The SMAD2/3:SMAD4 complex transfers to

the nucleus

Chen, YG., Contreras, O., Heldin, CH., Huang, T., Huminiecki, L., Jassal, B., Moustakas, A., Orlic-Milacic, M.

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

The contents of this document may be freely copied and distributed in any media, provided the authors, plus the institutions, are credited, as stated under the terms of <u>Creative Commons Attribution 4.0 International (CC BY 4.0)</u> <u>License</u>. For more information see our <u>license</u>.

15/05/2024

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. 7
- Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics*, 33, 3461-3467. A
- 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. *オ*

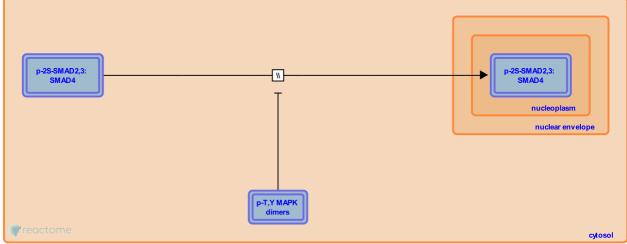
This document contains 1 reaction (see Table of Contents)

The SMAD2/3:SMAD4 complex transfers to the nucleus **7**

Stable identifier: R-HSA-173488

Type: omitted

Compartments: cytosol, nucleoplasm



The phosphorylated R-SMAD:CO-SMAD complex rapidly translocates to the nucleus (Xu et al. 2000, Kurisaki et al. 2001, Xiao et al. 2003) where it binds directly to DNA and interacts with a plethora of transcription co-factors. Translocation of SMAD2 and SMAD3 to the nucleus is negatively regulated by ERK-mediated phosphorylation (Kretzschmar et al. 1999). Regulation of target gene expression can be either positive or negative. A classic example of a target gene of the pathway are the genes encoding for I-SMADs. Thus, TGF-beta/SMAD signaling induces the expression of the negative regulators of the pathway (negative feedback loop).

Literature references

- Yoneda, Y., Moustakas, A., Heldin, CH., Kose, S., Kurisaki, A. (2001). Transforming growth factor-beta induces nuclear import of Smad3 in an importin-beta1 and Ran-dependent manner. *Mol Biol Cell*, *12*, 1079-91.
- Lin, X., Feng, XH., Duan, X., Liang, YY., Dai, F. (2010). Coupling of dephosphorylation and nuclear export of Smads in TGF-beta signaling. *Methods Mol. Biol.*, 647, 125-37.
- Hill, CS. (2009). Nucleocytoplasmic shuttling of Smad proteins. Cell Res., 19, 36-46. 7
- Lodish, HF., Latek, R., Xiao, Z. (2003). An extended bipartite nuclear localization signal in Smad4 is required for its nuclear import and transcriptional activity. *Oncogene, 22*, 1057-69.
- Massague, J., Xu, L., Chen, YG. (2000). The nuclear import function of Smad2 is masked by SARA and unmasked by TGFbeta-dependent phosphorylation. *Nat Cell Biol, 2*, 559-62. 🛪

Editions

2006-02-02	Authored	Jassal, B., Heldin, CH., Moustakas, A., Huminiecki, L.
2006-02-10	Edited	Jassal, B.
2006-04-18	Reviewed	Heldin, CH.
2012-05-14	Reviewed	Huang, T.
2012-11-14	Reviewed	Chen, YG.
2022-05-02	Reviewed	Contreras, O.
2022-05-09	Edited	Orlic-Milacic, M.