus or mitochondria allowing it to remain silent to cell-intrinsic sensors. However, damaged or mislocalised self-DNA is sensed by our innate immune systems, resulting in the production of type I interferons (IFNI), chemokines and inflammatory cytokines. During DNA virus infection the detection of viral DNA genomes by pattern recognition receptors (PRRs) is essential for the initiation of IFNI responses and host defence against these pathogens. It is intriguing that a number of molecular mechanisms have been found to be common to both of these DNA-induced stress responses and this has potentially important consequences for both sides of the host/pathogen arms race.

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Introduction

The type 1 interferon (IFNI) response is critical for fighting viral infection and is initiated in vertebrates by an array of genome-encoded pattern recognition receptors (PRRs) that bind and respond to the presence of pathogen-associated molecular patterns (PAMPs). PRRs have evolved to sense PAMPs and/or damage-associated molecular patterns (DAMPs), the latter being mislocalised self-molecules indicative of cellular stress or damage [1,2]. In the context of virus infection, nucleic acid PAMPs are essential for initiating both IFNI production and for the inflammatory responses that attract leukocytes to assist in mounting a complete immune response [1]. Recent discoveries of intracellular PRRs that sense foreign or mislocalised self-DNA in the cytoplasm have led to a rapid expansion of the field, and have indicated that, in addition to viral infection, the immunostimulatory activity of DNA as a PAMP or a DAMP has significant consequences for bacterial and parasite infections, autoimmunity, vaccine development and carcinogenesis [1,3,4].

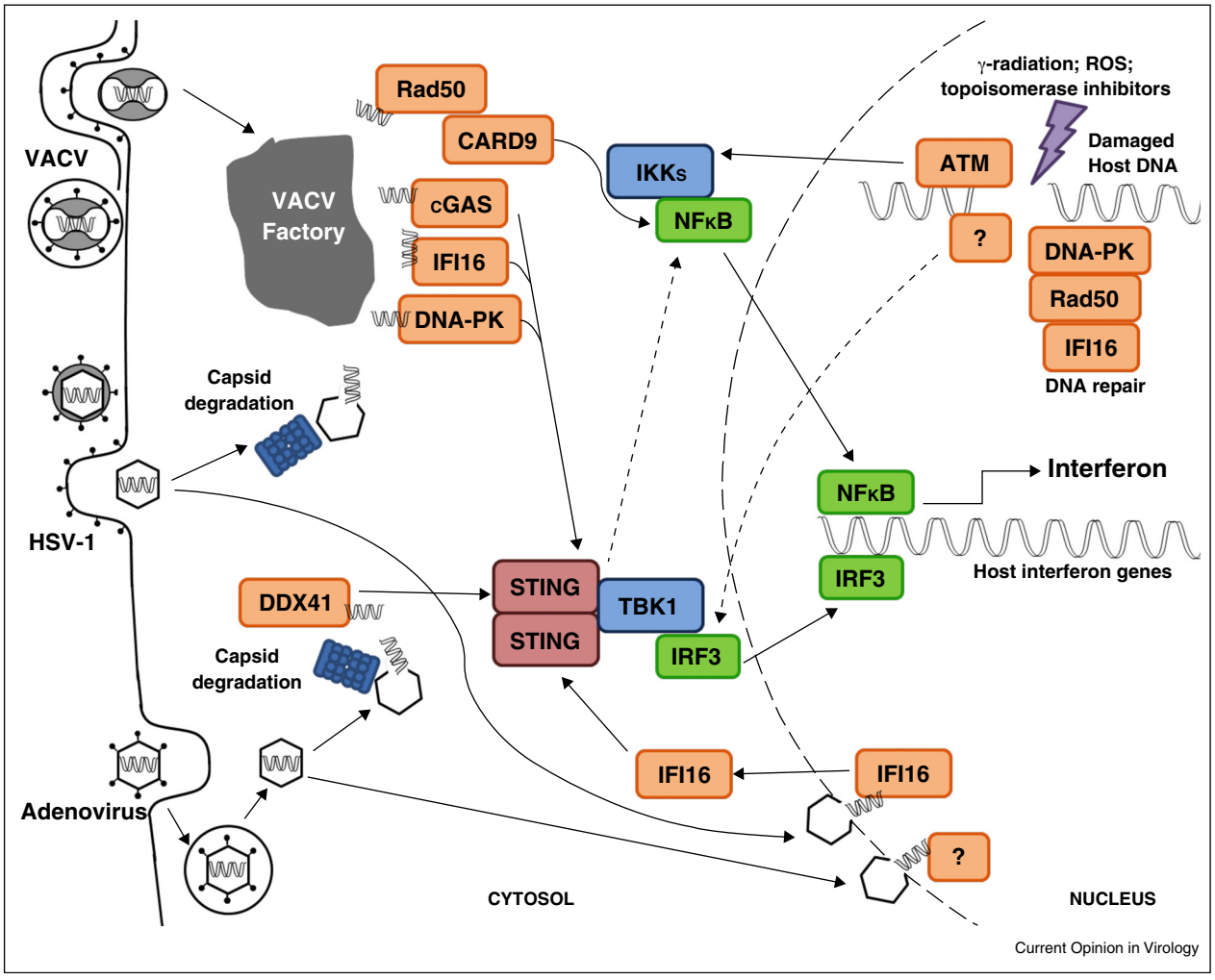
There is significant sharing of machinery between the innate immune system and the systems that regulate the cellular responses to damaged self-DNA. The output responses following detection of cellular stresses are similar, including cytokine production, cell cycle regulation and programmed cell death, and both of these systems have evolved to sense and respond to specific stresses. It might be expected, therefore, that intracellular detection of infection or damaged self-DNA would activate several common downstream signalling responses. Indeed this is the case, since both DNA virus infection and genotoxic stress result in IFNI and cytokine production via nuclear factor kappa-B (NF-κB) and interferon regulatory factor (IRF) activation [5–8], and cell death induction [9–12]. On the other hand, new discoveries that several proteins that function to repair damaged self-DNA are also PRRs that sense viral DNA may have more surprising implications for the immune response to infection and the efficiency of, and signalling responses to, DNA damage.

There remain, however, many unanswered questions that bridge these two fields. 1) What are the precise DNA ligands for innate immune sensing during virus infection or damaged self-DNA and how does this relate to the PRRs? 2) How has viral inhibition of innate responses affected both DNA sensing and the response to damaged self-DNA? 3) Is there innate sensing of viral and self DNA in the nucleus by DNA damage response proteins and/or PRRs? This review aims to discuss these questions from the perspective of sensing DNA virus infection.

Intracellular viral DNA sensing mechanisms

Normally only small amounts of self-DNA are present outside of the nucleus and mitochondria, and DNA entering other compartments is broken down by DNases such as DNaseII in endosomes and 3′ repair exonuclease 1 (TREX1) in the cytoplasm. Mutation of these nucleases in mice and humans leads to systemic autoinflammation and interferonopathy driven by a build-up of mislocalised DNA [2,13,14,15]. It has also been observed that direct transfection of pure, naked DNA into the cytoplasm of human cells can initiate an IFNI response via the adaptor protein stimulator of interferon genes (STING) [16], TANK-binding kinase-1 (TBK1) [17] and interferon regulatory factor 3 (IRF3) [18]. These discoveries ultimately led to the identification of PRRs for cytoplasmic DNA.

Figure 1



The induction of interferon by foreign and damaged self-DNA. DNA virus genomes stimulate intracellular DNA sensing PRRs, most of which act via the STING-TBK1-IRF3 pathway. Cytosolic DNA sensors recognise cytosolic-replicating vaccinia, or the DNA from defective or degraded herpesvirus or adenovirus virions. IFI16 has been shown to be a nuclear sensor of HSV-1 DNA that can shuttle out of the nucleus to activate STING. DNA damage is repaired in the nucleus by several proteins that function in the innate immune response and, at the same time, can induce interferon production via ATM, the IKK complex, NF-κB and IRF3. DNA sensors are shown in orange, transcription factors in green, and kinases in blue. ROS, reactive oxygen species.

DNA-dependent protein kinase (DNA-PK) [19], interferon γ-inducible protein 16 (IFI16) [20], cyclic GMP-AMP synthase (cGAS) [21•], RAD50 [22••], DDX41 [23] and others [24] have been shown to function in this manner (Figure 1).

The importance of intracellular DNA sensing for the immune response to DNA virus infection has been demonstrated by many studies. Infection of cells by poxviruses, herpesviruses and adenoviruses is sensed by DNA PRRs (Figure 1), and is essential for host defence against these infections [19,21•,22••,25–29]. This is perhaps clearest for poxviruses, such as vaccinia virus (VACV), which replicate their large DNA genome exclusively in the cytoplasm. VACV DNA is released directly into the cytoplasm following entry and secondary virion uncoating [30]. Viral DNA replication then occurs at discrete cytoplasmic sites, or 'factories', that are devoid of cellular organelles. Thousands of copies of VACV genome can accumulate in viral factories in the first 6 h following infection and, although it is not clear at what stage of the entry and replication process the viral genome is first sensed, this large accumulation of foreign DNA makes an excellent target for cytoplasmic DNA PRRs that detect its presence and respond by activating IRF3-dependent IFNI [19,31]. To counteract these responses, VACV has evolved inhibitors of PRR signalling, including a protein, C16, that binds directly to a subunit of DNA-PK to inhibit its DNA sensing activities [32••], as well as many others that target downstream signalling pathways