<Thrombus formation and fibrinolysis>

plasminogen activator (PA)
혈장내 plasminogen → plasmin
섬유소응고 → fibrin / fibrinogen degradation products (FDP)

* The main causes of thrombus formation in ischemic stroke: atherosclerosis (죽상경화증)
cardio-embolic (심장색전증)

atrial fibrillation → atherosclerotic plaque rupture / cardio-embolic thrombosis

↓

zymogens activated ← coagulation cascade > + platelet activation

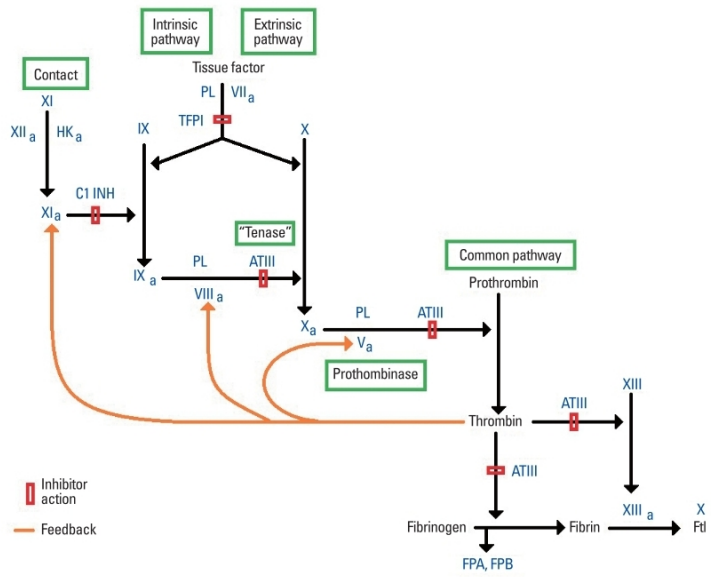

Figure 2. The coagulation process. The intrinsic pathway involves activation of components from within the vasculature (activation of Factor IX by Factor IXa). The extrinsic pathway is the principal initiating pathway for in vivo blood coagulation. The pathway involves the exposure of Tissue Factor (TF), a glycoprotein, and phospholipids to blood, these components are from the surface membranes of fibroblasts that are within and around blood vessels. TF and phospholipids, when exposed to blood, interact with Factor VIIa to convert Factor IX to Factor IXa (from the intrinsic system). Factori VIIIa is then formed from interactions between Factor IX and phospholipids. Factor VIIIa and Factor X then combine to form Factor Xa. Factor Xa then interacts with phospholipids to form Factor Va and a "prothombinase". This is the stage where the intrinsic and extrinsic pathways converge and form the common pathway. Prothombinase the uses feedback mechanism for Factor VIIIa and Factor XIa as a check to ensure that coagulation is still required, and if so, forms a thrombin. Thrombolytic drugs have action of factor XIII to break the fibrin crosslinks.[55]

<Thrombolytic drugs>

: plasminogen → plasmin ⇒ dissolve thrombi

* Tissue Plasminogen activator (t-PA): serine protease
lysine binding of t-PA → activation of plasminogen around a thrombus
activation of circulating plasminogen ↓
plasminogen → plasmin ⇒ thrombus → fibrin degradation products
(the inhibitory effect of alpha 2-antiplasmin & type 1 plasminogen activator inhibitor restricts.)

Table 1. A comparison of the current thrombolytic drugs that are available in term of plasma half life, fibrin specificity and susceptibility to inhibition[57]

Agent	Half-life (min	Fibrin selectivity	PAI-1 inhibition
Urokinase	15	-	+++
Alteplase	4-8	++	+++
Staphylokinase	6	---	-
Monteplase	23	+/-	+++
Pamiteplase	30-47	++	+++
Lanoteplase	23-37	+	-
Reteplase	14-18	+	++
Tenecteplase	11-20	+++	-
Desmoteplase	138	++++++	?

tPA drugs

first generation

Streptokinase (← streptococci bacteria): non lysine → fibrinogensis
(← high level of fibrin in the blood)

study stopped ← thrombosis
haemorrhage / tissue oedema

* specificity of tPA drugs for plasminogen bound fibrin
⇒ conversion of plasminogen → plasma occurs in clots with minimal circulating plasma

Urokinase (formed by kidneys, found in urine): fibrinogensis
→ limited clinical use

second generation

Alteplase: recombinant of human rtPA, purified glycoprotein of 527 amino acids

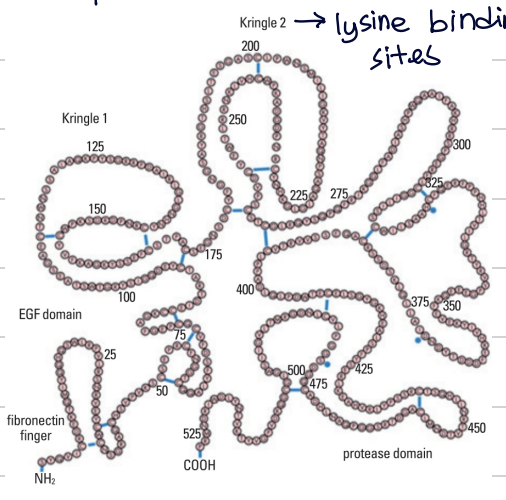

Figure 3. The molecular structure of alteplase.[56]

* FDA 승인

differentiate TNK from Alterphase

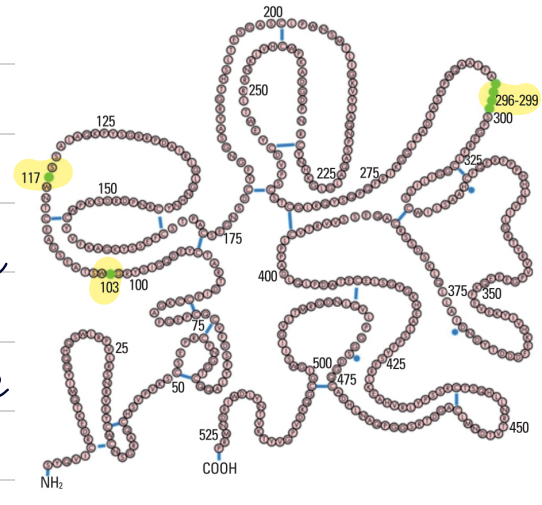

Figure 4. Molecular structure of tenecteplase.

third generation

Tenecteplase (TNK-tPA): recombinant DNA from a mammalian cell line.
527 amino acid glycoprotein
no longer half life & greater binding affinity for fibrin

Desmoteplase: extracted from the saliva of vampire bats
more selective for fibrin, no known effect on BBB
half life 4 hours (Alteplase 5 min, Reteplase 13 min,
Tenecteplase 17 min)