Dissolution of Fibrin Clot

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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.

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


Reactome database release: 71

This document contains 1 pathway and 19 reactions (see Table of Contents)
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**


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**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**


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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

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


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

**Literature references**


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

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https://www.reactome.org
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: fibrin multimer, crosslinked -> fibrin digestion products (plasmin), crosslinked fibrin multimer:tissue plasminogen activator (one-chain) -> crosslinked fibrin multimer:tissue plasminogen activator (two-chain), alpha-2-antiplasmin + plasmin -> alpha-2-antiplasmin:plasmin

Literature references


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

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

**Literature references**


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crosslinked fibrin multimer:tissue plasminogen activator (two-chain) + plasminogen $\rightarrow$ crosslinked fibrin multimer:tissue plasminogen activator (two-chain):p-lasminogen

**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) $\rightarrow$ crosslinked fibrin multimer:tissue plasminogen activator (two-chain)

**Followed by:** crosslinked fibrin multimer:tissue plasminogen activator (two-chain):plasminogen $\rightarrow$ crosslinked fibrin multimer:tissue plasminogen activator (two-chain) + plasmin

**Literature references**

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, crosslinked -> fibrin digestion products (plasmin)

**Literature references**


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 occurrence 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, O.F., de Vries, C., Hohmann, C., Veerman, H., 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.*

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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 occurrence 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., de Vries, C., Hohmann, C., Veerman, H., 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.*

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

Literature references


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urokinase plasminogen activator + urokinase plasminogen activator receptor (u-PAR) -> urokinase plasminogen activator:uPAR

**Location:** Dissolution of Fibrin Clot

**Stable identifier:** R-HSA-158959

**Type:** binding

**Compartments:** extracellular region, plasma membrane

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 glycosyl-phosphatidylinositol 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)

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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)

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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 -> plasmin + 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)

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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:** extracellular region, plasma membrane

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)

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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**


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:** extracellular region, plasma membrane

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

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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:** extracellular region, plasma membrane

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

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</table>
Table of Contents

Introduction 1

Dissolution of Fibrin Clot 2

• histidine-rich glycoprotein + plasminogen <-> histidine-rich glycoprotein:plasminogen 4

• histidine-rich glycoprotein:plasminogen <-> histidine-rich glycoprotein + plasminogen 5

• crosslinked fibrin multimer + tissue plasminogen activator (one-chain) -> crosslinked fibrin multimer:tissue plasminogen activator (one-chain) 6

• crosslinked fibrin multimer:tissue plasminogen activator (one-chain) + plasminogen -> crosslinked fibrin multimer:tissue plasminogen activator (one-chain):plasminogen 7

• crosslinked fibrin multimer:tissue plasminogen activator (one-chain):plasminogen -> crosslinked fibrin multimer:tissue plasminogen activator (one-chain) + plasmin 10

• fibrin multimer, crosslinked -> fibrin digestion products (plasmin) 10

• crosslinked fibrin multimer:tissue plasminogen activator (one-chain) -> crosslinked fibrin multimer:tissue plasminogen activator (two-chain) 11

• crosslinked fibrin multimer:tissue plasminogen activator (two-chain) + plasminogen -> crosslinked fibrin multimer:tissue plasminogen activator (two-chain):plasminogen 12

• crosslinked fibrin multimer:tissue plasminogen activator (two-chain):plasminogen -> crosslinked fibrin multimer:tissue plasminogen activator (two-chain) + plasmin 13

• fibrin multimer, crosslinked:tissue plasminogen activator (two-chain) + plasminogen activator inhibitor 1 -> fibrin multimer, crosslinked:tissue plasminogen activator (two-chain):plasminogen activator inhibitor 1 14

• fibrin multimer, crosslinked:tissue plasminogen activator (one-chain) + plasminogen activator inhibitor 1 -> fibrin multimer, crosslinked:tissue plasminogen activator (one-chain):plasminogen activator inhibitor 1 15

• alpha-2-antiplasmin + plasmin -> alpha-2-antiplasmin:plasmin 16

• urokinase plasminogen activator + urokinase plasminogen activator receptor (uPAR) -> urokinase plasminogen activator:uPAR 17

• plasminogen + histidine-rich glycoprotein -> plasminogen:histidine-rich glycoprotein 18

• plasminogen:histidine-rich glycoprotein -> plasmin + histidine-rich glycoprotein (uPA [one-chain] catalyst) 19

• urokinase plasminogen activator (one-chain):uPAR -> urokinase plasminogen activator (two-chain):uPAR 21

• plasminogen:histidine-rich glycoprotein -> plasmin + histidine-rich glycoprotein (uPA [two-chain] catalyst) 22

• urokinase plasminogen activator (two-chain):uPAR + plasminogen activator inhibitor 1 (PAI-1) -> PAI-1:urokinase plasminogen activator (two-chain):uPAR 23

• urokinase plasminogen activator (two-chain):uPAR + plasminogen activator inhibitor 2 (PAI-2) -> PAI-2:urokinase plasminogen activator (two-chain):uPAR 24

Table of Contents 25