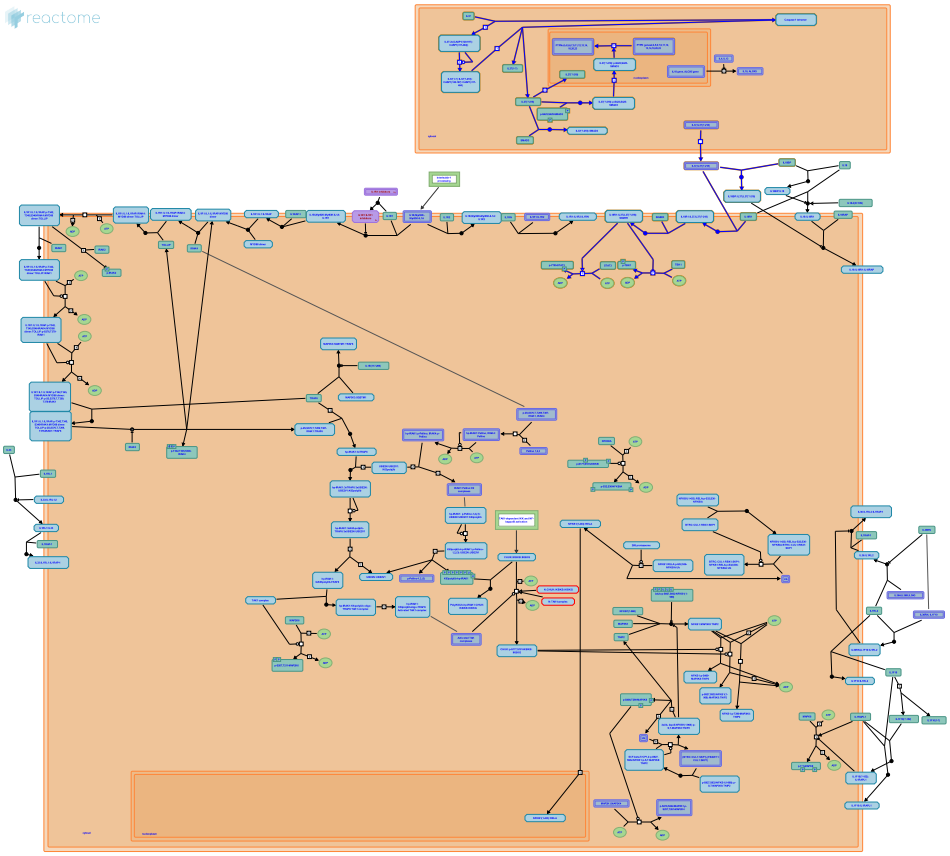
Interleukin-37 signaling



Carriero, R., Duenas, C., Garlanda, C., Jupe, S., Mantovani, A., Meldal, BH., Varusai, TM.

European Bioinformatics Institute, New York University Langone Medical Center, Ontario Institute for Cancer Research, Oregon Health and Science University.

24/04/2024

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. ↗

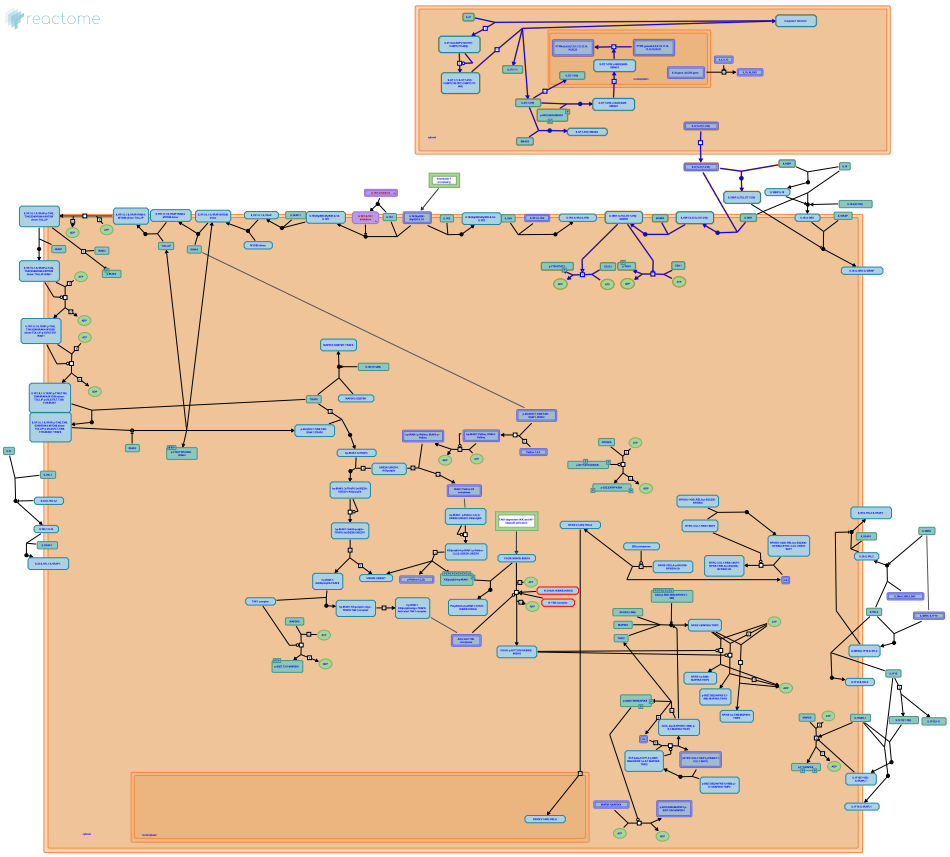
Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

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. ↗

Interleukin-37 signaling ↗

Stable identifier: R-HSA-9008059

Compartments: cytosol, plasma membrane, extracellular region



Interleukins (IL) are immunomodulatory proteins that elicit a wide array of responses in cells and tissues. Interleukin 37 (IL37), also known as IL 1F7, is a member of the IL 1 family (Sharma et al. 2008). Isoform b of IL37 (referred just as IL37) is synthesized as a precursor that requires processing (primarily by caspase 1) to attain full receptor agonist or antagonist function (Kumar et al. 2002). Both full length and processed IL37 can bind to the IL 18 binding protein (IL 18BP) and the Interleukin 18 receptor 1 (IL 18R1) (Shi et al. 2003). Upon binding to the IL18R1, IL37 recruits Single Ig IL 1 related receptor (SIGIRR) (Nold-Petry et al. 2015). The IL37:IL18R1 complex can activate phosphorylation of Signal transducer and activator of transcription 3 (STAT3), Tyrosine protein kinase Mer and Phosphatidylinositol 3,4,5 trisphosphate 3 phosphatase and dual specificity protein phosphatase PTEN and can also inhibit Nuclear factor NF kappa B p105 subunit (NFKB) (Nold-Petry et al. 2015). Processed IL37 can be secreted from the cytosol to the extracellular space or translocated into the nucleus (Bulau et al. 2014). Full length IL37 can also be secreted from the cytosol to the extracellular space (Bulau et al. 2014). Processed IL37 can bind with Mothers against decapentaplegic homolog 3 (SMAD3) in the cytosol and then translocate to the nucleus, where it facilitates transcription of Tyrosine protein phosphatase non receptors (PTPNs) (Nold et al. 2010, Luo et al. 2017). These events ultimately lead to suppression of cytokine production in several types of immune cells resulting in reduced inflammation.

Literature references

Dinarello, CA., Italiani, P., Pfaller, T., Pixner, C., Nold, MF., Lucchesi, D. et al. (2011). IL-37: a new anti-inflammatory cytokine of the IL-1 family. *Eur. Cytokine Netw., 22,* 127-47. ↗

Shi, H., Wu, B., Luo, X., Li, J., Zhuang, X., Jin, B. (2017). The emerging role of interleukin-37 in cardiovascular diseases. *Immun Inflamm Dis.* ↗

Editions

2017-08-08	Authored, Edited	Varusai, TM.
2017-11-02	Reviewed	Mantovani, A., Garlanda, C., Carriero, R.

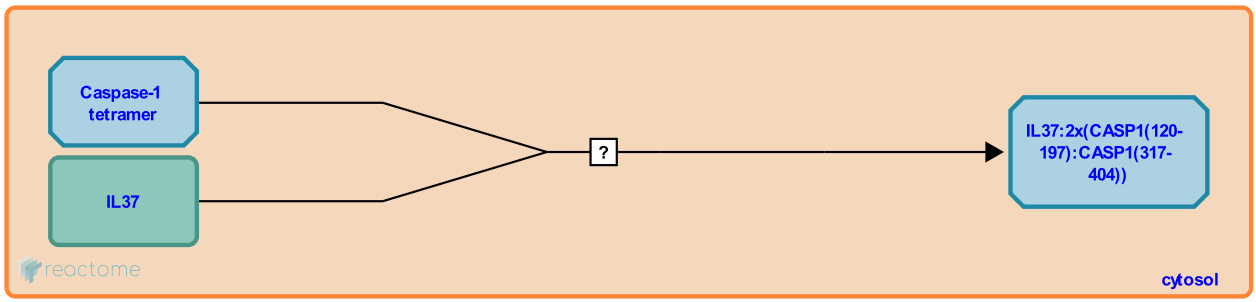
IL37 binds 2x(CASP1(120-197):CASP1(317-404))

Location: Interleukin-37 signaling

Stable identifier: R-HSA-9012542

Type: uncertain

Compartments: cytosol



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Preceded by: IL37(1-?) and IL37 (?-) dissocates from IL37(1-?):IL37(?-218):CASP1(120-197):CASP1(317-404)

Followed by: IL37:2x(CASP1(120-197):CASP1(317-404)) cleaves IL37

Literature references

Dinarello, CA., Sharma, S., Bufler, P., Reinhardt, D., Kim, SH., Gräf, R. et al. (2008). The IL-1 family member 7b translocates to the nucleus and down-regulates proinflammatory cytokines. *J. Immunol., 180*, 5477-82.

Filvaroff, E., Vandlen, R., Henzel, WJ., Pan, G., Risser, P., Yansura, D. et al. (2001). IL-1H, an interleukin 1-related protein that binds IL-18 receptor/IL-1Rrp. *Cytokine, 13*, 1-7.

Dinarello, CA., Bufler, P., Li, S., Rubartelli, A., Fink, M., Bulau, AM. et al. (2014). Role of caspase-1 in nuclear translocation of IL-37, release of the cytokine, and IL-37 inhibition of innate immune responses. *Proc. Natl. Acad. Sci. U.S.A., 111*, 2650-5.

Brigham-Burke, MR., Rieman, DJ., Kumar, S., Gambotto, A., Lotze, MT., Lehr, R. et al. (2002). Interleukin-1F7B (IL-1H4/IL-1F7) is processed by caspase-1 and mature IL-1F7B binds to the IL-18 receptor but does not induce IFN-gamma production. *Cytokine, 18*, 61-71.

Editions

2017-09-27	Edited	Varusai, TM.
2017-10-18	Authored	Duenas, C.
2017-11-02	Reviewed	Mantovani, A., Garlanda, C., Carriero, R.

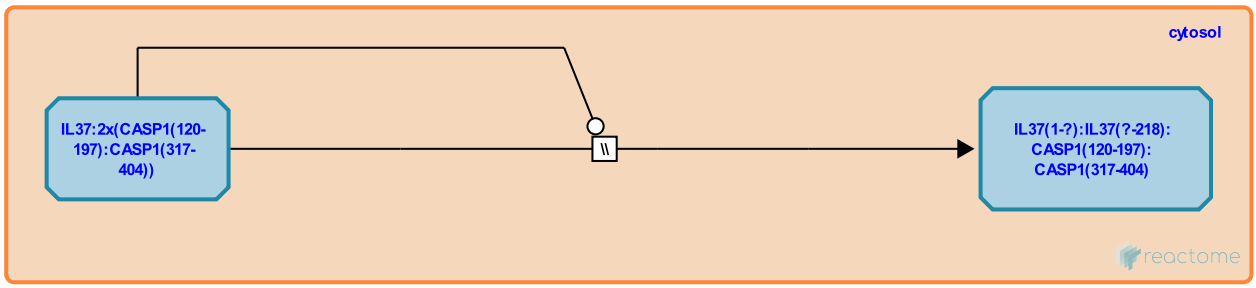
IL37:2x(CASP1(120-197):CASP1(317-404)) cleaves IL37 ↗

Location: Interleukin-37 signaling

Stable identifier: R-HSA-9012556

Type: omitted

Compartments: cytosol



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Preceded by: IL37 binds 2x(CASP1(120-197):CASP1(317-404))

Followed by: IL37(1-?) and IL37 (?-) dissocates from IL37(1-?):IL37(?-218):CASP1(120-197):CASP1(317-404)

Literature references

Dinarello, CA., Sharma, S., Bufler, P., Reinhardt, D., Kim, SH., Gräf, R. et al. (2008). The IL-1 family member 7b translocates to the nucleus and down-regulates proinflammatory cytokines. *J. Immunol., 180*, 5477-82. ↗

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Brigham-Burke, MR., Rieman, DJ., Kumar, S., Gambotto, A., Lotze, MT., Lehr, R. et al. (2002). Interleukin-1F7B (IL-1H4/IL-1F7) is processed by caspase-1 and mature IL-1F7B binds to the IL-18 receptor but does not induce IFN-gamma production. *Cytokine, 18*, 61-71. ↗

Editions

2017-09-27	Edited	Varusai, TM.
2017-10-18	Authored	Duenas, C.
2017-11-02	Reviewed	Mantovani, A., Garlanda, C., Carriero, R.

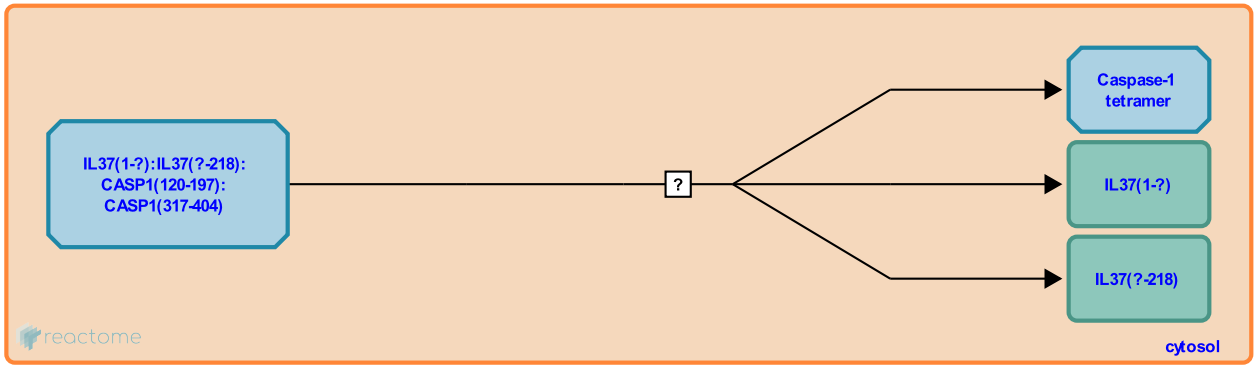
IL37(1-?) and IL37 (?-) dissocates from IL37(1-?):IL37(?-218):CASP1(120-197):CASP1(317-404)

Location: Interleukin-37 signaling

Stable identifier: R-HSA-9012689

Type: uncertain

Compartments: cytosol



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Preceded by: IL37:2x(CASP1(120-197):CASP1(317-404)) cleaves IL37

Followed by: IL37(?-218) binds SMAD3, IL37(?-218) translocates from the cytosol to the nucleus, IL37(?-218) binds p-S423,S425-SMAD3, IL37, IL37(?-218) translocates from cytosol to extracellular region, IL37 binds 2x(CASP1(120-197):CASP1(317-404))

Literature references

Dinarello, CA., Sharma, S., Bufler, P., Reinhardt, D., Kim, SH., Gräf, R. et al. (2008). The IL-1 family member 7b translocates to the nucleus and down-regulates proinflammatory cytokines. *J. Immunol., 180*, 5477-82.

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Dinarello, CA., Bufler, P., Li, S., Rubartelli, A., Fink, M., Bulau, AM. et al. (2014). Role of caspase-1 in nuclear translocation of IL-37, release of the cytokine, and IL-37 inhibition of innate immune responses. *Proc. Natl. Acad. Sci. U.S.A., 111*, 2650-5.

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Editions

2017-09-27	Edited	Varusai, TM.
2017-10-18	Authored	Duenas, C.
2017-11-02	Reviewed	Mantovani, A., Garlanda, C., Carriero, R.

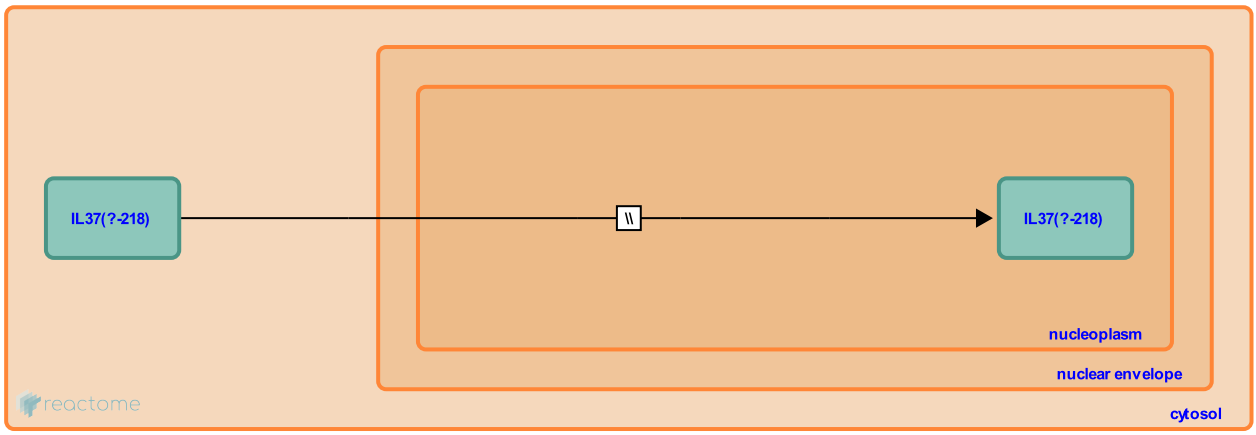
IL37(?-218) translocates from the cytosol to the nucleus ↗

Location: Interleukin-37 signaling

Stable identifier: R-HSA-9008696

Type: omitted

Compartments: nucleoplasm, cytosol



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Preceded by: IL37(1-?) and IL37 (?-) dissocates from IL37(1-?):IL37(?-218):CASP1(120-197):CASP1(317-404)

Literature references

Dinarello, CA., Bufler, P., Li, S., Rubartelli, A., Fink, M., Bulau, AM. et al. (2014). Role of caspase-1 in nuclear translocation of IL-37, release of the cytokine, and IL-37 inhibition of innate immune responses. *Proc. Natl. Acad. Sci. U.S.A., 111*, 2650-5. ↗

Editions

2017-09-27	Authored, Edited	Varusai, TM.
2017-11-02	Reviewed	Mantovani, A., Garlanda, C., Carriero, R.

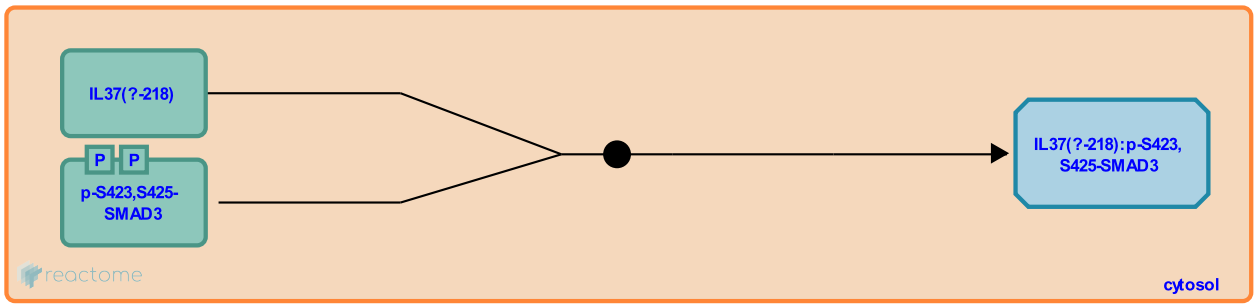
IL37(?-218) binds p-S423,S425-SMAD3 ↗

Location: Interleukin-37 signaling

Stable identifier: R-HSA-9009910

Type: binding

Compartments: cytosol



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Preceded by: IL37(1-?) and IL37 (?-) dissocates from IL37(1-?):IL37(?-218):CASP1(120-197):CASP1(317-404)

Followed by: IL37(?-218) binds SMAD3, IL37(?-218):p-S423,S425-SMAD3 translocates to the nucleus

Literature references

Dinarello, CA., Bufler, P., Nold, MF., Nold-Petry, CA., Palmer, BE., Zepp, JA. (2010). IL-37 is a fundamental inhibitor of innate immunity. *Nat. Immunol., 11*, 1014-22. ↗

Jaensson, H., Souchelnytskyi, S., Lomnytska, M., Hellman, U., Dubrovska, A., Grimsby, S. (2004). Proteomics-based identification of proteins interacting with Smad3: SREBP-2 forms a complex with Smad3 and inhibits its transcriptional activity. *FEBS Lett., 577*, 93-100. ↗

Editions

2017-09-27	Authored, Edited	Varusai, TM.
2017-11-02	Reviewed	Mantovani, A., Garlanda, C., Carriero, R.

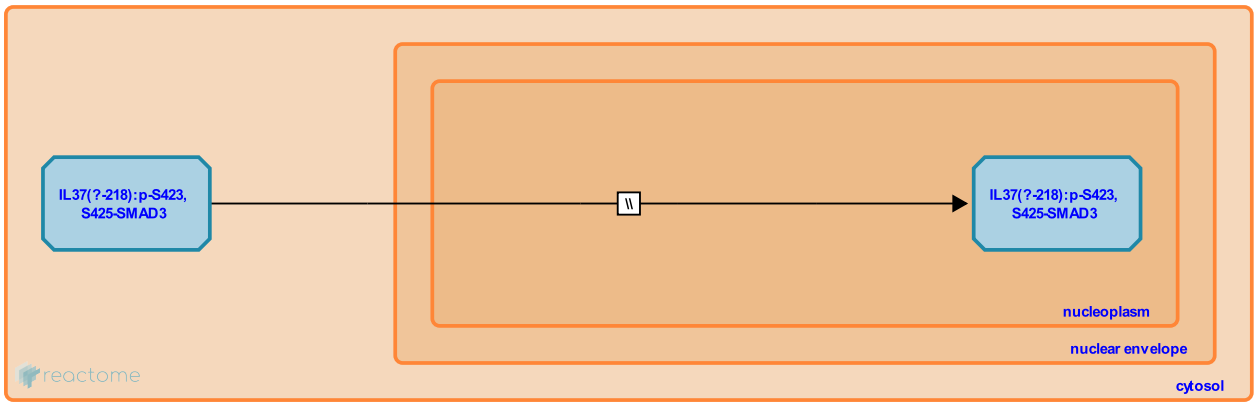
IL37(?-218):p-S423,S425-SMAD3 translocates to the nucleus ↗

Location: Interleukin-37 signaling

Stable identifier: R-HSA-9008928

Type: omitted

Compartments: nucleoplasm, cytosol



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Preceded by: IL37(?-218) binds p-S423,S425-SMAD3

Followed by: PTPNs gene transcription and translation

Literature references

Dinarello, CA., Bufler, P., Nold, MF., Nold-Petry, CA., Palmer, BE., Zepp, JA. (2010). IL-37 is a fundamental inhibitor of innate immunity. *Nat. Immunol., 11*, 1014-22. ↗

Fujita, M., Dinarello, CA., Bufler, P., Nold, M., Li, S., Kim, S. et al. (2016). Suppression of innate inflammation and immunity by interleukin-37. *Eur. J. Immunol., 46*, 1067-81. ↗

Jaensson, H., Souchelnytskyi, S., Lomnytska, M., Hellman, U., Dubrovska, A., Grimsby, S. (2004). Proteomics-based identification of proteins interacting with Smad3: SREBP-2 forms a complex with Smad3 and inhibits its transcriptional activity. *FEBS Lett., 577*, 93-100. ↗

Editions

2017-09-27	Authored, Edited	Varusai, TM.
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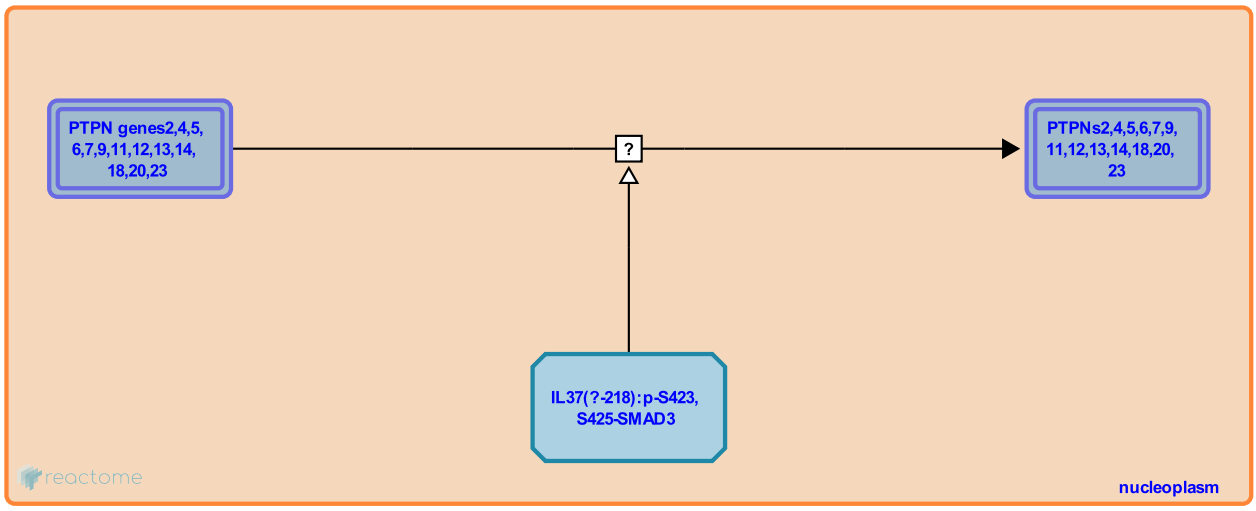
PTPNs gene transcription and translation ↗

Location: Interleukin-37 signaling

Stable identifier: R-HSA-9008894

Type: uncertain

Compartments: nucleoplasm



Tyrosine protein phosphatase non receptors (PTPNs) are a family of enzymes that act in coordination with protein tyrosine kinases to control various signalling pathways downstream. This event represents the transcription and translation of the PTPN set comprising the members: 2, 4, 5, 6, 7, 9, 11, 12, 13, 14, 18, 20 and 23. This event is positively regulated by IL-37b(? 218):SMAD3 and promotes dephosphorylation and suppression of the activation of tyrosine phosphorylation-dependent signaling pathways such as ERK, p38 MAPK, JNK, PI3K, NF-κB, and STAT3 pathways. (Luo et al., 2017).

Preceded by: IL37(?-218):p-S423,S425-SMAD3 translocates to the nucleus

Literature references

Li, D., Wang, SS., Zou, JM., Zhang, GM., Wang, Y., Huang, DS. et al. (2017). Intracellular IL-37b interacts with Smad3 to suppress multiple signaling pathways and the metastatic phenotype of tumor cells. *Oncogene, 36*, 2889-2899. ↗

Editions

2017-09-27	Authored, Edited	Varusai, TM.
2017-11-02	Reviewed	Mantovani, A., Garlanda, C., Carriero, R.

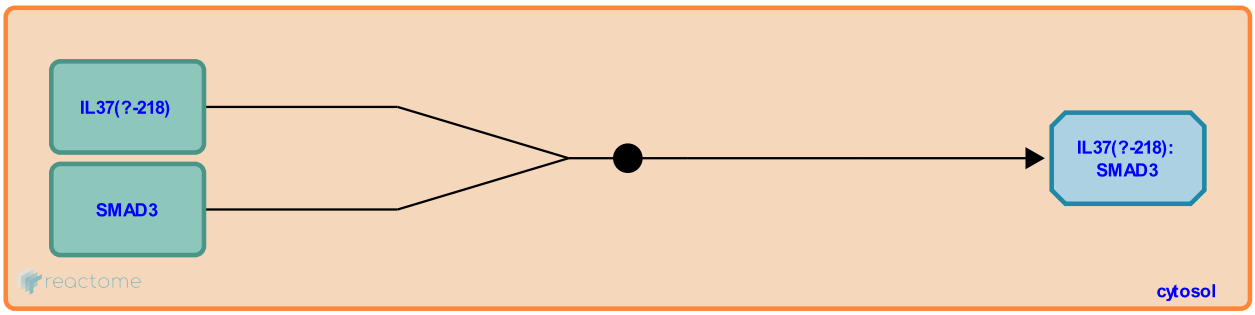
IL37(?-218) binds SMAD3 ↗

Location: Interleukin-37 signaling

Stable identifier: R-HSA-9008692

Type: binding

Compartments: cytosol



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Preceded by: IL37(?-218) binds p-S423,S425-SMAD3, IL37(1-?) and IL37 (?-) dissocates from IL37(1-?):IL37(?-218):CASP1(120-197):CASP1(317-404)

Literature references

Dinarello, CA., Bufler, P., Nold, MF., Nold-Petry, CA., Palmer, BE., Zepp, JA. (2010). IL-37 is a fundamental inhibitor of innate immunity. *Nat. Immunol., 11*, 1014-22. ↗

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Editions

2017-09-27	Authored, Edited	Varusai, TM.
2017-11-02	Reviewed	Mantovani, A., Garlanda, C., Carriero, R.

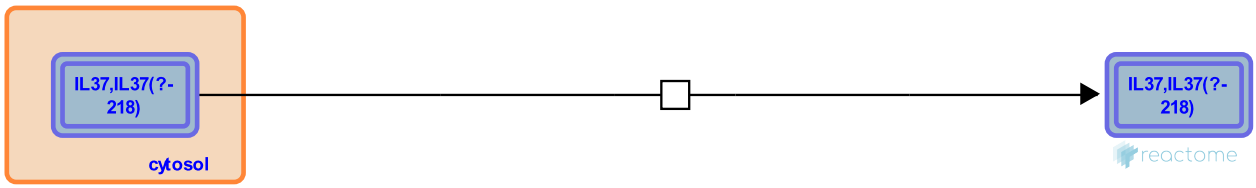
IL37, IL37(?-218) translocates from cytosol to extracellular region ↗

Location: Interleukin-37 signaling

Stable identifier: R-HSA-9008694

Type: transition

Compartments: extracellular region, cytosol



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Preceded by: IL37(1-?) and IL37 (?-) dissocates from IL37(1-?):IL37(?-218):CASP1(120-197):CASP1(317-404)

Followed by: IL37 binds IL18R1, IL37, IL37(?-218) binds IL18BP

Literature references

Dinarello, CA., Bufler, P., Li, S., Rubartelli, A., Fink, M., Bulau, AM. et al. (2014). Role of caspase-1 in nuclear translocation of IL-37, release of the cytokine, and IL-37 inhibition of innate immune responses. *Proc. Natl. Acad. Sci. U.S.A.*, *111*, 2650-5. ↗

Editions

2017-09-27	Authored, Edited	Varusai, TM.
2017-11-02	Reviewed	Mantovani, A., Garlanda, C., Carriero, R.

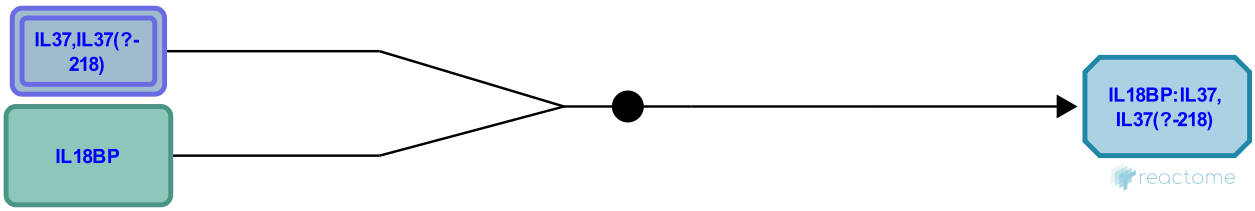
IL37, IL37(?-218) binds IL18BP ↗

Location: Interleukin-37 signaling

Stable identifier: R-HSA-9008587

Type: binding

Compartments: extracellular region



Interleukins (IL) are immunomodulatory proteins that elicit a wide array of responses in cells and tissues. Interleukin 37 (IL-37, IL-1 F7) is a member of the IL-1 family. There are five isoforms of IL-37 (a-e) of which transcript IL-37b is known to be functional (Sharma et al. 2008). This isoform is represented in UniProt as the canonical form of IL-37 and in Reactome as the full length, unprocessed form of IL-37. Like several other IL-1 family members, IL-37 is synthesized as a precursor that requires processing (primarily by caspase 1) to attain full receptor agonist or antagonist function. (Kumar et al. 2002). IL-18 binding protein (IL-18BP) binds IL-18 with high affinity inhibiting its activity (Kim et al. 2000). Both full length and processed IL-37 bind the third extracellular domain (D3) of IL-18BP. The binding of IL-18BP to IL-37 makes it unavailable for neutralization of IL-18 activity (Bufler et al. 2002). These events ultimately lead to suppression of cytokine production in several types of immune cells resulting in reduced inflammation.

Preceded by: IL37, IL37(?-218) translocates from cytosol to extracellular region

Literature references

Dinarello, CA., Bufler, P., Kim, SH., Azam, T., Kumar, S., Gamboni-Robertson, F. et al. (2002). A complex of the IL-1 homologue IL-1F7b and IL-18-binding protein reduces IL-18 activity. *Proc. Natl. Acad. Sci. U.S.A., 99*, 13723-8. ↗

Editions

2017-09-27	Authored, Edited	Varusai, TM.
2017-11-02	Reviewed	Mantovani, A., Garlanda, C., Carriero, R.

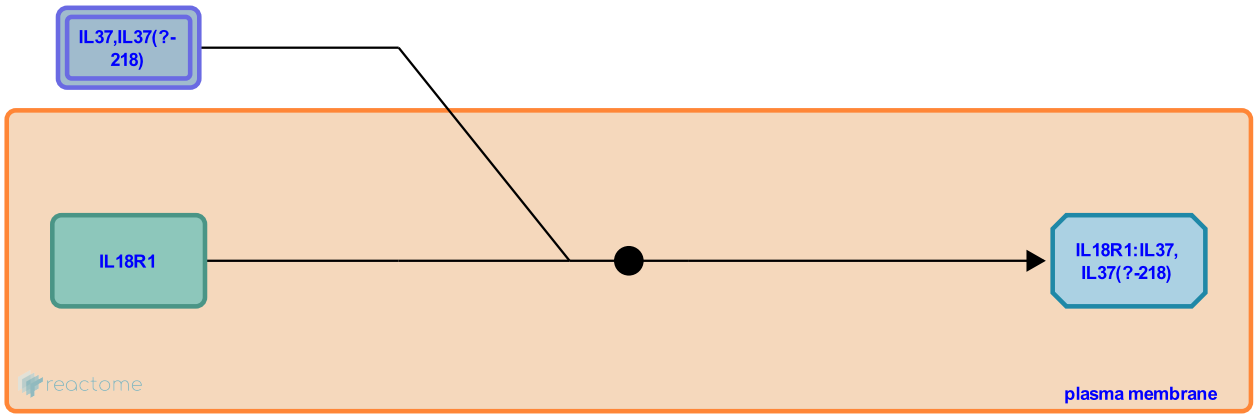
IL37 binds IL18R1 ↗

Location: Interleukin-37 signaling

Stable identifier: R-HSA-8848335

Type: binding

Compartments: plasma membrane, extracellular region



Interleukins (IL) are immunomodulatory proteins that elicit a wide array of responses in cells and tissues. Interleukin 37 (IL-37, IL-1F7) is a member of the IL-1 family. There are five isoforms of IL37 (a e) of which transcript IL-37 is known to be functional (Sharma et al. 2008). This isoform is represented in UniProt as the canonical form of IL-37 and in Reactome as the full length, unprocessed form of IL-37. Like several other IL-1 family members, IL-37 is synthesized as a precursor that requires processing (primarily by caspase 1) to attain full receptor agonist or antagonist function. (Kumar et al. 2002). Both full length and processed IL-37 can bind the Interleukin 18 receptor 1 (IL-18R1) but binding of processed IL-37 is more effective (Shi et al. 2003, Kumar et al. 2002). Subsequently, Single Ig IL-1 related receptor (SIGIRR, TIR 8,IL-1R8) is recruited and facilitates the suppression of cytokine production in several types of immune cells resulting in reduced inflammation.

Preceded by: IL37, IL37(?-218) translocates from cytosol to extracellular region

Followed by: IL37:IL18R1 binds SIGIRR

Literature references

Dinarello, CA., Sharma, S., Bufler, P., Reinhardt, D., Kim, SH., Gräf, R. et al. (2008). The IL-1 family member 7b translocates to the nucleus and down-regulates proinflammatory cytokines. *J. Immunol., 180*, 5477-82. ↗

Massague, J., Shi, Y. (2003). Mechanisms of TGF-beta signaling from cell membrane to the nucleus. *Cell, 113*, 685-700. ↗

Brigham-Burke, MR., Rieman, DJ., Kumar, S., Gambotto, A., Lotze, MT., Lehr, R. et al. (2002). Interleukin-1F7B (IL-1H4/IL-1F7) is processed by caspase-1 and mature IL-1F7B binds to the IL-18 receptor but does not induce IFN-gamma production. *Cytokine, 18*, 61-71. ↗

Editions

2014-06-04	Authored	Jupe, S.
2016-01-28	Edited	Jupe, S.
2016-01-28	Reviewed	Meldal, BH.

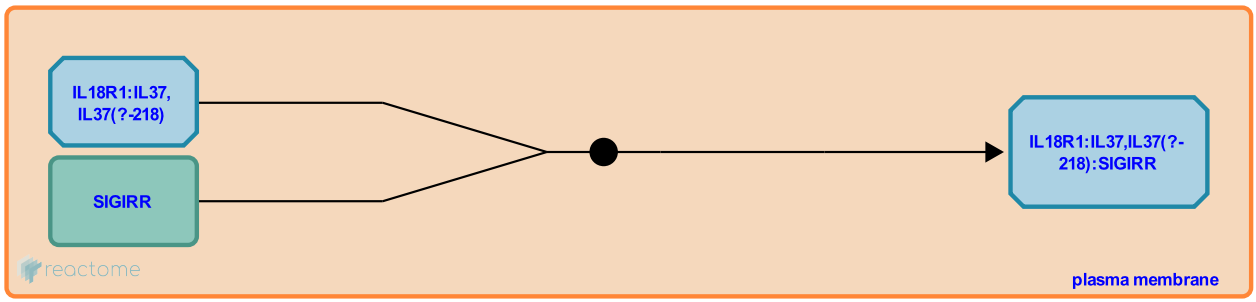
IL37:IL18R1 binds SIGIRR ↗

Location: Interleukin-37 signaling

Stable identifier: R-HSA-9008577

Type: binding

Compartments: plasma membrane



Interleukins (IL) are immunomodulatory proteins that elicit a wide array of responses in cells and tissues. Interleukin 37 (IL-37, IL-1 F7) is a member of the IL-1 family. There are five isoforms of IL-37 (a-e) of which transcript IL-37b is known to be functional (Sharma et al. 2008). This isoform is represented in UniProt as the canonical form of IL-37 and in Reactome as the full length, unprocessed form of IL-37. IL-37 can bind the Interleukin-18 receptor 1 (IL-18R1) (Shi et al. 2003, Kumar et al. 2002). Upon binding to IL-18R1, IL-37 facilitates the recruitment of Single Ig IL 1 related receptor (SIGIRR, TIR-8, IL-1R8) forming a complex (Nold Petry et al. 2015). These events ultimately lead to suppression of cytokine production in several types of immune cells resulting in reduced inflammation.

Preceded by: IL37 binds IL18R1

Followed by: STAT3 phosphorylation, TBK1 phosphorylation

Literature references

Lotz-Havla, AS., Dinarello, CA., Li, S., Rossello, FJ., Garlanda, C., Gersting, SW. et al. (2015). IL-37 requires the receptors IL-18Rα and IL-1R8 (SIGIRR) to carry out its multifaceted anti-inflammatory program upon innate signal transduction. *Nat. Immunol., 16*, 354-65. ↗

Editions

2017-09-27	Authored, Edited	Varusai, TM.
2017-11-02	Reviewed	Mantovani, A., Garlanda, C., Carriero, R.

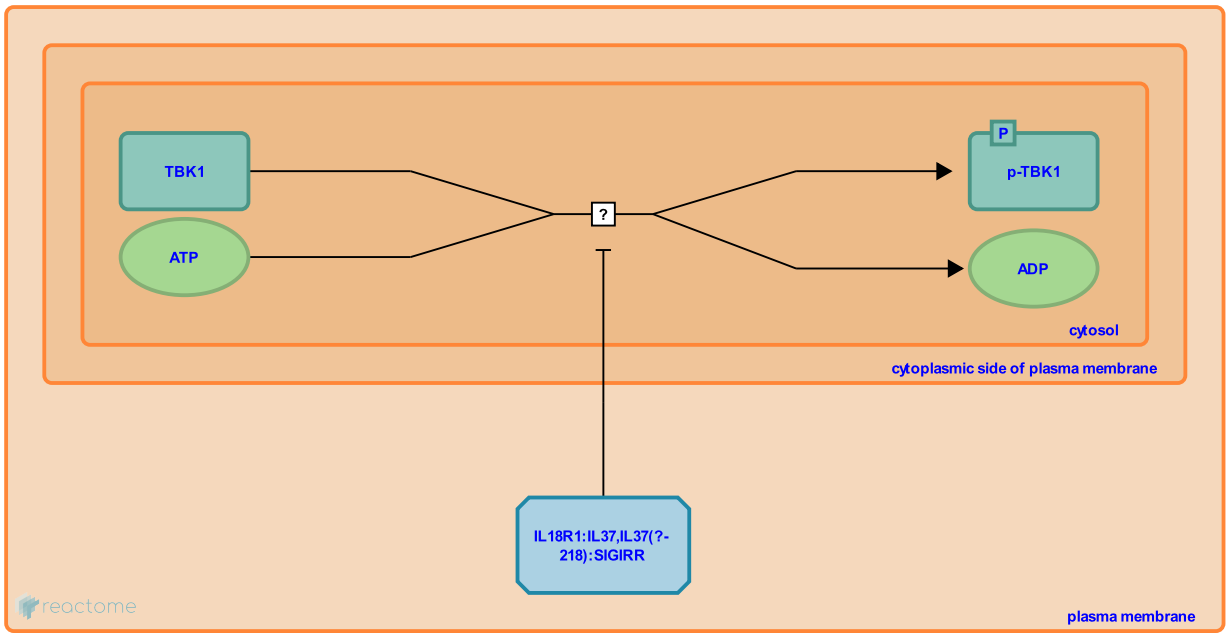
TBK1 phosphorylation ↗

Location: Interleukin-37 signaling

Stable identifier: R-HSA-9008684

Type: uncertain

Compartments: cytosol



Serine/threonine protein kinase TBK1 plays a key role in regulating inflammatory responses. TBK1 activity is regulated by phosphorylation of Ser 172 within the kinase activation loop (Kishore et al. 2002). TBK1 phosphorylation is thought to be an autoactivation event. The IL 37b:IL-18R1:SIGIRR complex can suppress TBK1 activity (Nold Petry et al. 2015, Clark K et al. 2009). This event is set as a black box event instance because the precise mechanism of TBK1 suppression by IL 37b:IL-18R1:SIGIRR complex is uncertain.

Preceded by: IL37:IL18R1 binds SIGIRR

Literature references

Kishore, N., Creely, D., Rouw, S., Reitz, B., Boddupalli, H., Mathialagan, S. et al. (2002). IKK-i and TBK-1 are enzymatically distinct from the homologous enzyme IKK-2: comparative analysis of recombinant human IKK-i, TBK-1, and IKK-2. *J. Biol. Chem., 277*, 13840-7. ↗

Editions

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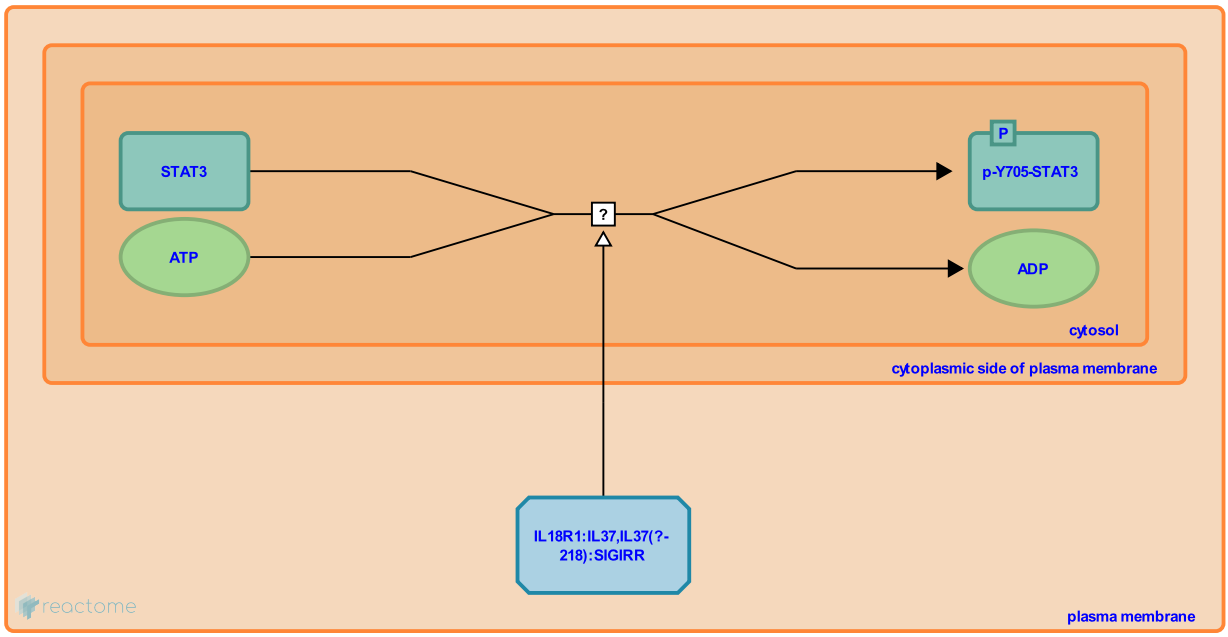
STAT3 phosphorylation ↗

Location: Interleukin-37 signaling

Stable identifier: R-HSA-9009072

Type: uncertain

Compartments: cytosol



Signal transducer and activator of transcription 3 (STAT3) acts downstream of various cellular receptors and is primarily involved in gene transcription. STAT3 is activated by serine/threonine kinases (Rebe et al. 2013). The IL-37:IL-18R1:SIGIRR complex can facilitate the phosphorylation and activation of STAT3 (Nold Petry et al. 2015). However, the precise mechanism is unclear. Hence, this event is represented as a black box.

Preceded by: IL37:IL18R1 binds SIGIRR

Literature references

Lotz-Havla, AS., Dinarello, CA., Li, S., Rossello, FJ., Garlanda, C., Gersting, SW. et al. (2015). IL-37 requires the receptors IL-18Rα and IL-1R8 (SIGIRR) to carry out its multifaceted anti-inflammatory program upon innate signal transduction. *Nat. Immunol., 16*, 354-65. ↗

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2017-11-02	Reviewed	Mantovani, A., Garlanda, C., Carriero, R.

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