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Review Article

Tissue plasminogen activator and inflammation: from phenotype to signaling mechanisms

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Abstract: In disease conditions, inflammatory cells, such as neutrophils, T cells, and monocytes/macrophages, are recruited in response to injury cues and express panoply of proinflammatory genes through a combination of transcription factors. Tissue plasminogen activator (tPA), a member of the serine protease family, has been shown to act as cytokine to activate profound receptor-mediated signaling events. In this review, we will discuss the role of tPA in inflammation in various models, and illuminate its signaling mechanisms underlying its modulation of inflammation.

Keywords: Tissue plasminogen activator, tPA, inflammation, phenotype, signaling mechanisms

Introduction

One of the notable histological hallmarks of inflammation is the accumulation of inflammatory cells at the site of injury. In response to injury, such as tissue damage or infection, inflammatory cells including neutrophils, monocytes/macrophages, and T cells are recruited to the injury sites. These cells not only play an important role in the clearance of pathogens, but also express a panoply of pro- and anti-inflammatory genes through a combination of transcription factors such as NF-κB, which regulates the induction, progression, and resolution of inflammation [1]. Excessive response will cause inflammatory disease and result in tissue destruction and fibrosis. tPA is a member of the serine protease family that plays a pivotal role in the homeostasis of blood coagulation/fibrinolysis and matrix regulation [2-5]. tPA has been shown to modulate the inflammatory response to tissue injury in various models [6, 7]. Recent studies demonstrate that tPA also acts as a cytokine to trigger profound receptor-mediated intracellular signaling events [2, 8-11]. In this review, we will discuss the role of tPA in inflammation, as well as its underlying signaling mechanisms.

The structure of tPA

tPA is a 69-kDa glycoprotein consisting of 527 or 530 amino acids. It is synthesized within cells and released as a single chain enzyme, which is subsequently cleaved by plasmin into a two-chain form (heavy chain and light chain). The single-chain tPA contains 4 domains: 1) a finger (F) domain, which is homologous to the first domain of the fibronectin; 2) an EGF domain, which is homologous to EGF; 3) two kringle (K) domain; and 4) the catalytic protease (P) domain. The heavy chain of two-chain tPA contains F, EGF, and K domains, whereas, the light chain contains the P domain. The active site of tPA consists of Histidine 322, Asparagine 371, and Serine 478 [12]. The single mutation of Serine 478 to Alanine renders tPA catalytically inactive, while its other function remains intact [13]. This mutant non-enzymatic tPA plays an instrumental role in identifying the protease-independent effects of tPA.

tPA is a hybrid molecule with dual functions: protease and cytokine

Although tPA is generally considered as a potent protease belonging to the serine protease family, mounting evidence demonstrates that tPA

also possesses various functions that are discrete from its proteolytic activity in a variety of physiological and pathological settings [14, 15]. Our recent studies demonstrate that tPA is actually a molecule with dual functions [2, 8-10, 16]. As a serine protease, tPA plays a pivotal role in the homeostasis of blood coagulation/fibrinolysis and extracellular matrix regulation [2]. As a cytokine, tPA executes multiple actions by binding to its membrane receptors and triggering profound intracellular signaling events [2, 8-11, 16]. This conceptual advance provides the ground for the explanation of many once bewildering functions of tPA [2, 17-22].

tPA receptors: LDL receptor-related protein-1 (LRP-1) and annexin A2

tPA does not have a dedicated and specific receptor. However, extensive studies have identified candidates that act functionally and biologically as tPA receptor by initiating intracellular signaling and mediating downstream cellular responses. There are at least two known receptors for tPA. One, the most known receptor, is LRP-1, which was originally identified as a tPA receptor on hepatocytes [23]; the other is annexin A2, which was initially found on microglia [24].

LRP-1, also known as α2-macroglobulin receptor (α2MR) [23] or type V TGF-β receptor (TβR-V) [25], is a member of the LDL receptor family that is implicated in lipoprotein metabolism and in the homeostasis of proteases and protease inhibitors [26, 27]. Expression of LRP-1 is ubiquitous. Mature LRP-1 consists of an extracellular 515-kDa α subunit and an 85-kDa β subunit with a transmembrane segment and cytoplasmic tail containing two NPxY motifs and numerous tyrosine residues [26, 28, 29]. Phosphorylation of the tyrosine residue(s) is essential for LRP-1 to relay its signal, though the exact mechanisms of the phosphorylation remain not complete understood. We have shown that tPA induces the phosphorylation of LRP-1 Tyr 4507, which is indispensable to tPA-mediated fibroblast proliferation [10]. There are four putative ligand-binding domains in the extracellular region of LRP-1; each of them contains two to eleven individual cysteine-rich repeats [26]. The domains II and IV in the LRP-1 have been identified as the binding sites for tPA [26, 30].

Annexin A2 is a member of the Ca^{2+}- and phospholipid-binding protein family. It has a unique structure that allows it to dock onto membrane in a peripheral and reversible manner [31]. Annexin A2 has been identified as a major membrane receptor of tPA on endothelial [32], microglia cells [33], and other cancer cells [34]; and is implicated in mediating certain signal transductions [20, 33, 35]. The core domain in the C terminus of annexin A2 consists of four highly α-helical annexin repeats which mediates its membrane binding [31]. tPA has been shown to bind to the hexapeptide LCKLSL (residues 7-12) in the N terminus of annexin A2 [36]. However, unlike the other well-known tPA receptor, LRP-1, annexin A2, as a membrane-associated protein, lacks the transmembrane domain, to which tPA can only dock [31, 34]. Recently, we demonstrated that under the stimulation of tPA, annexin A2 aggregates with integrin CD11b, leading to the activation of integrin-linked kinase (ILK) pathway [16]. Thus annexin A2 can transduce tPA signaling through its interaction with integrins.

Role of tPA in inflammation: studies from animal models

tPA has been shown to modulate inflammatory infiltration in numerous disease models [6, 7, 16, 37]. In an acute brain injury model, tPA was shown to mediate F4/80 macrophage accumulation and activation in the ischemic brain [37]. In a carbon-tetrachloride-induced liver fibrosis model, tPA-deficient mice demonstrated decreased infiltration of T cells in comparison with their wild-type counterparts [6]. Moreover, it was found that tPA promoted infiltration of macrophages or other leukocytes in both models of acute [7] and chronic kidney injury [16]. Thus, tPA appears to have broad implication in the modulation of infiltration and inflammation in diverse organs. Intriguingly, the increased inflammatory infiltration in most of those models is accompanied by the concomitant induction of tPA [8, 9, 17, 38], suggesting that tPA may be a common endogenous factor that modulates inflammatory infiltration and response in multiple organ systems.

tPA and cerebral inflammation

Zhang and Yepes group studied the role of tPA in microglial activation in an ischemic brain injury model [37]. Middle cerebral artery occlu-

sion (MCAO) was induced in the wild-type, tPA knockout (tPA-/-), and microglia-specific LRP-1 knockout (macLRP-/-) mice. They found that MCAO induces microglial activation, as demonstrated by ameboid morphology and double immune staining of β-isolectin and F4/80, as well as inflammatory markers such as iNOS, in the wild-type mice. However, MCAO-induced microglial activation is significantly decreased in tPA-/- and macLRP-/- mice. Intriguingly, administration of exogenous tPA increases microglial activation in tPA-/- mice but not in the macLRP-/- mice, suggesting that LRP-1-medited tPA cytokine function induces microglial activation and inflammatory response in the ischemic brain. The exact signaling mechanism of tPA effect remain unknown. But tPA has been shown to promote LRP-1-mediated NF-κB signaling in the same ischemic brain injury model [39].

tPA and liver inflammation

In a carbon-tetrachloride-induced liver fibrosis model, Higazi A, *et al* demonstrated that carbon-tetrachloride induces liver fibrosis, inflammatory infiltration, and increased serum level of IFN-γ, IL-4 and IL-10 in wild-type mice [6]. Flow cytometry analysis indicated that the intrahepatic infiltration mainly consists of CD4 and CD8-positive T cells. However, tPA-/- mice displayed significantly decreased fibrosis, intrahepatic infiltration of T cells, and lower level of cytokines.

tPA and renal inflammation

tPA has been shown to promotes renal inflammation in both models of acute and chronic kidney injury. In a renal ischemia-reperfusion injury model, Roelofs, *et al* found that tPA-deficient mice display significantly less neutrophil influx into the interstitial region and quicker recovery of renal function than wild-type mice [7]. In addition, wild-type mice treated with tPA-antisense oligonucleotides show less histological damage, better renal function, and less neutrophil influx than the control mice. Of note, these tPA effects are independent of compliment C3 and plasmin activity. In the obstruction-induced chronic kidney injury model [16], we demonstrated that obstruction-induced CD11b-positive macrophage infiltration, NF-κB activation, and proinflammatory chemokine expression are attenuated in tPA-deficient mice. Moreover, the interstitial cells with activated NF-κB are largely CD11b-positive macrophages, indicating a possible important role of macrophages in tPA-mediated NF-κB activation. The different types of infiltrating cells in the acute and chronic kidney injury models may reflect the temporal order of inflammatory recruitment in response to injury.

tPA and bacterial infection

The role of tPA in bacterial infection has been investigated in both kidney and lung infection models. In an *E. coli*-induced acute pyelonephritis model [40], it was found that tPA-/- kidneys contains significantly higher number of bacteria, as well as higher levels of IL-1β and TNF-α. The ability of tPA-deficient neutrophils to generate oxidative burst reaction and eliminate *E. coli* is dramatically impaired. In line with this observation, Renckens R, *et al* demonstrated that over-expression of tPA markedly improves host defense against *K. pneumonia*-induced pneumonia as indicated by less bacterial growth and dissemination, reduced distant organ injury, and decreased mortality [41]. Since innate immunity plays a fundamental role in the host defense against pathogens, these studies indicate that tPA may also play an important role in the modulation of innate immunity.

tPA and inflammation: mechanistic studies

tPA and NF-κB activation

NF-κB activation is a central event in the initiation and progression of inflammation. The members of the NF-κB family of transcription factors exist in form of homo- and heterodimers that formed among the five members of NF-κB family: p50, p52, p65 (RelA), RelB, and c-Rel. In physiological status, NF-κBs are retained in the cytoplasm by its specific inhibitor, IκB [42, 43]. Upon activation, IκB will be phosphorylated, which leads to its degradation, resulting in the release and nuclear translocation of p65/p50 (canonical activation) or RelB/p52 (non-canonical activation), and subsequently DNA binding and gene transcription [42, 43]. Role of tPA in NF-κB activation is context dependent [16, 39]. tPA may execute cell type-specific biological functions by binding to different membrane receptors (LRP-1 or annexin A2) and initiating different intracellular signaling events.

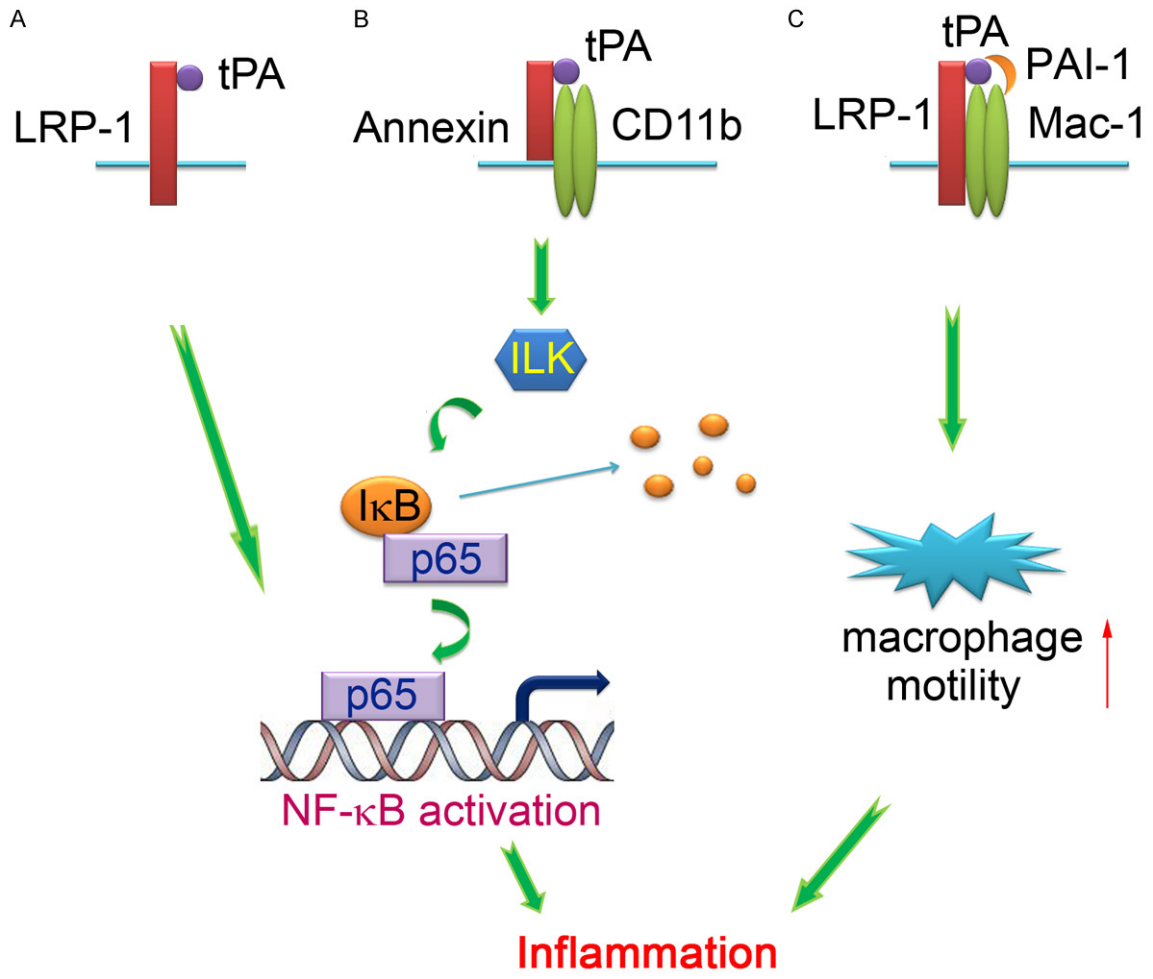

Figure 1. Mechanisms of tPA in modulating inflammation. A: tPA binds to LRP-1 and induces activation of NF-κB. B: tPA promotes the aggregation of annexin A2 and integrin CD11b, leading to activation of ILK, phosphorylation and degradation of IκB, and eventually activation of NF-κB. C: tPA forms complex with LRP-1, PAI-1, and Mac-1, which results in the increased macrophage migration.

We investigated the role of tPA in NF-κB activation, and found that tPA activates NF-κB pathway and induces the expression of the associated proinflammatory chemokines in macrophages through a novel signaling cascade involving annexin A2-mediated aggregation of integrin CD11b and the subsequent activation of ILK pathway [16]. We further demonstrated that annexin A2 mediates tPA-induced NF-κB activation in macrophages; and it induces the interaction and aggregation of annexin A2 with CD11b, leading to the clustering and activation of integrin CD11b signaling, which in turn activates its downstream ILK and phosphorylates IκB. Phosphorylation of IκB leads to its degradation and the release of NF-κB dimers into nuclei, resulting in the subsequent DNA binding and transcription of target proinflammatory genes (**Figure 1B**). Blockade of any step within this signaling cascade by various strategies, such as annexin A2 and ILK siRNAs, CD11b knockout or neutralizing antibody, or infection with dominant-negative ILK-kd or C-terminal ILK adenoviral vectors, eliminates tPA-induced NF-κB activation. We also found that tPA modulates NF-κB signaling *in vivo*, because obstruction-induced phosphorylation of p65 and chemokine expression are dramatically reduced in the kidneys from tPA-deficient mice, accompanying with decreased collagen deposition and macrophage infiltration.

In contrast, Zhang X, *et al* demonstrated that tPA and LRP-1 mediates cerebral ischemia-induced NF-κB activation (**Figure 1A**) [39]. They found that ischemic insult induces NF-κB acti-

vation, which is attenuated after LRP inhibition or tPA knockout. Exogenous administration of tPA into the tPA-/- mice restores the level of NF-κB activation comparable with that in wild-type mice. However, tPA-/- mice received intracerebral injection of tPA in combination with RAP, a specific LRP-1 antagonist, display similar level of NF-κB activation in comparison with tPA-deficient mice. These finding indicate that LRP-1 mediates tPA-induced NF-κB activation in brain.

tPA and macrophage motility

Macrophages play an important role in the initiation and modulation of inflammation. Enhanced motility is one of the main contributing factors that lead to the recruitment and accumulation of macrophages around the site of injury. Cao, *et al* investigated the role and the underlying mechanism of tPA in the regulation of macrophage motility [44]. They demonstrated that LPS-induced peritoneal macrophage efflux is attenuated in the tPA-deficient mice, and genetic inactivation of integrin Mac-1, tPA, PAI-1 or LRP-1 abrogates macrophage migration. Further investigations showed that tPA forms complex with LRP-1, Mac-1, and PAI-1, which is essential to macrophage migration (**Figure 1C**). We recently found that tPA activates FAK and Rac-1 signaling, which is known to play an important role in cell motility, in macrophages (unpublished data), suggesting that the integrin downstream signaling through FAK/Rac-1 may mediate tPA-induced macrophage migration.

tPA and inflammation: future perspective

Although numerous studies clearly indicate that tPA play an important role in the modulation of inflammation. There are still many gaps in our understanding of the molecular mechanisms underlying the actions of tPA need to be filled, such as the subsets of tPA-mediated infiltrating macrophages and T cells, the downstream signaling mechanisms of tPA-promoted macrophage motility, and the role and mechanism of tPA in the interaction with the signaling mediators within innate immunity. Future investigations towards the above aspects will eventually lead to the development of specific treatments targeting the autoimmune and inflammatory diseases.

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Disclosure of conflict of interest

None.

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References

[1] Mosser DM and Edwards JP. Exploring the full spectrum of macrophage activation. Nat Rev Immunol 2008; 8: 958-969.

[2] Hu K, Lin L, Tan X, Yang J, Bu G, Mars WM and Liu Y. tPA protects renal interstitial fibroblasts and myofibroblasts from apoptosis. J Am Soc Nephrol 2008; 19: 503-514.

[3] Mars WM, Zarnegar R and Michalopoulos GK. Activation of hepatocyte growth factor by the plasminogen activators uPA and tPA. Am J Pathol 1993; 143: 949-958.

[4] Yee JA, Yan L, Dominguez JC, Allan EH and Martin TJ. Plasminogen-dependent activation of latent transforming growth factor beta (TGF beta) by growing cultures of osteoblast-like cells. J Cell Physiol 1993; 157: 528-534.

[5] Fredriksson L, Li H, Fieber C, Li X and Eriksson U. Tissue plasminogen activator is a potent activator of PDGF-CC. Embo J 2004; 23: 3793-3802.

[6] Higazi AA, El-Haj M, Melhem A, Horani A, Pappo O, Alvarez CE, Muhanna N, Friedman SL and Safadi R. Immunomodulatory effects of plasminogen activators on hepatic fibrogenesis. Clin Exp Immunol 2008; 152: 163-173.

[7] Roelofs JJ, Rouschop KM, Leemans JC, Claessen N, de Boer AM, Frederiks WM, Lijnen HR, Weening JJ and Florquin S. Tissue-type plasminogen activator modulates inflammatory responses and renal function in ischemia reperfusion injury. J Am Soc Nephrol 2006; 17: 131-140.

[8] Hu K, Wu C, Mars WM and Liu Y. Tissue-type plasminogen activator promotes murine myofibroblast activation through LDL receptor-related protein 1-mediated integrin signaling. J Clin Invest 2007; 117: 3821-3832.

[9] Hu K, Yang J, Tanaka S, Gonias SL, Mars WM and Liu Y. Tissue-type plasminogen activator acts as a cytokine that triggers intracellular

signal transduction and induces matrix metalloproteinase-9 gene expression. J Biol Chem 2006; 281: 2120-2127.
[10] Lin L, Bu G, Mars WM, Reeves WB, Tanaka S and Hu K. tPA activates LDL receptor-related protein 1-mediated mitogenic signaling involving the p90RSK and GSK3beta pathway. Am J Pathol 2010; 177: 1687-1696.
[11] Shi Y, Mantuano E, Inoue G, Campana WM and Gonias SL. Ligand binding to LRP1 transactivates Trk receptors by a Src family kinase-dependent pathway. Sci Signal 2009; 2: ra18.
[12] Vivien D, Gauberti M, Montagne A, Defer G and Touze E. Impact of tissue plasminogen activator on the neurovascular unit: from clinical data to experimental evidence. J Cereb Blood Flow Metab 2011; 31: 2119-2134.
[13] Olson ST, Swanson R, Day D, Verhamme I, Kvassman J and Shore JD. Resolution of Michaelis complex, acylation, and conformational change steps in the reactions of the serpin, plasminogen activator inhibitor-1, with tissue plasminogen activator and trypsin. Biochemistry 2001; 40: 11742-11756.
[14] Fernandez-Monreal M, Lopez-Atalaya JP, Benchenane K, Leveille F, Cacquevel M, Plawinski L, MacKenzie ET, Bu G, Buisson A and Vivien D. Is tissue-type plasminogen activator a neuromodulator? Mol Cell Neurosci 2004; 25: 594-601.
[15] Benarroch EE. Tissue plasminogen activator: beyond thrombolysis. Neurol 2007; 69: 799-802.
[16] Lin L, Wu C and Hu K. Tissue Plasminogen Activator Activates NF-kappaB through a Pathway Involving Annexin A2/CD11b and Integrin-Linked Kinase. J Am Soc Nephrol 2012; 23: 1329-1338.
[17] Yepes M, Sandkvist M, Moore EG, Bugge TH, Strickland DK and Lawrence DA. Tissue-type plasminogen activator induces opening of the blood-brain barrier via the LDL receptor-related protein. J Clin Invest 2003; 112: 1533-1540.
[18] Nagai N, Yamamoto S, Tsuboi T, Ihara H, Urano T, Takada Y, Terakawa S and Takada A. Tissue-type plasminogen activator is involved in the process of neuronal death induced by oxygen-glucose deprivation in culture. J Cereb Blood Flow Metab 2001; 21: 631-4.
[19] Welling TH, Huber TS, Messina LM and Stanley JC. Tissue plasminogen activator increases canine endothelial cell proliferation rate through a plasmin-independent, receptor-mediated mechanism. J Surg Res 1996; 66: 36-42.
[20] Ortiz-Zapater E, Peiro S, Roda O, Corominas JM, Aguilar S, Ampurdanes C, Real FX and Navarro P. Tissue plasminogen activator induces pancreatic cancer cell proliferation by a non-catalytic mechanism that requires extracellular signal-regulated kinase 1/2 activation through epidermal growth factor receptor and annexin A2. Am J Pathol 2007; 170: 1573-1584.
[21] Wang X, Asahi M and Lo EH. Tissue type plasminogen activator amplifies hemoglobin-induced neurotoxicity in rat neuronal cultures. Neurosci Lett 1999; 274: 79-82.
[22] Armstead WM, Nassar T, Akkawi S, Smith DH, Chen XH, Cines DB and Higazi AA. Neutralizing the neurotoxic effects of exogenous and endogenous tPA. Nat Neurosci 2006; 9: 1150-1155.
[23] Bu G, Williams S, Strickland DK and Schwartz AL. Low density lipoprotein receptor-related protein/alpha 2-macroglobulin receptor is an hepatic receptor for tissue-type plasminogen activator. Proc Natl Acad Sci U S A 1992; 89: 7427-7431.
[24] Siao CJ and Tsirka SE. Tissue plasminogen activator mediates microglial activation via its finger domain through annexin II. J Neurosci 2002; 22: 3352-3358.
[25] Huang SS, Ling TY, Tseng WF, Huang YH, Tang FM, Leal SM and Huang JS. Cellular growth inhibition by IGFBP-3 and TGF-beta1 requires LRP-1. Faseb J 2003; 17: 2068-2081.
[26] Herz J and Strickland DK. LRP: a multifunctional scavenger and signaling receptor. J Clin Invest 2001; 108: 779-784.
[27] Lillis AP, Van Duyn LB, Murphy-Ullrich JE and Strickland DK. LDL receptor-related protein 1: unique tissue-specific functions revealed by selective gene knockout studies. Physiol Rev 2008; 88: 887-918.
[28] Hussain MM. Structural, biochemical and signaling properties of the low-density lipoprotein receptor gene family. Front Biosci 2001; 6: D417-428.
[29] Strickland DK and Ranganathan S. Diverse role of LDL receptor-related protein in the clearance of proteases and in signaling. J Thromb Haemost 2003; 1: 1663-1670.
[30] Obermoeller-McCormick LM, Li Y, Osaka H, FitzGerald DJ, Schwartz AL and Bu G. Dissection of receptor folding and ligand-binding property with functional minireceptors of LDL receptor-related protein. J Cell Sci 2001; 114: 899-908.
[31] Rescher U and Gerke V. Annexins--unique membrane binding proteins with diverse functions. J Cell Sci 2004; 117: 2631-2639.
[32] Cesarman GM, Guevara CA and Hajjar KA. An endothelial cell receptor for plasminogen/tissue plasminogen activator (t-PA). II. Annexin II-mediated enhancement of t-PA-dependent plasminogen activation. J Biol Chem 1994; 269: 21198-21203.

[33] Siao CJ and Tsirka SE. Tissue plasminogen activator mediates microglial activation via its finger domain through annexin II. J Neurosci 2002; 22: 3352-3358.
[34] Kim J and Hajjar KA. Annexin II: a plasminogen-plasminogen activator co-receptor. Front Biosci 2002; 7: d341-348.
[35] Babbin BA, Parkos CA, Mandell KJ, Winfree LM, Laur O, Ivanov AI and Nusrat A. Annexin 2 regulates intestinal epithelial cell spreading and wound closure through Rho-related signaling. Am J Pathol 2007; 170: 951-966.
[36] Hajjar KA, Mauri L, Jacovina AT, Zhong F, Mirza UA, Padovan JC and Chait BT. Tissue plasminogen activator binding to the annexin II tail domain. Direct modulation by homocysteine. J Biol Chem 1998; 273: 9987-9993.
[37] Zhang C, An J, Strickland DK and Yepes M. The low-density lipoprotein receptor-related protein 1 mediates tissue-type plasminogen activator-induced microglial activation in the ischemic brain. Am J Pathol 2009; 174: 586-594.
[38] Wang YF, Tsirka SE, Strickland S, Stieg PE, Soriano SG and Lipton SA. Tissue plasminogen activator (tPA) increases neuronal damage after focal cerebral ischemia in wild-type and tPA-deficient mice. Nat Med 1998; 4: 228-231.
[39] Zhang X, Polavarapu R, She H, Mao Z and Yepes M. Tissue-type plasminogen activator and the low-density lipoprotein receptor-related protein mediate cerebral ischemia-induced nuclear factor-kappaB pathway activation. Am J Pathol 2007; 171: 1281-1290.
[40] Roelofs JJ, Rouschop KM, Teske GJ, Wagenaar GT, Claessen N, Weening JJ, van der Poll T and Florquin S. Endogenous tissue-type plasminogen activator is protective during ascending urinary tract infection. Nephrol Dial Transplant 2009; 24: 801-808.
[41] Renckens R, Roelofs JJ, Stegenga ME, Florquin S, Levi M, Carmeliet P, Van't Veer C and van der Poll T. Transgenic tissue-type plasminogen activator expression improves host defense during Klebsiella pneumonia. J Thromb Haemost 2008; 6: 660-668.
[42] Bonizzi G and Karin M. The two NF-kappaB activation pathways and their role in innate and adaptive immunity. Trends Immunol 2004; 25: 280-288.
[43] Sanz AB, Sanchez-Nino MD, Ramos AM, Moreno JA, Santamaria B, Ruiz-Ortega M, Egido J and Ortiz A. NF-kappaB in renal inflammation. J Am Soc Nephrol 2010; 21: 1254-1262.
[44] Cao C, Lawrence DA, Li Y, Von Arnim CA, Herz J, Su EJ, Makarova A, Hyman BT, Strickland DK and Zhang L. Endocytic receptor LRP together with tPA and PAI-1 coordinates Mac-1-dependent macrophage migration. Embo J 2006; 25: 1860-1870.