

# Activated thrombin (factor IIa) cleaves

## PAR3,4, activating them

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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

- 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*

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Stable identifier: R-HSA-114697

Type: transition

Compartments: extracellular region, plasma membrane



Thrombin signaling is mediated at least in part by a small family of G protein-coupled Proteinase Activated Receptors (PARs). Human platelet activation by thrombin is mediated predominantly by PAR1; PAR4-induced platelet responses are less pronounced. PAR2 is not present in human platelets. PARs 1, 3 and 4 are activated when thrombin cleaves an N-terminal exodomain. This cleavage event unmasks a new N-terminus that serves as a tethered ligand that binds intramolecularly to the body of the receptor to effect transmembrane signaling. Intermolecular ligation of one PAR molecule by another can occur but, not surprisingly, appears to be less efficient than self-ligation. A synthetic peptide of sequence SFLLRN, the first six amino acids of the new N-terminus generated when thrombin cleaves PAR1, can activate PAR1 independent of protease and receptor cleavage. In addition to providing evidence for the tethered ligand mechanism, such tethered ligand-mimicking peptides have provided a convenient pharmacological tool for probing the effects of PAR activation in cells and tissues.

#### Literature references

- Zheng, YW., Zeng, D., Kahn, ML., Connolly, AJ., Coughlin, SR., Tram, T. et al. (1997). Protease-activated receptor 3 is a second thrombin receptor in humans. *Nature*, 386, 502-6.
- Whitmore, TE., Xu, WF., Yee, DP., Andersen, H., Presnell, SR., Ching, A. et al. (1998). Cloning and characterization of human protease-activated receptor 4. *Proc Natl Acad Sci U S A*, 95, 6642-6. *¬*
- Wheaton, VI., Vu, TK., Coughlin, SR., Hung, DT. (1991). Molecular cloning of a functional thrombin receptor reveals a novel proteolytic mechanism of receptor activation. *Cell, 64*, 1057-68.

#### Editions

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Authored, Edited

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