Cytosolic sensors of pathogen-associated DNA


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Introduction

Reactome is open-source, open access, manually curated and peer-reviewed pathway database. Pathway annotations are authored by expert biologists, in collaboration with Reactome editorial staff and cross-referenced to many bioinformatics databases. A system of evidence tracking ensures that all assertions are backed up by the primary literature. Reactome is used by clinicians, geneticists, genomics researchers, and molecular biologists to interpret the results of high-throughput experimental studies, by bioinformaticians seeking to develop novel algorithms for mining knowledge from genomic studies, and by systems biologists building predictive models of normal and disease variant pathways.

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Literature references


Reactome database release: 79

This document contains 6 pathways and 4 reactions (see Table of Contents)
Presence of pathogen-associated DNA in cytosol induces type I IFN production. Several intracellular receptors have been implicated to some degree. These include DNA-dependent activator of interferon (IFN)-regulatory factors (DAI) (also called Z-DNA-binding protein 1, ZBP1), absent in melanoma 2 (AIM2), RNA polymerase III (Pol III), IFN-inducible protein IFI16, leucine-rich repeat flightless interacting protein-1 (LRRFIP1), DEAH-box helicases (DHX9 and DHX36), DEAD-box helicase DDX41, meiotic recombination 11 homolog A (MRE11), DNA-dependent protein kinase (DNA-PK), cyclic GMP-AMP synthase (cGAS) and stimulator of interferon genes (STING).

Detection of cytosolic DNA requires multiple and possibly redundant sensors leading to activation of the transcription factor NF-kappaB and TBK1-mediated phosphorylation of the transcription factor IRF3. Cytosolic DNA also activates caspase-1-dependent maturation of the pro-inflammatory cytokines interleukin IL-1beta and IL-18. This pathway is mediated by AIM2.

**Literature references**


**Editions**

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ZBP1 (DAI) mediated induction of type I IFNs

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Z-DNA-binding protein-1 (ZBP1), also known as, DNA-dependent activator of IFN-regulatory factors (DAI) was reported to initiate innate immune responses in murine L929 cells upon stimulation by multiple types of exogenously added DNA (Takaoka A et al 2007). Human cytomegalovirus (HCMV) was shown to stimulate ZBP1-mediated induction of IRF3 in human foreskin (DeFilippis VR et al 2010). ZBP1 was also implicated in activation of NF-kappaB pathways in human embryonic kidney HEK293T cells (Kaiser WJ et al 2008, Rebsamen M et al 2009). However, the role and importance of ZBP1 as dsDNA sensor remain controversial, since knocking down ZBP1 expression in other human or murine cell types by siRNA had very little effect on cellular responses to cytosolic DNA, suggesting the presence of alternative pathway (Wang ZC et al 2008, Lippmann J et al 2008). Tissue-specific expression of human ZBP1 also suggests that ZBP1 may function in cell-type specific way (Rothenburg S et al 2002).

Literature references


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STING (stimulator of IFN genes; also known as MITA/ERIS/MPYS/TMEM173) is an endoplasmic reticulum (ER) resident, which is required for effective type I IFN production in response to nucleic acids. Indeed, select pathogen-derived DNA or RNA were shown to activate STING in human and mouse cells (Ishikawa H and Barber GN 2008; Ishikawa H et al. 2009; Sun W et al. 2009; Prantner D et al. 2010). Importantly, in vitro studies have shown that STING is essential for Mycobacterium tuberculosis (Manzanillo PS et al. 2012), Plasmodium falciparum (Sharma S et al. 2011) and human immunodeficiency virus (HIV) induced type I IFN production [Yan N et al 2010]. Mycobacterium tuberculosis, plasmodium falciparum and HIV are three deadliest pathogens, which kill millions of people each year worldwide.

STING has been also implicated in type I IFN response which was stimulated by fusion of viral and target-cell membrane in a manner independent of DNA, RNA and viral capsid [Holm CK et al 2012].

Under steady state conditions, STING is positioned at the translocon complex within the ER membrane. However upon stimulation with intracellular DNA it translocates from ER to perinuclear vesicles via the Golgi by mechanisms that remain unclear (Ishikawa H and Barber GN 2008; Sun W et al. 2009; Ishikawa H et al. 2009; Saitoh T et al. 2009). Mouse Sting trafficking in dsDNA-stimulated mouse embryonic fibroblasts (MEF) cells was found to depend on autophagy-related gene 9a (Atg9a) (Saitoh T et al. 2009).

STING was reported to function as a signaling adaptor or coreceptor in response to cytosolic dsDNA (Unterholzner L et al. 2010; Zhang Z et al. 2011). STING was also shown to function as a direct DNA sensor to induce the innate immune response in human telomerase fibroblasts (hTERT-BJ1) and murine embryonic fibroblasts (MEFs) (Abe T et al. 2013). Additionally, STING is thought to function as a direct sensor of cyclic dinucleotides. STING was shown to interact directly with c-di-GMP in human embryonic kidney HEK293T cell lysates (Burdette DL et al. 2011). Once STING is stimulated, its C-terminus serves as a sig-
naling scaffold to recruit IRF3 and TBK1, which leads to TBK1-dependent phosphorylation of IRF3 (Tanka Y and Chen ZJ 2012).

Mouse, but not human STING, can also bind vascular disrupting agents 5,6-dimethylxanthenone-4-acetic acid (DMXAA) and the antiviral small molecule 10-carboxymethyl-9-acridanone (CMA) to induce type I IFN production, suggesting a species-specific drug effect on the STING-mediated host response (Conlon J et al. 2013; Cavlar T et al. 2013).

**Literature references**


RNA polymerase III transcribes microbial dsDNA to dsRNA

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