Review
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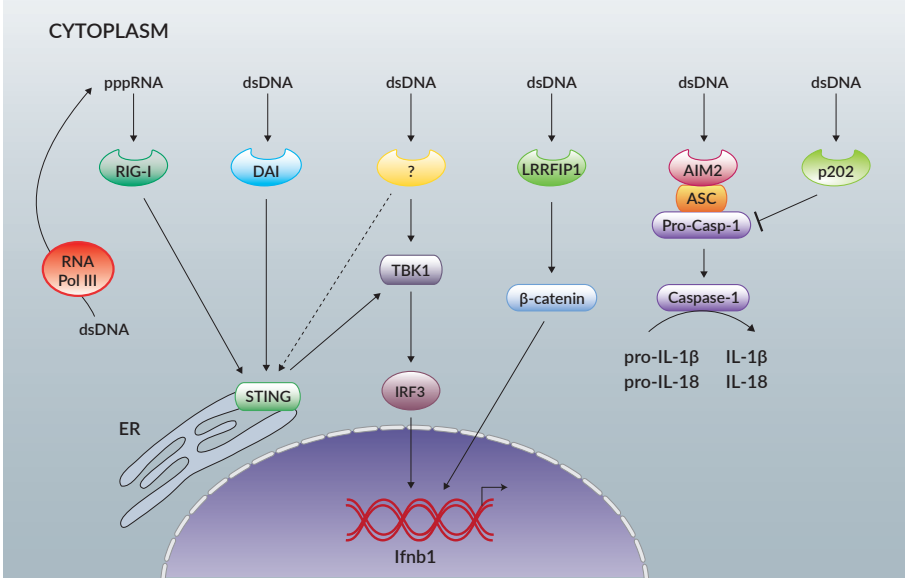
Recognition of Cytosolic DNA

The innate immune system reacts to diverse molecules of microbial origin, termed pathogen-associated molecular patterns (PAMPs), or released from damaged or dying cells, called damage-associated molecular patterns (DAMPs).
These molecules include nucleic acids, such as DNA. While the recognition of extra-cellular DNA involves mainly Toll-like receptor 9, recognition of cytosolic DNA appears to involve several sensors.

DAI

The first identified cytosolic DNA sensor, named DNA-dependent activator of IFN-regulatory factors (DAI), binds cytosolic dsDNA and leads to the production of type I IFNs[1]. However, DAI deficiency does not affect the induction of type I IFNs in response to poly(dA:dT), a synthetic analog of B-DNA, suggesting that redundant cytosolic DNA sensors exist[2].



RIG-I

Unexpectedly, the next candidate receptor was the RNA helicase retinoic acid-inducible gene-I (RIG-I), an RNA-binding and not DNA-binding protein. A human cell line deficient for RIG-I was shown to lack the ability to recognize poly(dA:dT)[3].
Recently, two independent teams confirmed the involvement of RIG-I in the response to dsDNA and demonstrated that rather than the cytosolic DNA, an RNA intermediate was responsible for RIG-I activation. They found that transfected poly(dA:dT) is transcribed by RNA polymerase III in the cytoplasm and potentially in the nucleus into a double-stranded RNA intermediate. This dsRNA molecule contains a 5'-triphosphate moiety and is recognized by RIG-I[4, 5].

Both DAI and RIG-I induce the production of type I IFNs through the TBK1/IRF3 pathway.
The endoplasmic reticulum (ER)-resident transmembrane protein stimulator of IFN genes (STING) is a key component of this pathway[6]. STING seems to function as an adaptor protein upstream of TBK1.

LRRFIP1

Recently, a third IFN-inducer cytosolic dsDNA sensor has been identified[7]. This sensor LRRFIP1 can recognize AT-rich B-form dsDNA as well as GC-rich Z-form dsDNA.
With the use of LRRFIP1-specific siRNA, Yang et al. demonstrated that LRRFIP1 triggers the production of IFN-β in a β-catenin-dependent manner. β-Catenin binds to the C-terminal domain of IRF3 inducing an increase in IFN-β expression.

AIM2

Although the production of type I IFNs is the main pathway induced by cytosolic dsDNA, production of the pro-inflammatory cytokines IL-1β and IL-18 has also been observed. Recently, several groups have identify AIM2 (absent in melanoma 2), a member of the hematopoietic interferon-inducible nuclear protein HIN-200 family, as a cytosolic dsDNA sensor which activation promotes the assembly of an inflammasome[8-10]. DNA of various origins, such as poly(dA:dT), plasmidic DNA and DNA from the bacterium L. monocytogenes have been shown to activate AIM2[11]. Upon activation, AIM2 interacts with ASC, a common adapter of the inflammasomes, leading to the cleavage of caspase-1 and the secretion of IL-1β and IL-18.
p202 is another member of the HIN200 family shown to bind cytoplasmic dsDNA but, in contrast to AIM2, it represses caspase activation[12].

The recognition of cytosolic DNA is more complicated than first anticipated. Several sensors have been identified that trigger different signaling pathways in a cell type-specific manner. Still, the general consensus is that another unknown cytosolic DNA-recognition system , independent of the TLRs and RIG-I, may exist. Further studies to elucidate the complex mechanisms of cytosolic DNA recognition may help the development of new strategies to treat inflammatory diseases.

USA : TEL : 858 457 5873 / FAX : 858 457 5843 • EUROPE : TEL : +33 (0)5.62.71.69.39 / FAX : +33 (0)5.62.71.69.30
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REFERENCES

1. Takaoka A. et al., 2007. DAI (DLM-1/ZBP1) is a cytosolic DNA sensor and an activator of innate immune response. Nature. 448(7152):501-5.
2. Ishii KJ. et al., 2008. TANK-binding kinase-1 delineates innate and adaptive immune responses to DNA vaccines. Nature. 451(7179):725-9.
3. Cheng G. et al., 2007. Double-stranded DNA and double-stranded RNA induce a common antiviral signaling pathway in human cells. Proc Natl Acad Sci U S A. ;104(21):9035-40.
4. Ablasser A. et al., 2009. RIG-Idependent sensing of poly(dA:dT) through the induction of an RNA polymerase III-transcribed RNA intermediate. Nat Immunol. 10(10):1065-72.
5. Chiu YH. et al., 2009. RNA polymerase III detects cytosolic DNA and induces type I interferons through the RIG-I pathway. Cell. 138(3):576-91.
6. Ishikawa H. & Barber GN., 2008. STING is an endoplasmic reticulum adaptor that facilitates innate immune signalling. Nature. 455(7213):674-8.
7. Yang P. et al., 2010. The cytosolic nucleic acid sensor LRRFIP1 mediates the production of type I interferon via a beta-catenindependent pathway. Nat Immunol. 11(6):487-94.
8. Hornung v. et al., 2009. AIM2 recognizes cytosolic dsDNA and forms a caspase-1-activating inflammasome with ASC. Nature. 458(7237):514-8.
9. Fernandes-Alnemri T. et al., 2009. AIM2 activates the inflammasome and cell death in response to cytoplasmic DNA. Nature. 458(7237):509-13.
10. Bürckstümmer T. et al., 2009. An orthogonal proteomic-genomic screen identifies AIM2 as a cytoplasmic DNA sensor for the inflammasome. Nat Immunol. 10(3):266-72.
11. Jones Jw. et al., 2010.Absent in melanoma 2 is required for innate immune recognition of Francisella tularensis. PNAS, 107(21):9771-6.
12. Roberts TL. et al., 2009. HIN-200 proteins regulate caspase activation in response to foreign cytoplasmic DNA. Science ;323(5917):1057-60.

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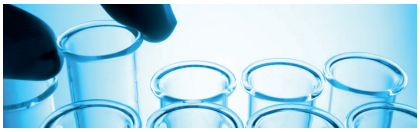
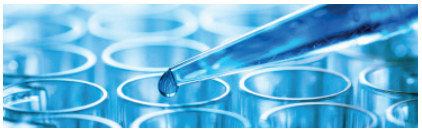
TLR Ligands


NOD Ligands

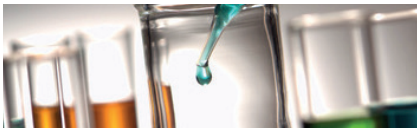

RLR Ligands


CLR Ligands


CDS & STING Ligands


Inflammasome Inducers


Multi-PRR Ligands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