

Thrombin and Its Receptors

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Thrombin

- A multifunctional serine protease
- Generated when coagulation cascade is triggered by vascular injury
- Plays a critical role in embryogenesis

Thrombin Functions

- Conversion of fibrinogen to fibrin
- Activation of multiple clotting factors including itself
- Activation of Protein C
- Most potent activator of platelets
- Causes endothelial cell secretion
- Is a mitogen for fibroblasts and vascular smooth muscle cells

Thrombin-Effects On Endothelium

- Causes delivery of leukocyte adhesion molecule P-selectin to the endothelial surface
- Causes secretion of von Willebrand factor
- Causes growth factor secretion
- Causes cytokine production

Thrombin Talks to Cells Through PARs

- PAR - Protease-Activated Receptor
- PAR1 is the primary thrombin receptor on human platelets
- Member of the seven transmembrane domain G protein-coupled receptor family
- It is activated by a novel mechanism

Thrombin Activation of PAR

- PAR1's amino-terminal exodomain contains a thrombin cleavage site LDPR/S
- Exodomain also contains a domain similar to Hirudin's domain that interacts with thrombin's fibrinogen-binding exosite
- Mutation of R⁴¹/S⁴² to “uncleavable” R/P renders the receptor unactivatable by thrombin

How Does R⁴¹/S⁴² Cleavage Cause Transmembrane Signaling

- S⁴²FLLRN⁴⁷ is the sequence of the new amino terminal portion of the cleaved receptor
- Synthetic peptide SFLLRN is an agonist for the receptor and bypasses the need for cleavage
- SFLLRN is a tethered-ligand for the receptor

The Tethered-Ligand Receptor

- The thrombin receptor contains its own agonist
- The agonist is not available until after cleavage
- The tethered peptide subsequently docks intramolecularly with an extracellular site on the receptor
- Docking results in transmembrane signaling.

Thrombin Activation of PAR1 is Irreversible

- This is different from other G-protein-coupled receptors such as the Ξ_2 -adrenergic
- √ Signaling is stopped by rapid phosphorylation and internalization of the receptor
- √ Unlike other similar receptors, the PAR1 cannot be recycled
- √ It is rapidly degraded in lysosomes