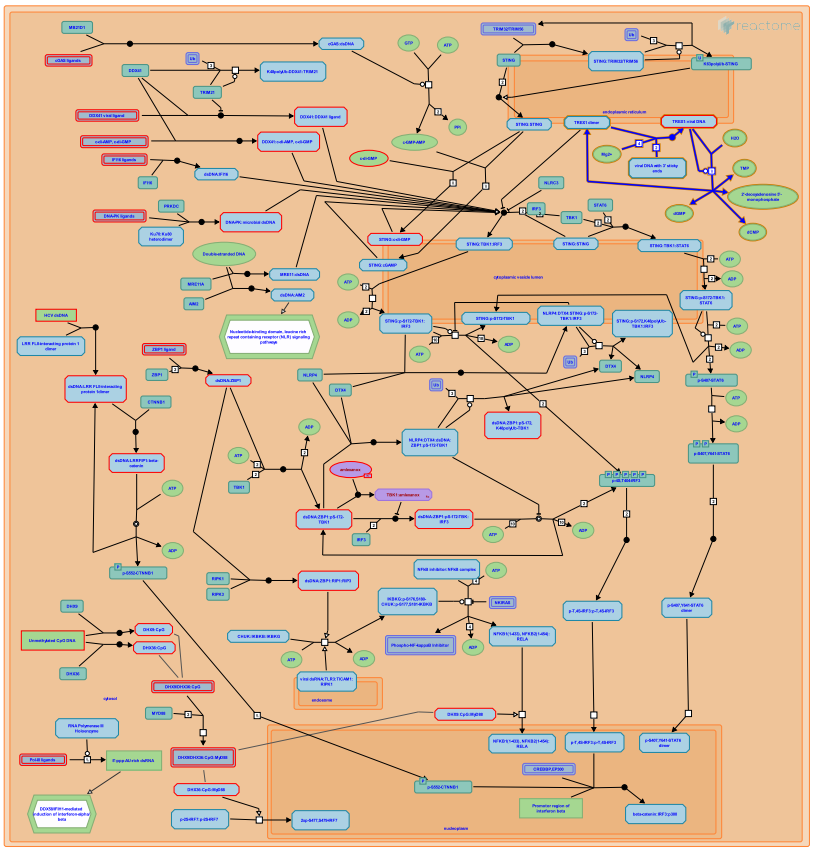
Regulation by TREX1



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This is just an excerpt of a full-length report for this pathway. To access the complete report, please download it at the Reactome Textbook.

05/05/2024

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.
The development of Reactome is supported by grants from the US National Institutes of Health (P41 HG003751), University of Toronto (CFREF Medicine by Design), European Union (EU STRP, EMI-CD), and the European Molecular Biology Laboratory (EBI Industry program).

Literature references

Fabregat, A., Sidiropoulos, K., Viteri, G., Forner, O., Marin-Garcia, P., Arnau, V. et al. (2017). Reactome pathway analysis: a high-performance in-memory approach. *BMC bioinformatics, 18*, 142. ↗

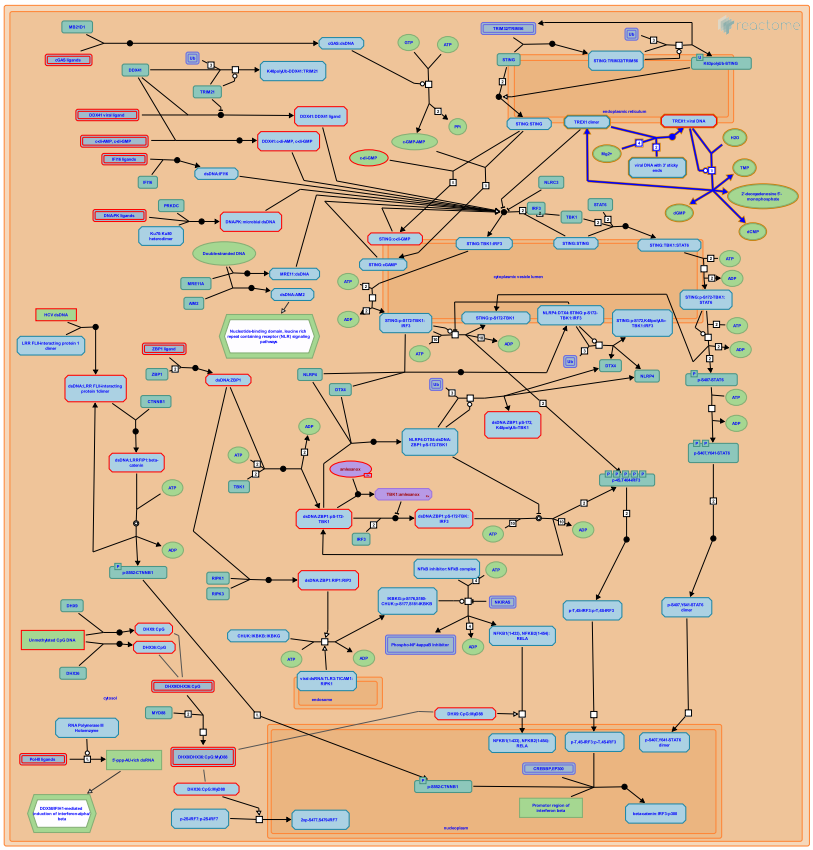
Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology, 14*, e1005968. ↗

Regulation by TREX1 ↗

Stable identifier: R-HSA-3248023



Three prime repair exonuclease 1 (TREX1) is a DNase type III enzyme, which targets and digests unpaired nucleotides on ssDNA and dsDNA ends through a 3'to 5' exonuclease activity (Perrino FW et al. 1994; de Silva U et al. 2007; Lehtinen DA et al. 2008; Fye JM et al 2011). TREX1 is an endoplasmic reticulum (ER)-associated protein, which is anchored to ER membrane via the C-terminal transmembrane domain (Chowdhury D et al. 2006; Richards A et al. 2007; Stetson DB et al. 2009). TREX1 has been implicated in innate immune responses against self (damaged or retrotransposons-derived DNA) and retroviral-derived DNA (Stetson DB et al. 2009; Yan N et al. 2010; Hasan M et al. 2012). TREX1 deficiency in human and mouse cells led to accumulation of cytosolic DNA which resulted in a continual activation of cytosolic DNA-sensors. In addition, cells lacking TREX1 function were less susceptible to infection with different types of RNA viruses (Yan N et al. 2010; Hasan M et al. 2012).Thus, the physiological role of the exonuclease TREX1 is to digest cytosolic host DNA to avoid autoimmunity. Loss-of-function mutations in the gene encoding human TREX1 are associated with several autoimmune diseases (Aicardi-Goutieres syndrome (AGS), familial chilblain lupus (FCL), systemic lupus erythematosus (SLE)) that result in increased levels of interferon and circulating antibodies to DNA (Crow YJ et al. 2006; Rice G et al. 2007; Lee-Kirsch MA et al. 2007). During infection with human immunodeficiency virus (HIV) or other RNA viruses, TREX1 activity may inhibit the innate immune responses by processing viral DNA generated during reverse transcription (Yan N et al. 2010; Hasan M et al. 2012). It's not yet known whether TREX1 is also involved in regulation of host responses to DNA viruses.

Detection of nucleic acids is known to launch signaling cascades leading to induction of type I interferons, which in turn orchestrate an immune response that involves the expression of hundreds of interferon-stimulated genes (ISGs). It is interesting to note that interferon(IFN)-independent activation of a subset of ISGs was detected in mouse and human cells lacking functional TREX1 (Hasan M et al. 2012). Hasan et al. have also observed that TREX1-deficiency resulted in an increased lysosomal compartment. Trex1 was found to control mTORC1 activity in mouse embryonic fibroblasts (MEF), which in turn negatively regulates translocation of transcription factor EB (TFEB) to the nucleus thereby controlling lysosomal biogenesis (Hasan M et al. 2012; Roczniak-Ferguson A et al. 2012). The authors linked the altered lysosomal compartment to innate immune responses by suggesting that lysosomal biogenesis (regulated by TFEB and mTORC1) acted upstream of IFN-independent ISG expression (regulated by IRF3 and IRF7) (Hasan M et al. 2012).

Literature references

Lieberman, J., Yan, N., Regalado-Magdos, AD., Lee-Kirsch, MA., Stiggelbout, B. (2010). The cytosolic exonuclease TREX1 inhibits the innate immune response to human immunodeficiency virus type 1. *Nat. Immunol., 11*, 1005-13. ↗

Ko, JS., Heidmann, T., Medzhitov, R., Stetson, DB. (2008). Trex1 prevents cell-intrinsic initiation of autoimmunity. *Cell, 134*, 587-98. ↗

Editions

2013-02-06	Authored	Shamovsky, V.
2013-02-11	Reviewed	D'Eustachio, P.
2013-05-17	Edited	Shamovsky, V.
2013-05-22	Reviewed	Jin, L., Wu, J.

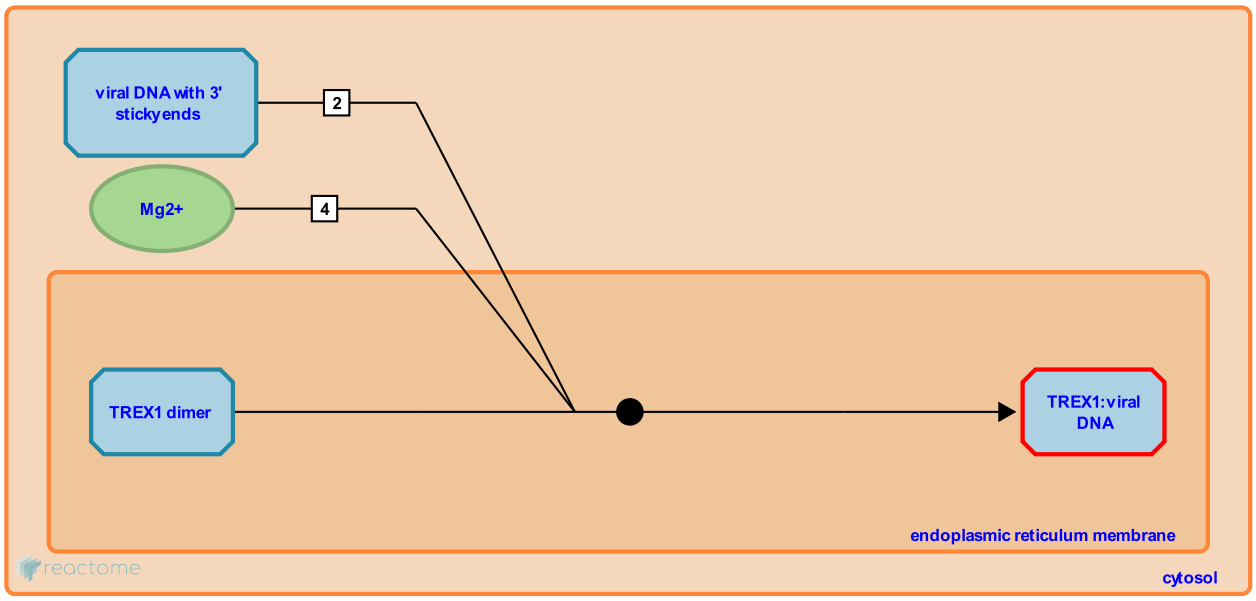
TREX1 binds retroviral-derived DNA ↗

Location: Regulation by TREX1

Stable identifier: R-HSA-3244605

Type: binding

Compartments: endoplasmic reticulum membrane, cytosol



TREX1 was shown to bind and degrade the HIV DNA fragments, which were generated during reverse transcription in HIV-infected human cells (Yan N et al. 2010). Other studies showed that TREX1 may regulate host responses to infection with several different types of RNA viruses (Hasan M et al. 2012). TREX1 is thought to clear viral derived DNA from the cytoplasm and thereby inhibit the activation of cytosolic DNA sensors (Yan N et al. 2010; Hasan M et al. 2012).

Structural studies of the human and mouse TREX proteins revealed the dimeric nature of the TREX family exonucleases (Brucet M et al. 2007; de Silva U et al. 2007, 2009; Perrino FW et al. 2005; Bailey SL et al 2012). Besides, the stable TREX1 dimer was purified from bacterial cells expressing affinity-tagged human TREX1 proteins (Orebaugh CD et al. 2011).Comparative structural analysis of wild type (wt) and natural mutant variants of TREX1 in complex with ssDNA provided some insights into mechanism of the TREX1 exonuclease activity (Bailey SL et al 2012). The reaction begins with the binding of metal ions and DNA substrate in the enzyme active site, which results in the transition of catalytic histidine residue H195 from a disordered to an ordered state. The distance between two divalent metal ions is also essential for catalytic activity. The authors proposed a mechanism where the two protomers in TREX1 dimer alternate back and forth between active and resting states as they degrade substrate. The activity status is mediated by the dual conformation of H195, which is coordinated with the shift of the metal ion from 3.1 A when H195 is out of the active site (resting) to 3.6 A when H195 moves into the active site (active) (Bailey SL et al 2012). In addition, the structures of the TREX1 mutant proteins (dominant D200H, D200N and D18N homodimer mutants derived from AGS and FCL patients, as well as the recessive V201D mutant) provided insight into the dysfunction relating to human diseases (Bailey SL et al. 2012). The comparative analysis of the exonuclease activity of the dominant mutant TREX1 proteins (homo- and heterodimers generated from wt- and mutant TREX1 monomers) are in agreement with findings of Bailey et al.(Lehtinen DA et al. 2008; Fye JM et al. 2011; Bailey SL et al. 2012).

Followed by: Viral DNA cleavage by TREX1

Literature references

Brugarolas, J., Yan, N., Lee-Kirsch, MA., Levine, B., Dozmorov, I., Wakeland, EK. et al. (2013). Trex1 regulates lysosomal biogenesis and interferon-independent activation of antiviral genes. *Nat. Immunol., 14*, 61-71. ↗

Lieberman, J., Yan, N., Regalado-Magdos, AD., Lee-Kirsch, MA., Stiggelbout, B. (2010). The cytosolic exonuclease TREX1 inhibits the innate immune response to human immunodeficiency virus type 1. *Nat. Immunol., 11*, 1005-13. ↗

Editions

2013-02-06	Authored	Shamovsky, V.
2013-02-11	Reviewed	D'Eustachio, P.
2013-05-17	Edited	Shamovsky, V.
2013-05-22	Reviewed	Jin, L., Wu, J.

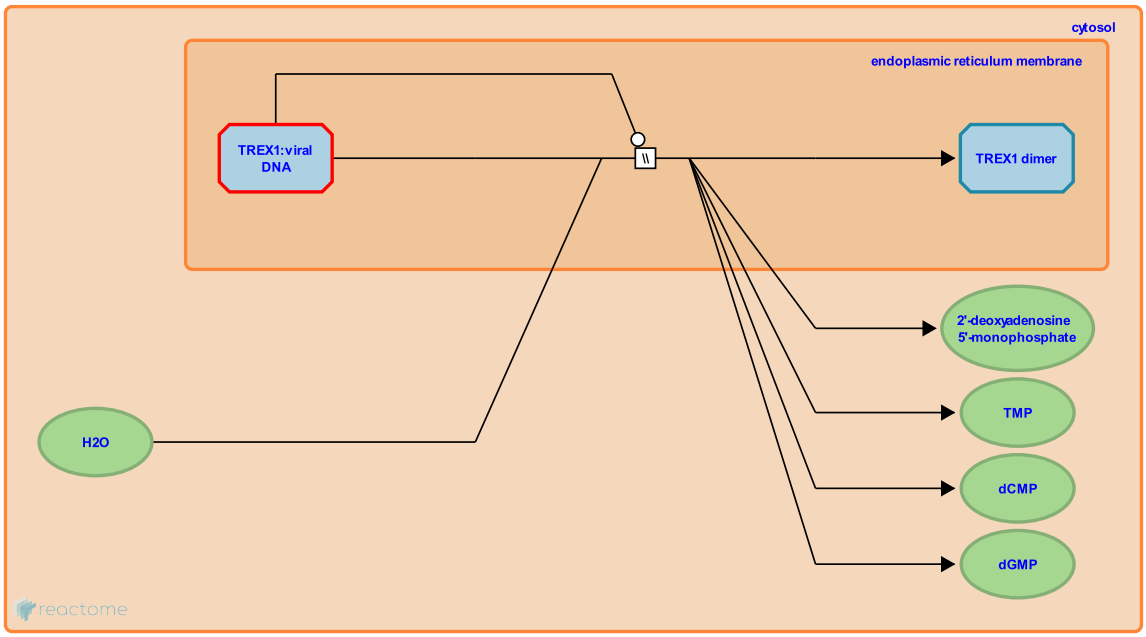
Viral DNA cleavage by TREX1 ↗

Location: Regulation by TREX1

Stable identifier: R-HSA-3245943

Type: omitted

Compartments: endoplasmic reticulum membrane, cytosol



TREX1 digests unpaired nucleotides on ssDNA and dsDNA ends through a 3' to 5' exonuclease activity (Perrino FW et al. 1994; de Silva U et al. 2007; Lehtinen DA et al. 2008; Fye JM et al 2011). Upon viral infection the TREX1-deficient human and mouse cells were found to be more resistant to different types of RNA viruses, suggesting that TREX1 activity may inhibit the host innate immune responses by clearing viral DNA generated during reverse transcription (Yan N et al. 2010; Hasan M et al. 2012).

Preceded by: TREX1 binds retroviral-derived DNA

Literature references

Lieberman, J., Yan, N., Regalado-Magdos, AD., Lee-Kirsch, MA., Stiggelbout, B. (2010). The cytosolic exonuclease TREX1 inhibits the innate immune response to human immunodeficiency virus type 1. *Nat. Immunol., 11*, 1005-13. ↗

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