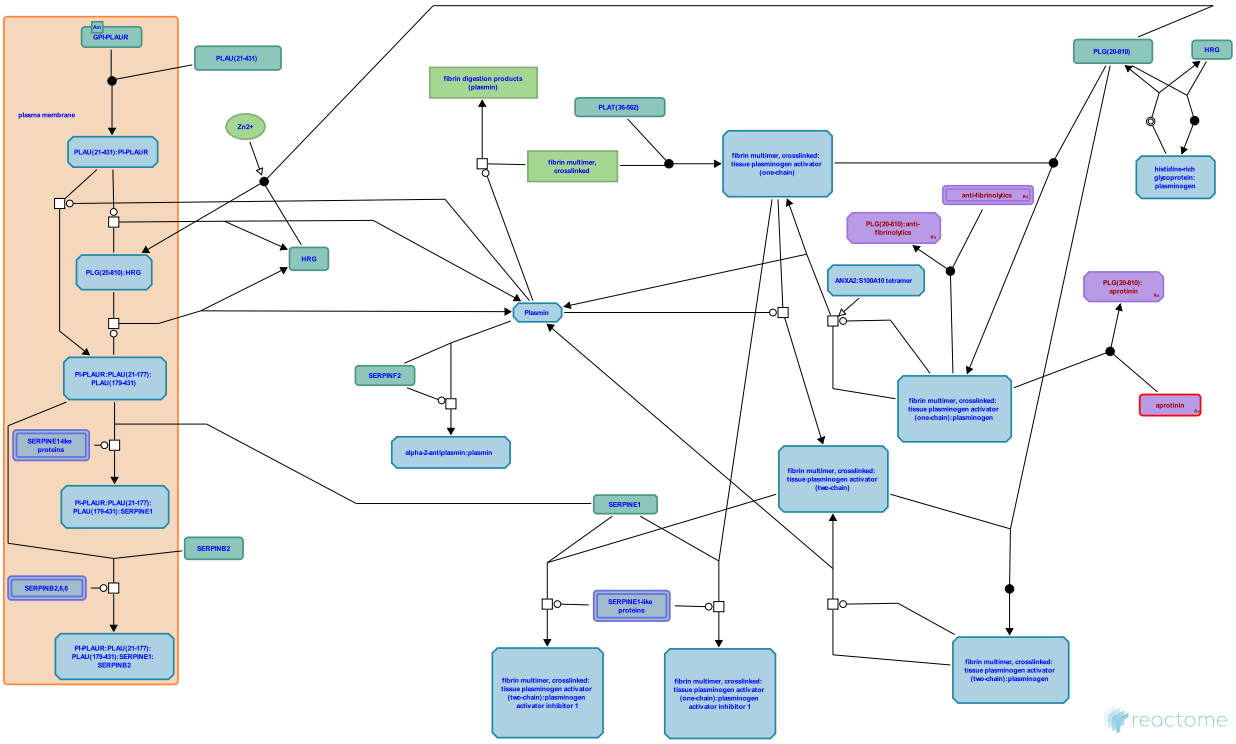
Dissolution of Fibrin Clot



D'Eustachio, P., Huddart, R., Jassal, B., Matthews, L., Rush, MG.

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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.

26/04/2024

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. ↗

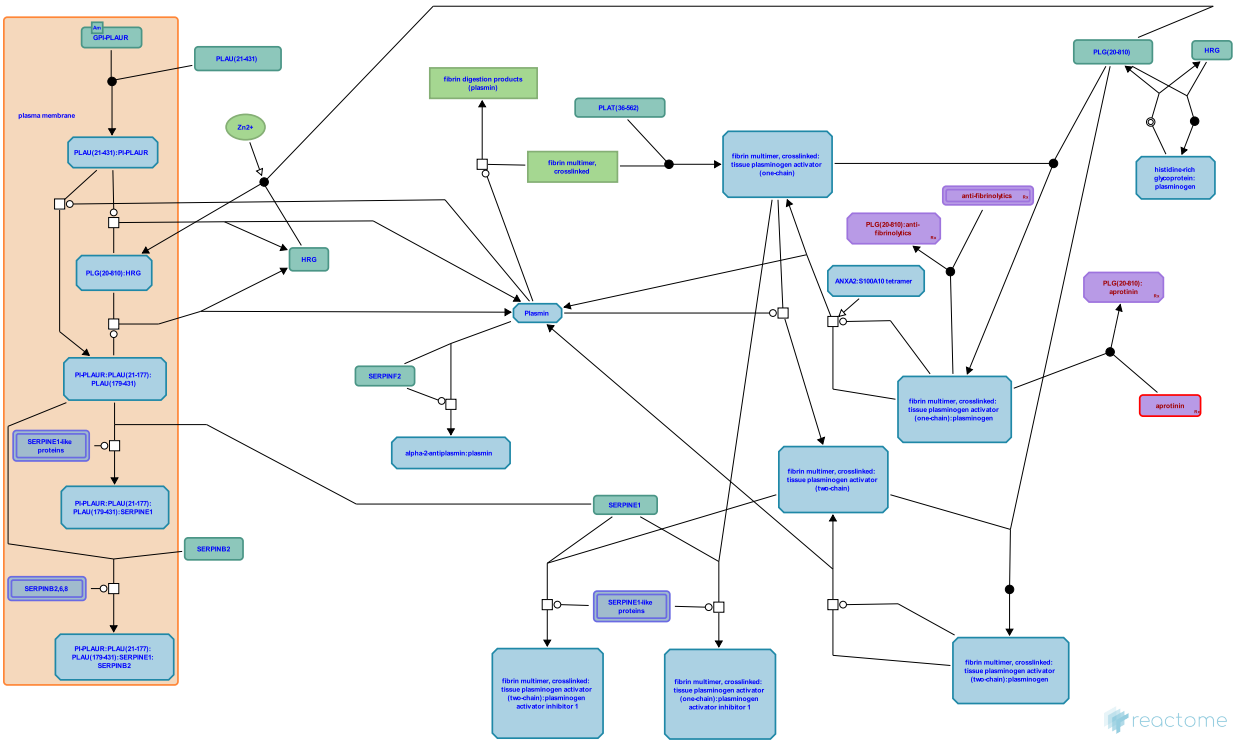
Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

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. ↗

Dissolution of Fibrin Clot ↗

Stable identifier: R-HSA-75205



The crosslinked fibrin multimers in a clot are broken down to soluble polypeptides by plasmin, a serine protease. Plasmin can be generated from its inactive precursor plasminogen and recruited to the site of a fibrin clot in two ways, by interaction with tissue plasminogen activator at the surface of a fibrin clot, and by interaction with urokinase plasminogen activator at a cell surface. The first mechanism appears to be the major one responsible for the dissolution of clots within blood vessels. The second, although capable of mediating clot dissolution, may normally play a major role in tissue remodeling, cell migration, and inflammation (Chapman 1997; Lijnen 2001).
Clot dissolution is regulated in two ways. First, efficient plasmin activation and fibrinolysis occur only in complexes formed at the clot surface or on a cell membrane - proteins free in the blood are inefficient catalysts and are rapidly inactivated. Second, both plasminogen activators and plasmin itself are inactivated by specific serpins, proteins that bind to serine proteases to form stable, enzymatically inactive complexes (Kohler and Grant 2000).
These events are outlined in the drawing: black arrows connect the substrates (inputs) and products (outputs) of individual reactions, and blue lines connect output activated enzymes to the other reactions that they catalyze.

Literature references

Lijnen, HR. (2001). Elements of the fibrinolytic system. *Ann N Y Acad Sci, 936*, 226-36. ↗

Kohler, HP., Grant, PJ. (2000). Plasminogen-activator inhibitor type 1 and coronary artery disease. *N Engl J Med, 342*, 1792-801. ↗

Chapman, HA. (1997). Plasminogen activators, integrins, and the coordinated regulation of cell adhesion and migration. *Curr Opin Cell Biol, 9*, 714-24. ↗

Editions

2008-01-11	Reviewed	Rush, MG.
2024-03-06	Edited	D'Eustachio, P.

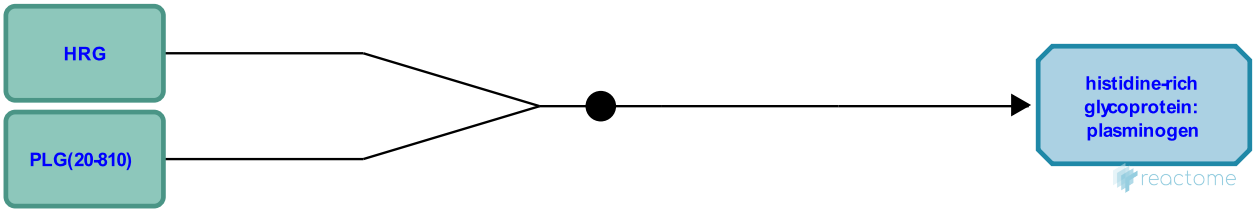
histidine-rich glycoprotein + plasminogen <-> histidine-rich glycoprotein:plasminogen ↗

Location: Dissolution of Fibrin Clot

Stable identifier: R-HSA-158722

Type: binding

Compartments: extracellular region



Plasminogen reversibly binds histidine-rich glycoprotein (HRG). The resulting complex interacts poorly with fibrin, suggesting that HRG might have an anti-fibrinolytic (clot-stabilizing) effect in vivo (Lijnen et al. 1980). Consistent with this suggestion, individuals with chronically reduced plasma HRG concentrations are susceptible to thrombosis (Shigekiyo et al. 1998).

Literature references

Yoshitake, S., Koide, T., Foster, D., Davie, EW. (1986). Amino acid sequence of human histidine-rich glycoprotein derived from the nucleotide sequence of its cDNA. *Biochemistry, 25*, 2220-5. ↗

Hoylaerts, M., Lijnen, HR. (1980). Isolation and characterization of a human plasma protein with affinity for the lysine binding sites in plasminogen. Role in the regulation of fibrinolysis and identification as histidine-rich glycoprotein. *J Biol Chem, 255*, 10214-22. ↗

Fujikawa, K., Yoshida, H., Koide, T., Matsumoto, K., Shigekiyo, T., Azuma, H. et al. (1998). HRG Tokushima: molecular and cellular characterization of histidine-rich glycoprotein (HRG) deficiency. *Blood, 91*, 128-33. ↗

Editions

2005-02-06	Authored	D'Eustachio, P.
2024-03-06	Edited	D'Eustachio, P.

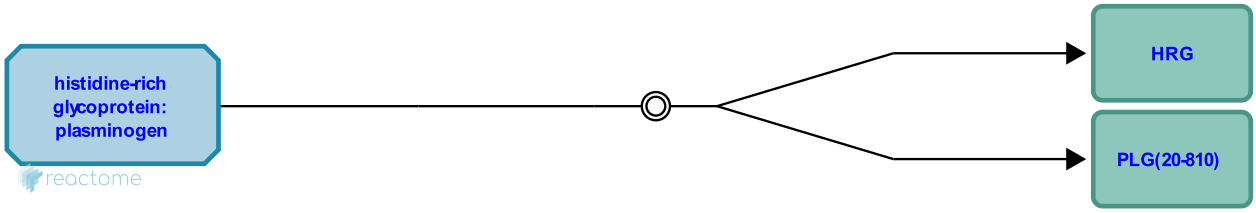
histidine-rich glycoprotein:plasminogen <-> histidine-rich glycoprotein + plasminogen ↗

Location: Dissolution of Fibrin Clot

Stable identifier: R-HSA-158721

Type: dissociation

Compartments: extracellular region



Plasminogen reversibly binds histidine-rich glycoprotein (HRG). The resulting complex interacts poorly with fibrin, suggesting that HRG might have an anti-fibrinolytic (clot-stabilizing) effect in vivo (Lijnen et al. 1980). Consistent with this suggestion, individuals with chronically reduced plasma HRG concentrations are susceptible to thrombosis (Shigekiyo et al. 1998).

Followed by: crosslinked fibrin multimer:tissue plasminogen activator (one-chain) + plasminogen -> crosslinked fibrin multimer:tissue plasminogen activator (one-chain):plasminogen

Literature references

Yoshitake, S., Koide, T., Foster, D., Davie, EW. (1986). Amino acid sequence of human histidine-rich glycoprotein derived from the nucleotide sequence of its cDNA. *Biochemistry, 25*, 2220-5. ↗

Hoylaerts, M., Lijnen, HR. (1980). Isolation and characterization of a human plasma protein with affinity for the lysine binding sites in plasminogen. Role in the regulation of fibrinolysis and identification as histidine-rich glycoprotein. *J Biol Chem, 255*, 10214-22. ↗

Fujikawa, K., Yoshida, H., Koide, T., Matsumoto, K., Shigekiyo, T., Azuma, H. et al. (1998). HRG Tokushima: molecular and cellular characterization of histidine-rich glycoprotein (HRG) deficiency. *Blood, 91*, 128-33. ↗

Editions

2005-02-06	Authored	D'Eustachio, P.
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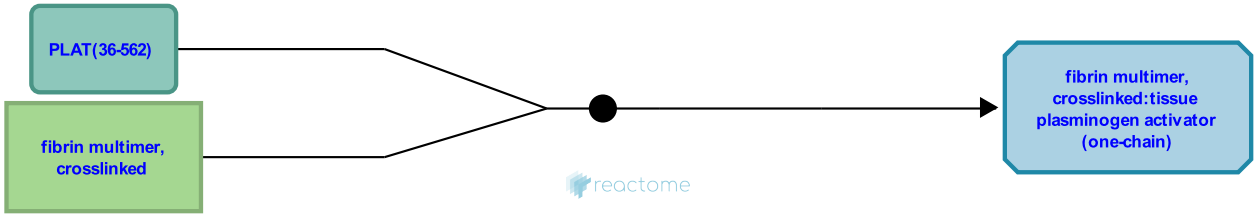
crosslinked fibrin multimer + tissue plasminogen activator (one-chain) -> crosslinked fibrin multimer:tissue plasminogen activator (one-chain) ↗

Location: Dissolution of Fibrin Clot

Stable identifier: R-HSA-158781

Type: binding

Compartments: extracellular region



The first step in the dissolution of a fibrin clot is the association of the one-chain form of tissue plasminogen activator with fibrin.

Followed by: fibrin multimer, crosslinked:tissue plasminogen activator (one-chain) + plasminogen activator inhibitor 1 -> fibrin multimer, crosslinked:tissue plasminogen activator (one-chain):plasminogen activator inhibitor 1, crosslinked fibrin multimer:tissue plasminogen activator (one-chain) + plasminogen -> crosslinked fibrin multimer:tissue plasminogen activator (one-chain):plasminogen

Literature references

Wallen, P., Jornvall, H., Kallstrom, M., Bergsdorf, N., Pohl, G. (1984). Tissue plasminogen activator: peptide analyses confirm an indirectly derived amino acid sequence, identify the active site serine residue, establish glycosylation sites, and localize variant differences. *Biochemistry, 23*, 3701-7. ↗

Higgins, DL., Vehar, GA. (1987). Interaction of one-chain and two-chain tissue plasminogen activator with intact and plasmin-degraded fibrin. *Biochemistry, 26*, 7786-91. ↗

Hoylaerts, M., Rijken, DC., Lijnen, HR. (1982). Kinetics of the activation of plasminogen by human tissue plasminogen activator. Role of fibrin. *J Biol Chem, 257*, 2912-9. ↗

Editions

2005-02-09	Authored	D'Eustachio, P.
2024-03-06	Edited	D'Eustachio, P.

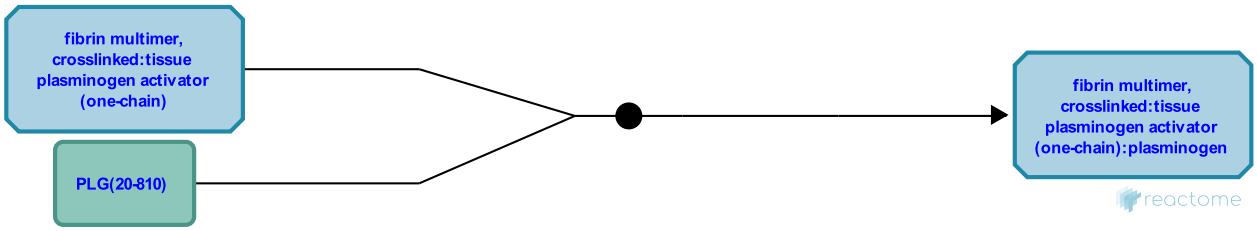
crosslinked fibrin multimer:tissue plasminogen activator (one-chain) + plasminogen -> crosslinked fibrin multimer:tissue plasminogen activator (one-chain):plasminogen ↗

Location: Dissolution of Fibrin Clot

Stable identifier: R-HSA-158784

Type: binding

Compartments: extracellular region



Plasminogen associates with tissue plasminogen activator bound to fibrin.

Preceded by: crosslinked fibrin multimer + tissue plasminogen activator (one-chain) -> crosslinked fibrin multimer:tissue plasminogen activator (one-chain), histidine-rich glycoprotein:plasminogen <-> histidine-rich glycoprotein + plasminogen

Followed by: crosslinked fibrin multimer:tissue plasminogen activator (one-chain):plasminogen -> crosslinked fibrin multimer:tissue plasminogen activator (one-chain) + plasmin

Literature references

Martzen, MR., Ichinose, A., Petersen, TE., Davie, EW. (1990). Characterization of the gene for human plasminogen, a key proenzyme in the fibrinolytic system. *J Biol Chem, 265*, 6104-11. ↗

Hoylaerts, M., Rijken, DC., Lijnen, HR. (1982). Kinetics of the activation of plasminogen by human tissue plasminogen activator. Role of fibrin. *J Biol Chem, 257*, 2912-9. ↗

Editions

2005-02-09	Authored	D'Eustachio, P.
2024-03-06	Edited	D'Eustachio, P.

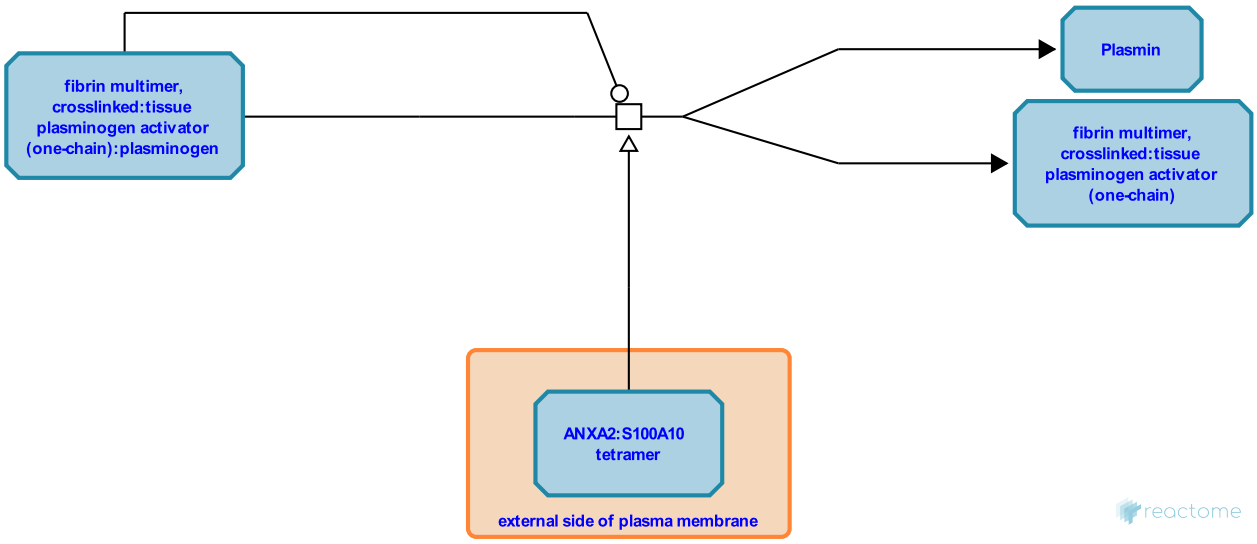
crosslinked fibrin multimer:tissue plasminogen activator (one-chain):plasminogen -> crosslinked fibrin multimer:tissue plasminogen activator (one-chain) + plasmin ↗

Location: Dissolution of Fibrin Clot

Stable identifier: R-HSA-158750

Type: transition

Compartments: extracellular region



Plasminogen bound to fibrin is cleaved and activated by tissue plasminogen activator also bound to the fibrin. The association of both plasminogen and tissue plasminogen activator with a fibrin clot juxtaposes the two molecules, facilitating their interaction (Hoylaerts et al. 1982). Early studies suggested that tissue plasminogen activator itself might require activation (conversion to its two-chain form) before it could catalyze this reaction (e.g., Higgins and Vehar 1987). More recent work (Boose et al. 1989) indicates that the single-chain form of the molecule is catalytically active, although cleavage increases its activity and may thus serve to accelerate the later stages of fibrinolysis.

Annexin A2 (ANXA2) is a multicompartmental, multifunctional protein that forms a heterotetramer with its endothelial cell-surface binding partner protein S100-A10 (S100A10) (Rety et al. 1999). The tetramer is able to positively modulate tissue plasminogen activator-dependent activation of the fibrinolytic protease, plasmin from its plasminogen precursor (Luo et al. 2013, Hedhli et al. 2012).

Preceded by: crosslinked fibrin multimer:tissue plasminogen activator (one-chain) + plasminogen -> crosslinked fibrin multimer:tissue plasminogen activator (one-chain):plasminogen

Followed by: alpha-2-antiplasmin + plasmin -> alpha-2-antiplasmin:plasmin, fibrin multimer, cross-linked -> fibrin digestion products (plasmin), crosslinked fibrin multimer:tissue plasminogen activator (one-chain) -> crosslinked fibrin multimer:tissue plasminogen activator (two-chain)

Literature references

Falcone, DJ., Tsirka, SE., Kraemer, R., Hedhli, N., Santambrogio, L., Cesarman-Maus, G. et al. (2012). The annexin A2/S100A10 system in health and disease: emerging paradigms. *J. Biomed. Biotechnol., 2012*, 406273. ↗

Tabaries, S., Renouard, M., Réty, S., Gerke, V., Sopkova, J., Russo-Marie, F. et al. (1999). The crystal structure of a complex of p11 with the annexin II N-terminal peptide. *Nat. Struct. Biol., 6*, 89-95. ↗

Luo, M., Hajjar, KA. (2013). Annexin A2 system in human biology: cell surface and beyond. *Semin. Thromb. Hemost., 39*, 338-46. ↗

Boose, JA., Sambrook, J., Gething, MJ., Gerard, R., Kuismanen, E. (1989). The single-chain form of tissue-type plasminogen activator has catalytic activity: studies with a mutant enzyme that lacks the cleavage site. *Biochemistry, 28*, 635-43. ↗

Hoylaerts, M., Rijken, DC., Lijnen, HR. (1982). Kinetics of the activation of plasminogen by human tissue plasminogen activator. Role of fibrin. *J Biol Chem, 257*, 2912-9. ↗

Editions

2005-02-09	Authored	D'Eustachio, P.
2015-02-11	Revised	Jassal, B.
2024-03-06	Edited	D'Eustachio, P.

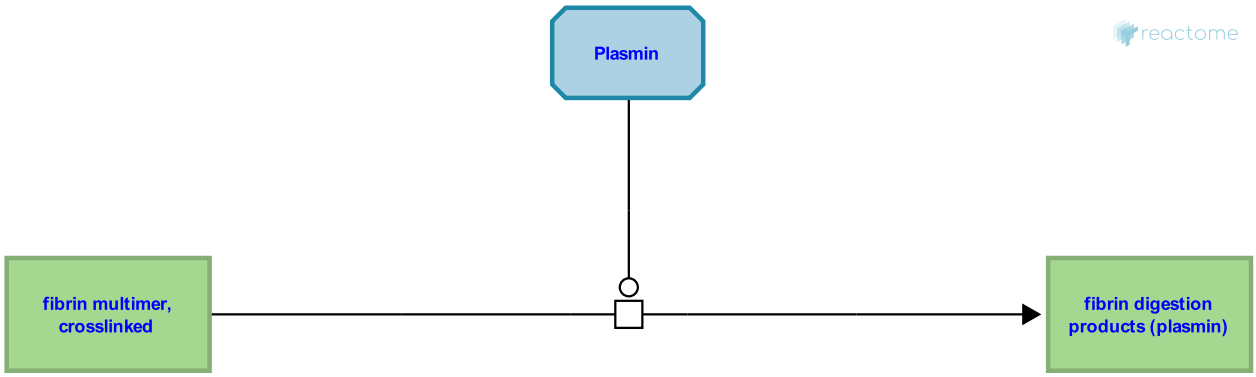
fibrin multimer, crosslinked -> fibrin digestion products (plasmin) ↗

Location: Dissolution of Fibrin Clot

Stable identifier: R-HSA-158766

Type: transition

Compartments: extracellular region



Plasmin, generated at the surfaces of the fibrin clot by tissue plasminogen activator or at the surfaces of cells by urokinase plasminogen activator, catalyzes the hydrolysis of fibrin to soluble fragments (Chapman 1997).

Preceded by: plasminogen:histidine-rich glycoprotein -> plasmin + histidine-rich glycoprotein (uPA [two-chain] catalyst), crosslinked fibrin multimer:tissue plasminogen activator (one-chain):plasminogen -> crosslinked fibrin multimer:tissue plasminogen activator (one-chain) + plasmin, crosslinked fibrin multimer:tissue plasminogen activator (two-chain):plasminogen -> crosslinked fibrin multimer:tissue plasminogen activator (two-chain) + plasmin, plasminogen:histidine-rich glycoprotein -> plasmin + histidine-rich glycoprotein (uPA [one-chain] catalyst)

Literature references

Martzen, MR., Ichinose, A., Petersen, TE., Davie, EW. (1990). Characterization of the gene for human plasminogen, a key proenzyme in the fibrinolytic system. *J Biol Chem, 265*, 6104-11. ↗

Editions

2005-02-09	Authored	D'Eustachio, P.
2024-03-06	Edited	D'Eustachio, P.

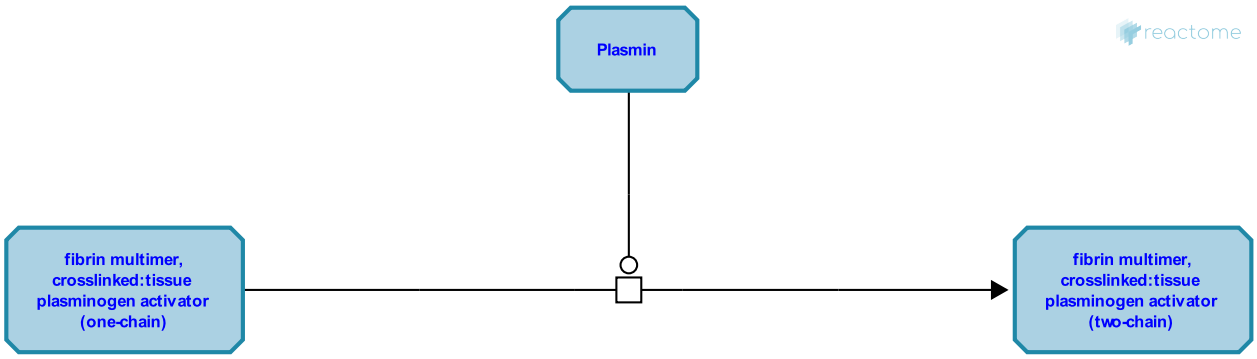
crosslinked fibrin multimer:tissue plasminogen activator (one-chain) -> crosslinked fibrin multimer:tissue plasminogen activator (two-chain) ↗

Location: Dissolution of Fibrin Clot

Stable identifier: R-HSA-158747

Type: transition

Compartments: extracellular region



Once plasmin has been activated, in the initial stage of the fibrinolysis process, it can catalyze the conversion of fibrin-bound tissue plasminogen activator (one-chain) to its more active two-chain form, increasing the rate at which additional plasminogen molecules can be activated.

Preceded by: crosslinked fibrin multimer:tissue plasminogen activator (one-chain):plasminogen -> crosslinked fibrin multimer:tissue plasminogen activator (one-chain) + plasmin

Followed by: fibrin multimer, crosslinked:tissue plasminogen activator (two-chain) + plasminogen activator inhibitor 1 -> fibrin multimer, crosslinked:tissue plasminogen activator (two-chain):plasminogen activator inhibitor 1, crosslinked fibrin multimer:tissue plasminogen activator (two-chain) + plasminogen -> crosslinked fibrin multimer:tissue plasminogen activator (two-chain):plasminogen

Literature references

Higgins, DL., Vehar, GA. (1987). Interaction of one-chain and two-chain tissue plasminogen activator with intact and plasmin-degraded fibrin. *Biochemistry, 26*, 7786-91. ↗

Boose, JA., Sambrook, J., Gething, MJ., Gerard, R., Kuismanen, E. (1989). The single-chain form of tissue-type plasminogen activator has catalytic activity: studies with a mutant enzyme that lacks the cleavage site. *Biochemistry, 28*, 635-43. ↗

Editions

2005-02-09	Authored	D'Eustachio, P.
2024-03-06	Edited	D'Eustachio, P.

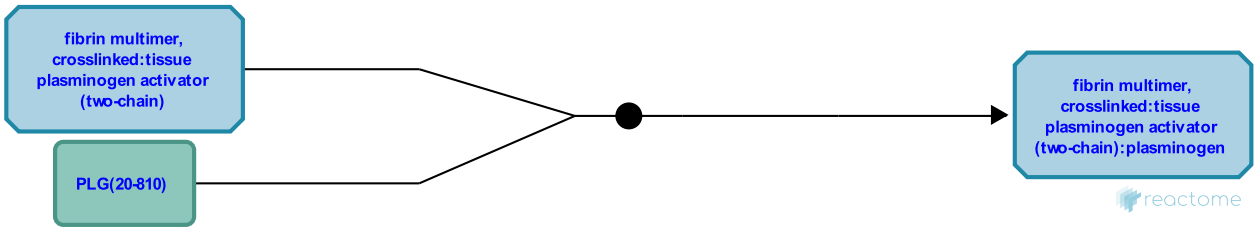
crosslinked fibrin multimer:tissue plasminogen activator (two-chain) + plasminogen -> crosslinked fibrin multimer:tissue plasminogen activator (two-chain):plasminogen ↗

Location: Dissolution of Fibrin Clot

Stable identifier: R-HSA-158756

Type: binding

Compartments: extracellular region



At the beginning of this reaction, 1 molecule of 'plasminogen', and 1 molecule of 'fibrin multimer, crosslinked:tissue plasminogen activator (two-chain)' are present. At the end of this reaction, 1 molecule of 'fibrin multimer, crosslinked:tissue plasminogen activator (two-chain):plasminogen' is present.

This reaction takes place in the 'extracellular region'.

Preceded by: crosslinked fibrin multimer:tissue plasminogen activator (one-chain) -> crosslinked fibrin multimer:tissue plasminogen activator (two-chain)

Followed by: crosslinked fibrin multimer:tissue plasminogen activator (two-chain):plasminogen -> crosslinked fibrin multimer:tissue plasminogen activator (two-chain) + plasmin

Literature references

Higgins, DL., Vehar, GA. (1987). Interaction of one-chain and two-chain tissue plasminogen activator with intact and plasmin-degraded fibrin. *Biochemistry, 26*, 7786-91. ↗

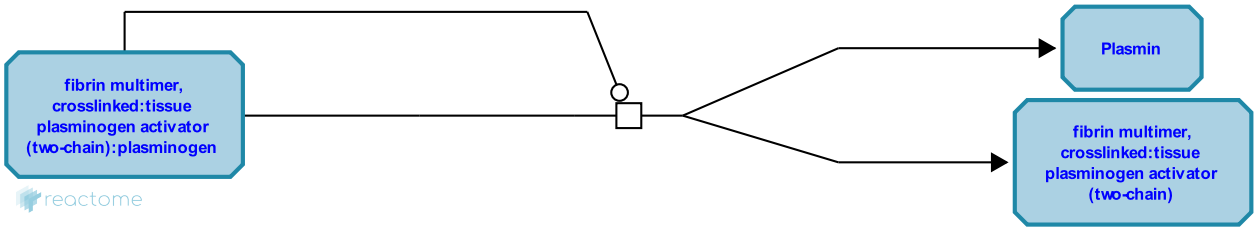
crosslinked fibrin multimer:tissue plasminogen activator (two-chain):plasminogen -> crosslinked fibrin multimer:tissue plasminogen activator (two-chain) + plasmin ↗

Location: Dissolution of Fibrin Clot

Stable identifier: R-HSA-158744

Type: transition

Compartments: extracellular region



At the beginning of this reaction, 1 molecule of 'fibrin multimer, crosslinked:tissue plasminogen activator (two-chain):plasminogen' is present. At the end of this reaction, 1 molecule of 'plasmin', and 1 molecule of 'fibrin multimer, crosslinked:tissue plasminogen activator (two-chain)' are present.

This reaction takes place in the 'extracellular region' and is mediated by the 'plasminogen activator activity' of 'fibrin multimer, crosslinked:tissue plasminogen activator (two-chain):plasminogen'.

Preceded by: crosslinked fibrin multimer:tissue plasminogen activator (two-chain) + plasminogen -> crosslinked fibrin multimer:tissue plasminogen activator (two-chain):plasminogen

Followed by: alpha-2-antiplasmin + plasmin -> alpha-2-antiplasmin:plasmin, fibrin multimer, cross-linked -> fibrin digestion products (plasmin)

Literature references

Higgins, DL., Vehar, GA. (1987). Interaction of one-chain and two-chain tissue plasminogen activator with intact and plasmin-degraded fibrin. *Biochemistry, 26*, 7786-91. ↗

Martzen, MR., Ichinose, A., Petersen, TE., Davie, EW. (1990). Characterization of the gene for human plasminogen, a key proenzyme in the fibrinolytic system. *J Biol Chem, 265*, 6104-11. ↗

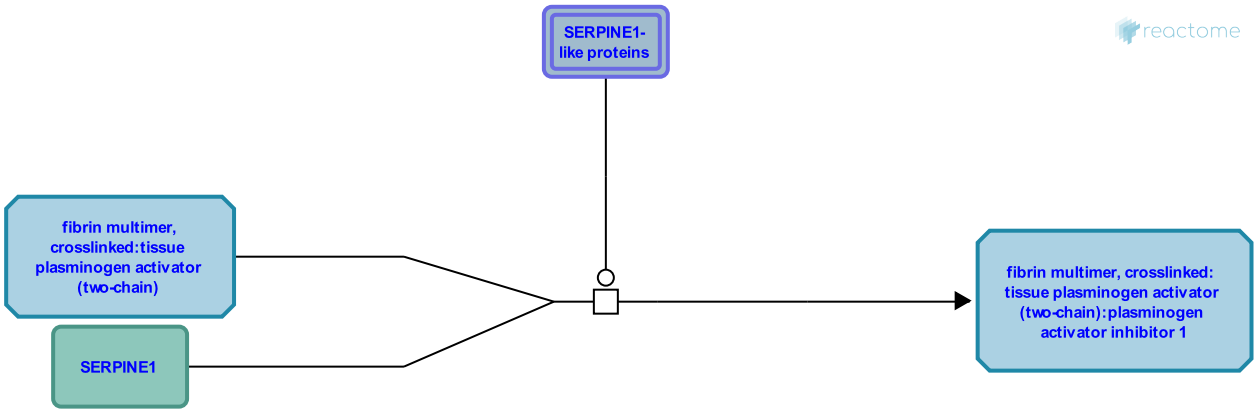
fibrin multimer, crosslinked:tissue plasminogen activator (two-chain) + plasminogen activator inhibitor 1 -> fibrin multimer, crosslinked:tissue plasminogen activator (two-chain):plasminogen activator inhibitor 1 ↗

Location: Dissolution of Fibrin Clot

Stable identifier: R-HSA-158800

Type: transition

Compartments: extracellular region



Plasminogen activator inhibitor 1, a serpin, binds to fibrin-associated tissue plasminogen activator. The resulting stable complex remains associated with fibrin but cannot activate plasminogen (Wagner et al. 1989). The importance of this step in the regulation of clot dissolution in vivo is indicated by the occurence of thrombosis in individuals with abnormally little tissue plasminogen activator or abnormally much plasminogen activator inhibitor (Juhan-Vague et al. 1987).

Preceded by: crosslinked fibrin multimer:tissue plasminogen activator (one-chain) -> crosslinked fibrin multimer:tissue plasminogen activator (two-chain)

Literature references

Wagner, OF., Veerman, H., Hohmann, C., de Vries, C., Pannekoek, H. (1989). Interaction between plasminogen activator inhibitor type 1 (PAI-1) bound to fibrin and either tissue-type plasminogen activator (t-PA) or urokinase-type plasminogen activator (u-PA). Binding of t-PA/PAI-1 complexes to fibrin mediated by both the finger and the kringle-2 domain of t-PA. *J Clin Invest, 84*, 647-55. ↗

Editions

2005-02-09	Authored	D'Eustachio, P.
2024-03-06	Edited	D'Eustachio, P.

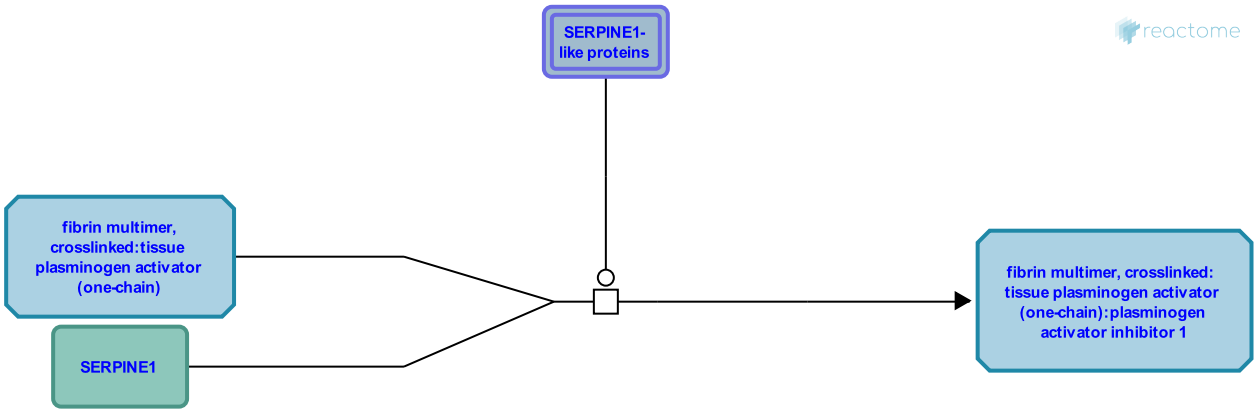
fibrin multimer, crosslinked:tissue plasminogen activator (one-chain) + plasminogen activator inhibitor 1 -> fibrin multimer, crosslinked:tissue plasminogen activator (one-chain):plasminogen activator inhibitor 1 ↗

Location: Dissolution of Fibrin Clot

Stable identifier: R-HSA-158795

Type: transition

Compartments: extracellular region



Plasminogen activator inhibitor 1, a serpin, binds to fibrin-associated tissue plasminogen activator. The resulting stable complex remains associated with fibrin but cannot activate plasminogen (Wagner et al. 1989). The importance of this step in the regulation of clot dissolution in vivo is indicated by the occurence of thrombosis in individuals with abnormally little tissue plasminogen activator or abnormally much plasminogen activator inhibitor (Juhan-Vague et al. 1987).

Preceded by: crosslinked fibrin multimer + tissue plasminogen activator (one-chain) -> crosslinked fibrin multimer:tissue plasminogen activator (one-chain)

Literature references

Wagner, OF., Veerman, H., Hohmann, C., de Vries, C., Pannekoek, H. (1989). Interaction between plasminogen activator inhibitor type 1 (PAI-1) bound to fibrin and either tissue-type plasminogen activator (t-PA) or urokinase-type plasminogen activator (u-PA). Binding of t-PA/PAI-1 complexes to fibrin mediated by both the finger and the kringle-2 domain of t-PA. *J Clin Invest, 84*, 647-55. ↗

Editions

2005-02-09	Authored	D'Eustachio, P.
2024-03-06	Edited	D'Eustachio, P.

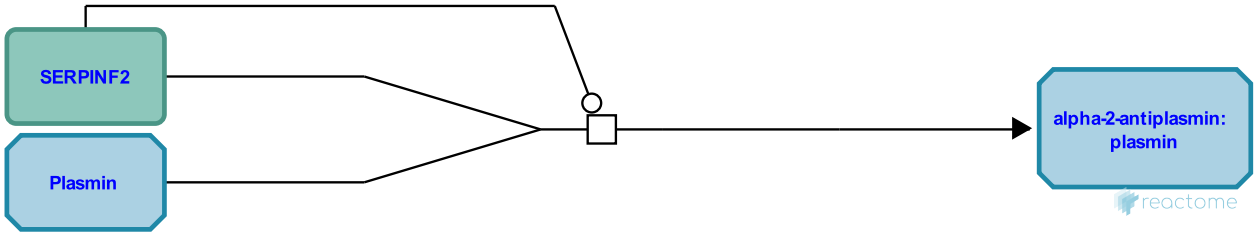
alpha-2-antiplasmin + plasmin -> alpha-2-antiplasmin:plasmin ↗

Location: Dissolution of Fibrin Clot

Stable identifier: R-HSA-158893

Type: transition

Compartments: extracellular region



Plasmin binds the serpin alpha-2-antiplasmin, forming a stable and catalytically inactive complex. While several serpin proteins bind and inactivate plasmin in vitro, alpha-2-antiplasmin appears to be the only one with substantial plasmin-neutralizing activity in vivo (Moroi and Aoki 1976; Lijnen et al. 1987).

Preceded by: crosslinked fibrin multimer:tissue plasminogen activator (one-chain):plasminogen -> crosslinked fibrin multimer:tissue plasminogen activator (one-chain) + plasmin, crosslinked fibrin multimer:tissue plasminogen activator (two-chain):plasminogen -> crosslinked fibrin multimer:tissue plasminogen activator (two-chain) + plasmin

Literature references

Holmes, WE., Rodriguez, H., Lijnen, HR., van Hoef, B., Wiman, B. (1987). Amino-acid sequence of human alpha 2-antiplasmin. *Eur J Biochem, 166*, 565-74. ↗

Moroi, M., Aoki, N. (1976). Isolation and characterization of alpha2-plasmin inhibitor from human plasma. A novel proteinase inhibitor which inhibits activator-induced clot lysis. *J Biol Chem, 251*, 5956-65. ↗

Editions

2005-02-11	Authored	D'Eustachio, P.
2024-03-06	Edited	D'Eustachio, P.

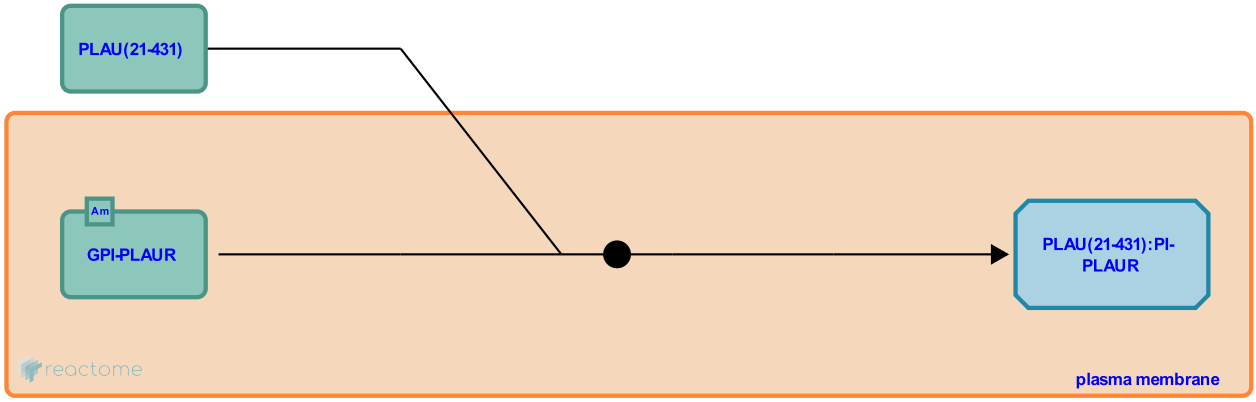
urokinase plasminogen activator + urokinase plasminogen activator receptor (uPAR) -> urokinase plasminogen activator:uPAR ↗

Location: Dissolution of Fibrin Clot

Stable identifier: R-HSA-158959

Type: binding

Compartments: plasma membrane, extracellular region



The uncleaved (one-chain) form of urokinase plasminogen activator associates with urokinase plasminogen activator receptor (uPAR), forming a complex at the cell surface (Cubellis et al. 1986). The complex is anchored to the outer face of the plasma membrane by a glycophosphatidylinositol moiety at the carboxy terminus of uPAR (Behrendt et al. 1990; Ploug et al. 1991).

Followed by: plasminogen:histidine-rich glycoprotein -> plasmin + histidine-rich glycoprotein (uPA [one-chain] catalyst)

Literature references

Ploug, M., Blasi, F., Nielsen, LS., Appella, E., Dano, K., Lober, D. et al. (1990). The human receptor for urokinase plasminogen activator. NH2-terminal amino acid sequence and glycosylation variants. *J Biol Chem, 265*, 6453-60. ↗

Blasi, F., Nolli, ML., Cubellis, MV., Cassani, G. (1986). Binding of single-chain prourokinase to the urokinase receptor of human U937 cells. *J Biol Chem, 261*, 15819-22. ↗

Ploug, M., Blasi, F., Dano, K., Ronne, E., Behrendt, N., Jensen, AL. (1991). Cellular receptor for urokinase plasminogen activator. Carboxyl-terminal processing and membrane anchoring by glycosyl-phosphatidylinositol. *J Biol Chem, 266*, 1926-33. ↗

Editions

2005-02-14	Authored	D'Eustachio, P.
2024-03-06	Edited	D'Eustachio, P.

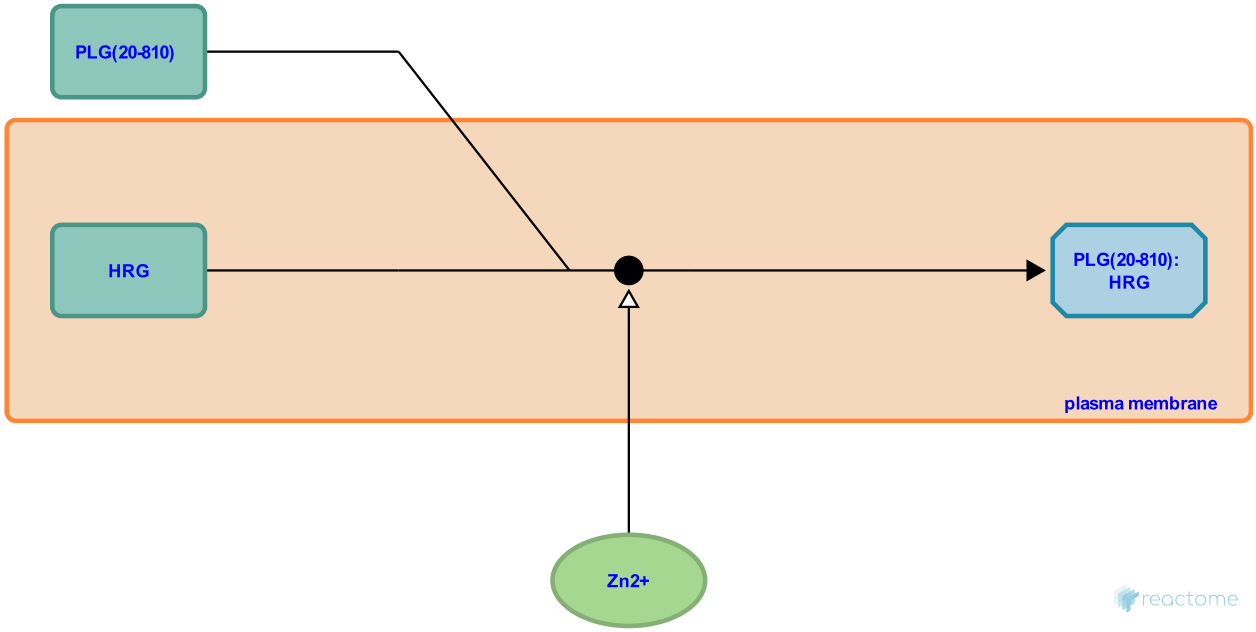
plasminogen + histidine-rich glycoprotein -> plasminogen:histidine-rich glycoprotein ↗

Location: Dissolution of Fibrin Clot

Stable identifier: R-HSA-158941

Type: binding

Compartments: plasma membrane, extracellular region



Extracellular plasminogen binds with high affinity to histidine-rich glycoprotein on the plasma membrane. Binding requires Zn++ in concentrations higher than those found in normal plasma, but that can be generated, e.g., by platelet activation (Jones et al. 2004).

Followed by: plasminogen:histidine-rich glycoprotein -> plasmin + histidine-rich glycoprotein (uPA [one-chain] catalyst)

Editions

2005-02-14	Authored	D'Eustachio, P.
2024-03-06	Edited	D'Eustachio, P.

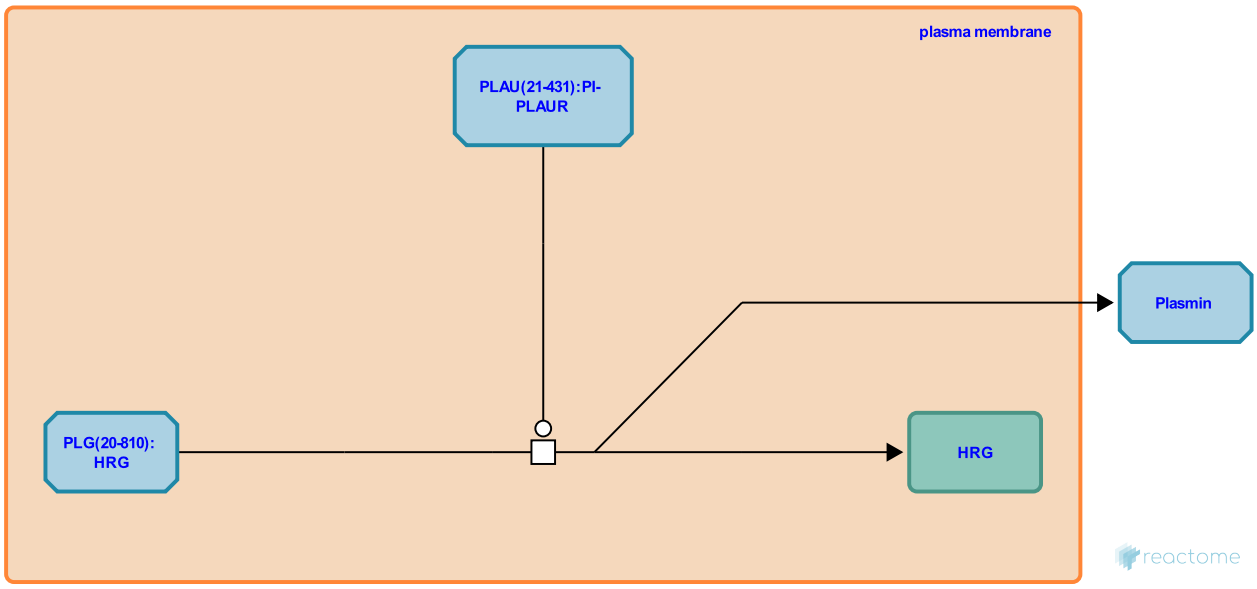
plasminogen:histidine-rich glycoprotein -> plasmin + histidine-rich glycoprotein (uPA [one-chain] catalyst) ↗

Location: Dissolution of Fibrin Clot

Stable identifier: R-HSA-158982

Type: transition

Compartments: plasma membrane, extracellular region



Plasminogen, tethered to the cell surface by its association with histidine-rich glycoprotein, is cleaved and activated to plasmin by the action of urokinase plasminogen activator bound to uPAR, its cell-surface receptor. The association of both substrate and enzyme with the cell surface is necessary for the reaction to proceed efficiently (Ellis et al. 1991). While the one-chain form of urokinase plasminogen activator is lower than that of the two-chain form, it is still sufficient to initiate the process of plasmin activation (Ellis et al. 1989; Lijnen et al. 1986).

Preceded by: plasminogen + histidine-rich glycoprotein -> plasminogen:histidine-rich glycoprotein, urokinase plasminogen activator + urokinase plasminogen activator receptor (uPAR) -> urokinase plasminogen activator:uPAR

Followed by: urokinase plasminogen activator (one-chain):uPAR -> urokinase plasminogen activator (two-chain):uPAR, fibrin multimer, crosslinked -> fibrin digestion products (plasmin)

Literature references

Ellis, V., Dano, K., Behrendt, N. (1991). Plasminogen activation by receptor-bound urokinase. A kinetic study with both cell-associated and isolated receptor. *J Biol Chem, 266*, 12752-8. ↗

Ellis, V., Kakkar, VV., Scully, MF. (1989). Plasminogen activation initiated by single-chain urokinase-type plasminogen activator. Potentiation by U937 monocytes. *J Biol Chem, 264*, 2185-8. ↗

Collen, D., Blaber, M., Winkler, ME., Lijnen, HR., Zamarron, C. (1986). Activation of plasminogen by pro-urokinase. I. Mechanism. *J Biol Chem, 261*, 1253-8. ↗

Editions

2005-02-14	Authored	D'Eustachio, P.
2024-03-06	Edited	D'Eustachio, P.

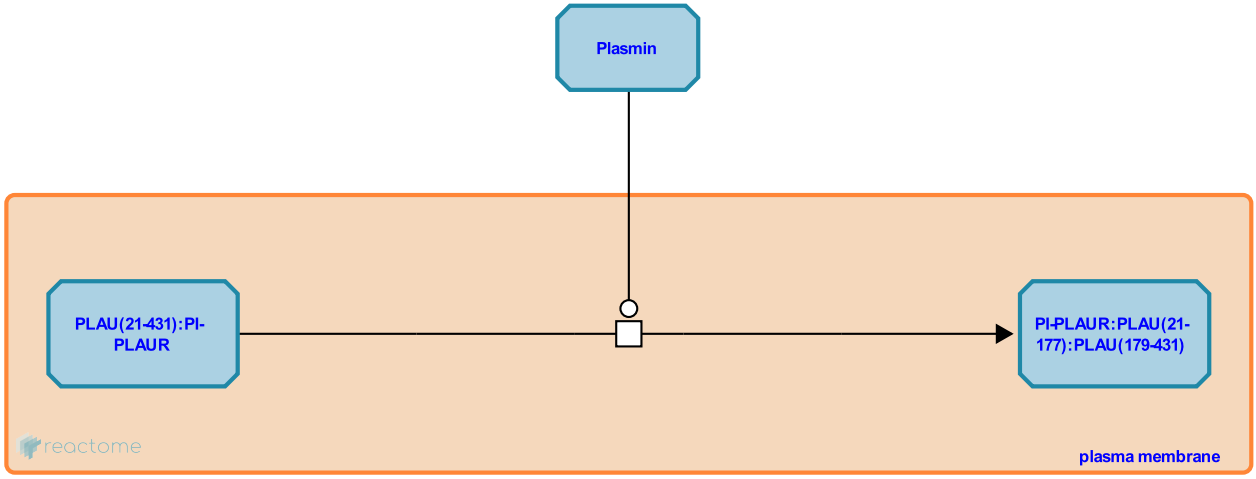
urokinase plasminogen activator (one-chain):uPAR -> urokinase plasminogen activator (two-chain):uPAR ↗

Location: Dissolution of Fibrin Clot

Stable identifier: R-HSA-158942

Type: transition

Compartments: plasma membrane, extracellular region



The small amount of plasmin generated by the activity of the one-chain form of urokinase plasminogen activator in turn cleaves urokinase plasminogen activator, converting it to its substantially more active two-chain form (Cubellis et al. 1986; Lijnen et al. 1991).

Preceded by: plasminogen:histidine-rich glycoprotein -> plasmin + histidine-rich glycoprotein (uPA [one-chain] catalyst)

Followed by: urokinase plasminogen activator (two-chain):uPAR + plasminogen activator inhibitor 1 (PAI-1) -> PAI-1:urokinase plasminogen activator (two-chain):uPAR, urokinase plasminogen activator (two-chain):uPAR + plasminogen activator inhibitor 2 (PAI-2) -> PAI-2:urokinase plasminogen activator (two-chain):uPAR, plasminogen:histidine-rich glycoprotein -> plasmin + histidine-rich glycoprotein (uPA [two-chain] catalyst)

Literature references

Blasi, F., Nolli, ML., Cubellis, MV., Cassani, G. (1986). Binding of single-chain prourokinase to the urokinase receptor of human U937 cells. *J Biol Chem, 261*, 15819-22. ↗

Collen, D., Blaber, M., Winkler, ME., Lijnen, HR., Zamarron, C. (1986). Activation of plasminogen by pro-urokinase. I. Mechanism. *J Biol Chem, 261*, 1253-8. ↗

Editions

2005-02-14	Authored	D'Eustachio, P.
2024-03-06	Edited	D'Eustachio, P.

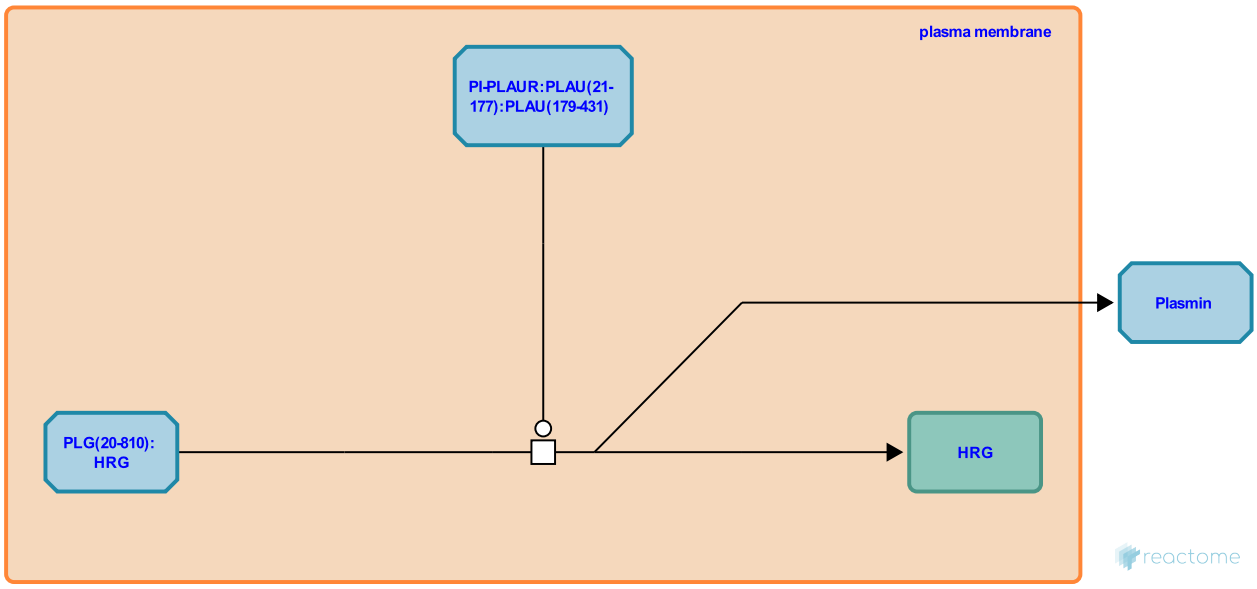
plasminogen:histidine-rich glycoprotein -> plasmin + histidine-rich glycoprotein (uPA [two-chain] catalyst) ↗

Location: Dissolution of Fibrin Clot

Stable identifier: R-HSA-158925

Type: transition

Compartments: plasma membrane, extracellular region



Plasminogen, tethered to the cell surface by its association with histidine-rich glycoprotein, is rapidly cleaved and activated to plasmin by the action of urokinase plasminogen activator(two-chain form) bound to uPAR, its cell-surface receptor. The association of both substrate and enzyme with the cell surface is necessary for the reaction to proceed efficiently (Ellis et al. 1989, 1991).

Preceded by: urokinase plasminogen activator (one-chain):uPAR -> urokinase plasminogen activator (two-chain):uPAR

Followed by: fibrin multimer, crosslinked -> fibrin digestion products (plasmin)

Literature references

Ellis, V., Dano, K., Behrendt, N. (1991). Plasminogen activation by receptor-bound urokinase. A kinetic study with both cell-associated and isolated receptor. *J Biol Chem, 266*, 12752-8. ↗

Ellis, V., Kakkar, VV., Scully, MF. (1989). Plasminogen activation initiated by single-chain urokinase-type plasminogen activator. Potentiation by U937 monocytes. *J Biol Chem, 264*, 2185-8. ↗

Editions

2005-02-14	Authored	D'Eustachio, P.
2024-03-06	Edited	D'Eustachio, P.

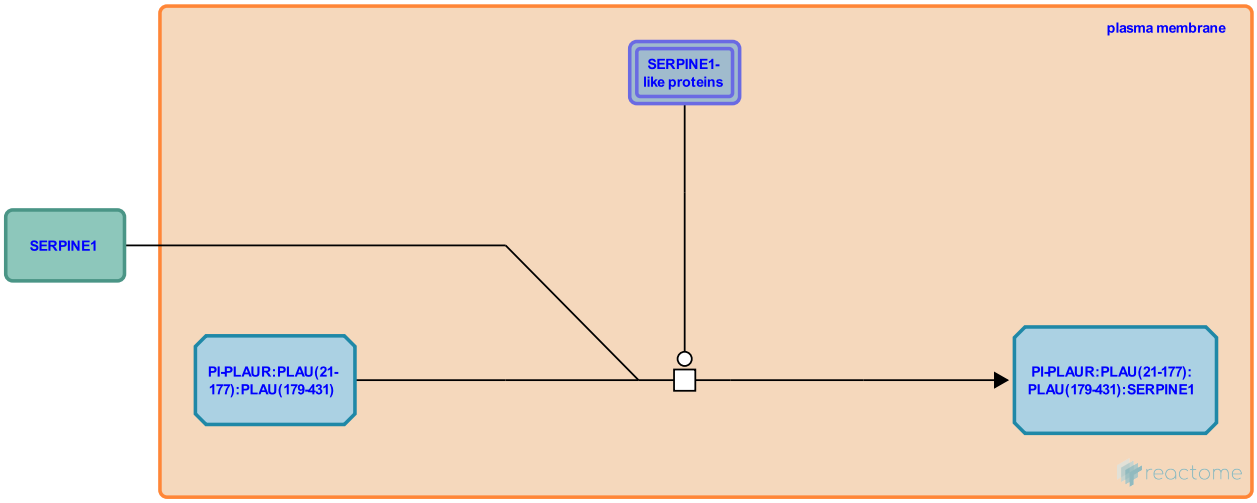
urokinase plasminogen activator (two-chain):uPAR + plasminogen activator inhibitor 1 (PAI-1) -> PAI-1:urokinase plasminogen activator (two-chain):uPAR ↗

Location: Dissolution of Fibrin Clot

Stable identifier: R-HSA-159005

Type: transition

Compartments: plasma membrane, extracellular region



Activated (two-chain) urokinase plasminogen activator binds plasminogen activator inhibitor 1, a serpin, to form a stable, inactive complex that remains associated with uPAR on the plasma membrane (Cubellis et al. 1989).

Preceded by: urokinase plasminogen activator (one-chain):uPAR -> urokinase plasminogen activator (two-chain):uPAR

Literature references

Blasi, F., Dano, K., Andreasen, P., Cubellis, MV., Mayer, M., Ragno, P. (1989). Accessibility of receptor-bound urokinase to type-1 plasminogen activator inhibitor. *Proc Natl Acad Sci U S A, 86*, 4828-32. ↗

Editions

2005-02-14	Authored	D'Eustachio, P.
2024-03-06	Edited	D'Eustachio, P.

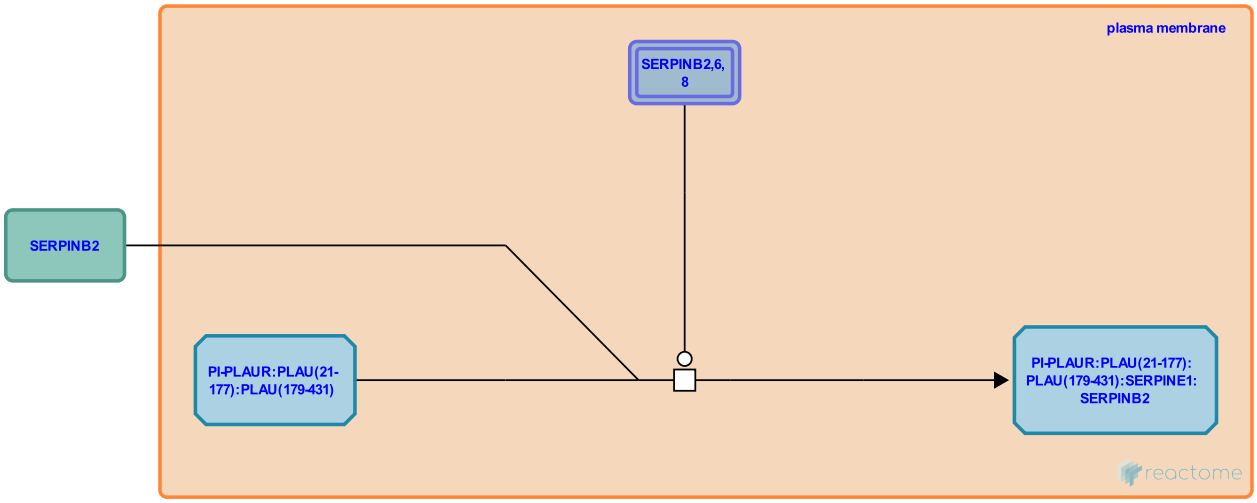
urokinase plasminogen activator (two-chain):uPAR + plasminogen activator inhibitor 2 (PAI-2) -> PAI-2:urokinase plasminogen activator (two-chain):uPAR ↗

Location: Dissolution of Fibrin Clot

Stable identifier: R-HSA-159001

Type: transition

Compartments: plasma membrane, extracellular region



Activated (two-chain) urokinase plasminogen activator binds plasminogen activator inhibitor 2, a serpin, to form a stable, inactive complex that remains associated with uPAR on the plasma membrane (Estreicher et al. 1990; Kruithof et al. 1986).

Preceded by: urokinase plasminogen activator (one-chain):uPAR -> urokinase plasminogen activator (two-chain):uPAR

Literature references

Vassalli, JD., Bachmann, F., Mattaliano, RJ., Kruithof, EK., Schleuning, WD. (1986). Purification and characterization of a plasminogen activator inhibitor from the histiocytic lymphoma cell line U-937. *J Biol Chem, 261*, 11207-13. ↗

Vassalli, JD., Orci, L., Carpentier, JL., Muhlhauser, J., Estreicher, A. (1990). The receptor for urokinase type plasminogen activator polarizes expression of the protease to the leading edge of migrating monocytes and promotes degradation of enzyme inhibitor complexes. *J Cell Biol, 111*, 783-92. ↗

Editions

2005-02-14	Authored	D'Eustachio, P.
2024-03-06	Edited	D'Eustachio, P.

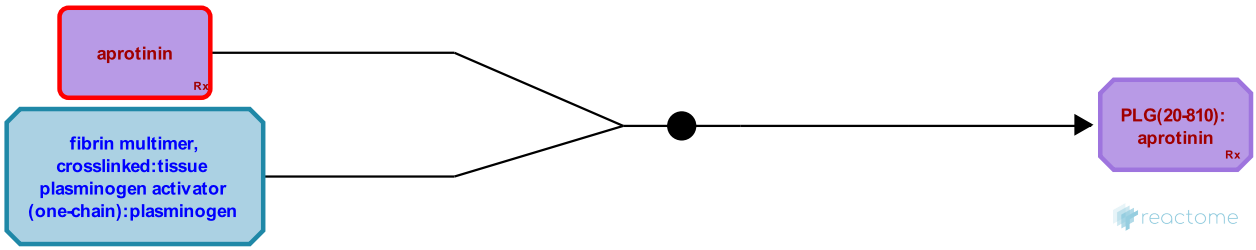
PLG(20-810) binds aprotinin ↗

Location: Dissolution of Fibrin Clot

Stable identifier: R-HSA-9724745

Type: binding

Compartments: extracellular region



Fibrinolysis is the process that leads to the breakdown of blood clots by the action of the serine protease plasmin. Aprotinin is a competitive inhibitor of several serine proteases including plasmin (Sperzel & Huetter 2007). It is a monomeric polypeptide derived from bovine lung tissue. By inhibiting the formation of plasmin and thereby inhibiting fibrinolysis, aprotinin can be used to reduce bleeding during complex surgery (Mahdy & Webster 2004).

Aprotinin has been shown to display anti-SARS-CoV-2 activity against four viral isolates (Bojkova et al. 2020). Protease inhibitors such as aprotinin may prevent virus entry into host cells by preventing the cleavage of the spike protein by ceulluar proteases.

Literature references

Sperzel, M., Huetter, J. (2007). Evaluation of aprotinin and tranexamic acid in different in vitro and in vivo models of fibrinolysis, coagulation and thrombus formation. *J. Thromb. Haemost., 5*, 2113-8. ↗

Editions

2021-03-25	Authored, Edited	Jassal, B.
2022-03-01	Reviewed	Huddart, R.
2022-05-10	Edited	Matthews, L.

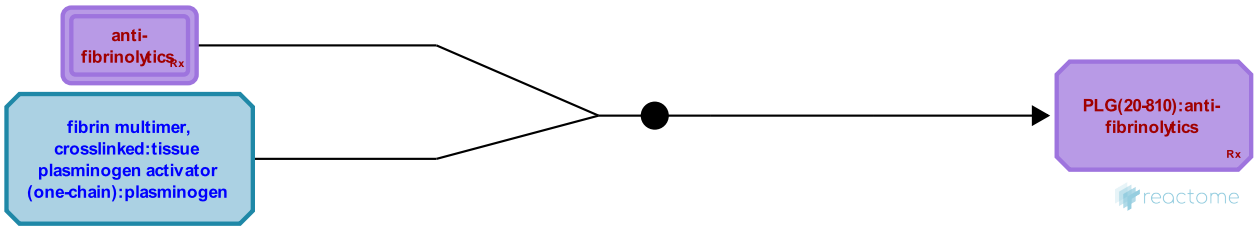
PLG(20-810) binds anti-fibrinolytics ↗

Location: Dissolution of Fibrin Clot

Stable identifier: R-HSA-9724753

Type: binding

Compartments: extracellular region



The plasminogen inhibitors aminocaproic acid (Sun et al. 2002) and tranexamic acid (Sperzel & Huetter 2007, Cheng et al. 2014) can be administered to patients undergoing coronary artery bypass graft surgery to reduce bleeding.

Literature references

Xue, Y., Pettersen, D., Gustafsson, D., Thelin, A., Schell, P., Fex, T. et al. (2014). Discovery of the Fibrinolysis Inhibitor AZD6564, Acting via Interference of a Protein-Protein Interaction. *ACS Med Chem Lett, 5*, 538-43. ↗

Zhang, J., Zhang, P., Wang, P., Gurewich, V., Chen, YH., Sun, Z. et al. (2002). The blockage of the high-affinity lysine binding sites of plasminogen by EACA significantly inhibits prourokinase-induced plasminogen activation. *Biochim Biophys Acta, 1596*, 182-92. ↗

Sperzel, M., Huetter, J. (2007). Evaluation of aprotinin and tranexamic acid in different in vitro and in vivo models of fibrinolysis, coagulation and thrombus formation. *J. Thromb. Haemost., 5*, 2113-8. ↗

Editions

2021-03-25	Authored, Edited	Jassal, B.
2022-03-01	Reviewed	Huddart, R.
2022-05-10	Edited	Matthews, L.

Table of Contents