generation of knockout models will aid in determining whether the other Peli proteins, Peli2 and Peli3, regulate T cell tolerance. Interestingly, Peli2 interacts with Bcl-10, a key intermediate signaling molecule in the TCR-CD28 pathway[11].

Finally, the findings of Chang *et al.*[2] justify population studies to explore the role of Peli1 in human autoimmune disease. Any *Peli1* mutations that affect its function and/or expression will probably to lead to autoimmunity. Furthermore, given that Peli1 effects c-Rel degradation and c-Rel is associated with lymphoid malignancies[3], it will be very interesting to determine if the Peli proteins are also involved in the cancer arena. In summary, the study by Chang *et al.* indicates Peli1 is a crucial regulator of T cell activation and autoimmunity[2], which represents an exciting discovery that adds to the molecular understanding of the regulatory mechanisms that underlie self-tolerance.

COMPETING FINANCIAL INTERESTS
The author declares no competing financial interests.

1. Goodnow, C.C., Sprent, J., Fazekas de St Groth, B. & Vinuesa, C.G. *Nature* **435**, 590–597 (2005).
2. Chang, M. *et al. Nat. Immunol.* **12**, 1002–1009 (2011).
3. Vallabhapurapu, S. & Karin, M. *Annu. Rev. Immunol.* **27**, 693–733 (2009).
4. Long, M., Park, S.G., Strickland, I., Hayden, M.S. & Ghosh, S. *Immunity* **31**, 921–931 (2009).
5. Moynagh, P.N. *Trends Immunol.* **30**, 33–42 (2009).
6. Chang, M., Jin, W. & Sun, S.C. *Nat. Immunol.* **10**, 1089–1095 (2009).
7. Smith, H. *et al. Proc. Natl. Acad. Sci. USA* **106**, 4584–4590 (2009).
8. Smith, H. *et al. Biochem. J.* **434**, 537–548 (2009).
9. Choi, K.C. *et al. Nat. Immunol.* **7**, 1057–1065 (2006).
10. Venuprasad, K. *Cancer Res.* **70**, 3009–3012 (2011).
11. Liu, Y. *et al. J. Biol. Chem.* **279**, 37436–37444 (2004).

STING-dependent signaling

Glen N Barber

The sensing of pathogen-associated DNA in the cytoplasm is an important trigger of host-defense responses that include the production of type I interferon. A new study suggests that the DExDc helicase DDX41 may function in dendritic cells as a DNA sensor to activate STING-dependent innate immune responses.

The innate immune system has evolved a series of cellular sensors and signaling pathways that activate host-defense mechanisms in response to microbial invasion[1]. However, how cells detect pathogens that contain double-stranded DNA (dsDNA), such as many types of cancer-causing viruses, intracellular bacteria and perhaps parasites, remains to be resolved. In this report, Zhang *et al.* identify the DExDc helicase family member DDX41 as a sensor of cytosolic DNA that can trigger the production of host antipathogen genes such as those that encode type I interferons in myeloid dendritic cells (DCs)[2]. The finding has potentially important implications for the understanding of innate immune processes, microbe-based pathogenesis and even autoimmune disease.

Interestingly, DDX41 is not the first DExDc helicase to be linked to the sensing microbial invasion and rapid facilitation of appropriate host-defense countermeasures. For example, the RNA helicases RIG-I, Mda5 and LGP2 are critically important for the detection of invading RNA viruses in almost all cells and for triggering the production of antiviral proteins[3]. The RIG-I family and DDX41 are cytosolic DExD/H proteins that directly associate with pathogen-derived nucleic acid released into the cytosol. RIG-I recognizes 5′-triphosphorylated double-stranded RNA (dsRNA), which is commonly produced by negative-stranded RNA viruses, whereas Mda5 recognizes larger, high-molecular-weight dsRNA species typically encoded by positive-stranded viruses[4]. The interaction of viral RNA with RIG-I and Mda5 induces a conformational change that enables interaction with the mitochondrial adaptor IPS-1 (also known as MAVS, CARDIF or VISA), which facilitates the activation of transcription factors (such as IRF3, IRF7 and NF-κB) that are responsible for inducing the transcription of many genes encoding molecules important for host defense, including type I interferon[1,5]. Zhang *et al.* show that DDX41 interacts with dsDNA species, including the genomes of DNA viruses such as vaccinia virus and herpes simplex virus type 1 (HSV-1)[2]. This event, described in myeloid DCs, similarly leads to the production of type I interferon via activation of IRF3 and NF-κB (**Fig. 1**), although it requires the assistance of the transmembrane-containing, endoplasmic reticulum–associated adaptor STING ('stimulator of interferon genes')[6]. STING has been shown to be essential for the production of type I interferon by cytosolic dsDNA in nearly all cells examined, including mouse embryonic fibroblasts, macrophages and DCs. Accordingly, loss of STING prevents the production of type I interferon in response to transfected plasmids, DNA viruses and certain intracellular bacteria, such as *Listeria monocytogenes* and possibly even parasites. Mice that lack STING are viable but extremely sensitive to lethal infection with HSV-1. Thus, the STING-regulated pathway is extremely important for host defense against DNA-based microbes.

There are approximately 59 members of the DExD/H family; Zhang *et al.* identify DDX41 by means of an RNA-mediated interference screen to individually suppress the expression of each of these helicases in cells[2]. They then assay the ability of such cells to produce type I interferon in response to cytosolic B-form DNA (poly(dA:dT)). They find that the suppression of DDX41 expression in DCs and monocytes impedes the transcription of type I interferons and cytokines such as interleukin 6 and tumor necrosis factor by dsDNA and HSV-1, similar to the loss of STING. HSV-1 replication is concomitantly greater in cells in which DDX41 is suppressed. Loss of DDX41, however, does not affect dsRNA-dependent production of type I interferons, which indicates specificity for the cytosolic DNA–dependent innate signaling pathway. Loss of DDX41 also does not affect the production of interleukin-1β by cytosolic DNA, which indicates that this helicase acts independently of the pathway for the production of proinflammatory cytokines dependent on the cytoplasmic DNA receptor AIM2 and mediated by caspase-1 (ref. 7).

As additional experiments by this group indicate that the DEADc box of DDX41 can bind dsDNA (B-form) but not synthetic ssRNA such as poly(U)[2], these data collectively suggest that DDX41 associates with dsDNA species from pathogens and subsequently recruits STING for the activation of type I interferons. Published studies have

Glen N. Barber is in the Department of Cell Biology, University of Miami School of Medicine, Miami, Florida, USA.
e-mail: gbarber@med.miami.edu

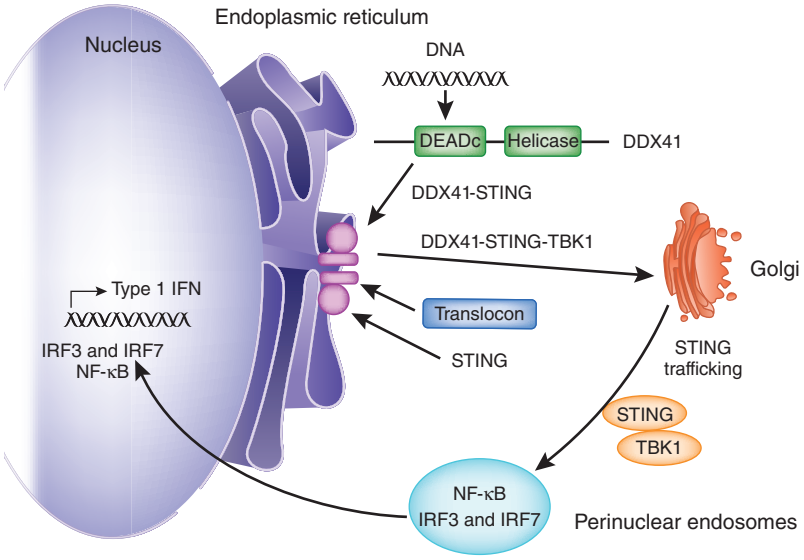

Figure 1 STING-dependent signaling. DNA from pathogens such as HSV-1 associates with cytoplasmic DDX41, which forms a complex with STING in the endoplasmic reticulum. This event triggers the trafficking of STING-TBK1 through the Golgi to perinuclear endosomal compartments, where TBK1 phosphorylates IRF3 and IRF7. NF-κB is also activated by unclarified mechanisms. IRF3 and IRF7 and NF-κB translocate to the nucleus to induce the transcription of genes encoding type I interferon (IFN) and other molecules of the innate immune response.

shown that in the presence of dsDNA species, STING traffics with the kinase TBK1 as a complex, from the endoplasmic reticulum to perinuclear endosomal compartments to activate IRF3, IRF7 and NF-κB by mechanisms that remain unclear[6]. The authors consequently demonstrate by overexpression studies that DDX41 can also associate with STING in the endoplasmic reticulum and traffic together with STING-TBK1 to endosomal compartments after associating with dsDNA (**Fig. 1**). Thus, DDX41 may be a sensor for cytosolic DNA and may trigger the production of molecules of the innate immune response in a STING-dependent manner.

Although these data provide a potential explanation for the inflammasome-independent sensing of dsDNA in the cytoplasm in certain cell types such as DCs, STING has also been shown to be essential for the production of type I interferons by cytosolic DNA in other types of cells such as fibroblasts, and the involvement of DDX41 in this process is unknown[8,9]. It also remains to be determined whether mice that lack DDX41 lose the ability to produce type I interferons in response to cytosolic DNA, as happens after the loss of STING. Other questions to consider include whether DDX41 is required for optimal DNA plasmid–based immunization, which is known to require the activity of TBK1 and STING[6].

Evidence indicates that various sensors and even redundant DNA pathways have evolved throughout evolution as a necessity for countering the threat of pathogen invasion. In this context, many sensors of cytoplasmic DNA have similarly been described, including the DNA-binding protein DAI and the interferon-inducible sensor IFI16 (which contains a pyrin domain and two DNA-binding HIN domains), both of which have also been reported to require STING for their function[10,11]. In addition, plasmacytoid DCs depend on Toll-like receptor 9 for detection of the nonmethylated CpG DNA commonly found in bacteria and viruses, an event that is reportedly STING independent. Thus, different sensors may exist in different cell types and recognize different nucleic acid–type ligands.

STING has also been shown to be important for the detection of bacteria-secreted cyclic dinucleotides by *L. monocytogenes*, which are potent activators of type I interferon, although it is unclear whether STING directly associates with such cyclic dinucleotides or requires an additional cofactor[12]. It remains conceivable that STING may also associate directly with dsDNA species, perhaps as a complex with molecules such as DDX41, although this also remains to be demonstrated. The elucidation of these important processes will clearly facilitate the understanding of innate immune signaling pathways, provide information on microbe-based pathogenesis and improve vaccine design and may conceivably shed light into the mechanisms of autoimmune disease.

COMPETING FINANCIAL INTERESTS
The author declares no competing financial interests.

Corrected after print 17 November 2011

1. Kumar, H., Kawai, T. & Akira, S. *Int. Rev. Immunol.* **30**, 16–34 (2011).
2. Zhang, Z. *et al. Nat. Immunol.* **12**, 959–965 (2011).
3. Onomoto, K., Onoguchi, K., Takahasi, K. & Fujita, T. *J. Interferon Cytokine Res.* **30**, 875–881 (2010).
4. Rehwinkel, J. & Reis e Sousa, C. *Science* **327**, 284–286 (2010).
5. Seth, R.B., Sun, L. & Chen, Z.J. *Cell Res.* **16**, 141–147 (2006).
6. Ishikawa, H. & Barber, G.N. *Cell. Mol. Life Sci.* **68**, 1157–1165 (2011).
7. Schroder, K. & Tschopp, J. *Cell* **140**, 821–832 (2010).
8. Ishikawa, H. & Barber, G.N. *Nature* **455**, 674–678 (2008).
9. Ishikawa, H., Ma, Z. & Barber, G.N. *Nature* **461**, 788–792 (2009).
10. Takaoka, A. *et al. Nature* **448**, 501–505 (2007).
11. Unterholzner, L. *et al. Nat. Immunol.* **11**, 997–1004 (2010).
12. Sauer, J.D. *et al. Infect. Immun.* **79**, 688–694 (2011).

Corrigendum: STING-dependent signaling

Glen N Barber

Nat. Immunol. **12, 929–930 (2011); published online 20 September 2011; corrected after print 17 November 2011.**

In the version of this News & Views initially published, the sensor DDX41 was reported to recognize Z-form DNA in addition to conventional B-form DNA. This finding remains inconclusive as it was not shown that the GC-rich oligonucleotides used the original study actually adopted the Z-DNA conformation. The error has been corrected in the HTML and PDF versions of the article.