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Review

Cancer therapy targeting the fibrinolytic system☆

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ABSTRACT

The tumor microenvironment is recognized as a key factor in the multiple stages of cancer progression, mediating local resistance, immune-escape and metastasis. Cancer growth and progression require remodeling of the tumor stromal microenvironment, such as the development of tumor-associated blood vessels, recruitment of bone marrow-derived cells and cytokine processing. Extracellular matrix breakdown achieved by proteases like the fibrinolytic factor plasmin and matrix metalloproteases is necessary for cell migration crucial for cancer invasion and metastasis. Key components of the fibrinolytic system are expressed in cells of the tumor microenvironment. Plasmin can control growth factor bioavailability, or the regulation of other proteases leading to angiogenesis, and inflammation. In this review, we will focus on the role of the fibrinolytic system in the tumor microenvironment summarizing our current understanding of the role of the fibrinolytic factors for the modulation of the local chemokine/cytokine milieu, resulting in myeloid cell recruitment, which can promote neoangiogenesis.

Contents

Abbreviations: CXCL5, chemokine, CXC, motif, ligand 5; EACA, lysine derivatives epsilon-aminocaproic acid; ECM, extracellular matrix; FDP, fibrin degradation product; FGF, fibroblast growth factor; G-CSF, granulocyte-colony stimulating factor; IBD, inflammatory bowel disease; IL, interleukin; ILK, integrin linked kinase; LRP, low-density lipoprotein (LDL) receptor-related protein; MCP-1, monocyte chemoattractant protein-1; MMP, matrix metalloproteinase; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; PA, plasminogen activator; PAI-1, plasminogen activator inhibitor-1; PLG, plasminogen; TA, tranexamic acid; TLR, Toll like receptor; TNF-α, tumor necrosis factor-α; tPA, tissue-type plasminogen activator; uPA, urokinase-type plasminogen activator; uPAR, urokinase-type plasminogen activator receptor; VEGF, vascular endothelial growth factor; YO-2, Trans-4-Aminomethylcyclohexanecarbonyl-Tyr (O-Pic)-octylamide.

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1. Introduction

Cancer research has long focused solely on the cancer cell itself, and the mutations in genes leading to altered cell behavior including uncontrolled cell growth. Although the identification of important genes supporting or suppressing tumor growth increased our understanding of the various cancer cell types, recent studies demonstrated that cancer cells establish a microenvironment to support their own growth and enhance metastasis. Microenvironmental cells include endothelial, stromal cells and leukocytes just to mention a few of them. These microenvironmental cells, can enhance tumor progression and drug-resistance, but also help cancers to evade the regulation of the immune system. The microenvironment also includes extracellular matrix proteins, protease, chemokines and cytokines. Studies highlighting the significance and functions of cells of the microenvironment are slowly emerging.

Proteases belong to several families of enzymes that catalyze protein breakdown. Around 2–4% of a typical genome encodes proteolytic enzymes [1]. Protease can be classified into serine, threonine, cysteine, aspartate, glutamic acid proteases, and matrix metalloproteinases (MMPs). The activation of fibrinolytic factors or MMPs seems to be associated with the growth and metastasis of certain tumors, and can even be enhanced after the administration of anticancer drugs [2] within cells of the tumor microenvironment, also known as the tumor niche.

1.1. Regulation of serine protease plasmin generation and its inhibition

The central molecule of the fibrinolytic system is one of the serine proteases plasmin (Fig. 1). Plasminogen (PLG), an inactive form of plasmin is produced in the kidney and liver [3]. PLG can be rendered into its active form plasmin through the tissue-type plasminogen activator (tPA) or urokinase plasminogen activator (uPA).

tPA is believed to activate PLG during fibrinolysis, whereas uPA activates cell-associated PLG. Plasmin activity is directly inhibited by α2-antiplasmin and α2-macroglobulin or can be indirectly controlled on the level of plasminogen activators (PAs) by PA inhibitor (PAI) type 1 and type 2. PLG binds to fibrin, to generate soluble fibrin degradation products [4], causing fibrinolysis (Fig. 1).

Coagulation and fibrinolysis are well coordinated under physiological conditions and insure blood flow, while preventing blood loss, and guarantying the timely removal of ongoing or acutely induced fibrin deposits. Plasmin can both activate and inactivate coagulation factors V and IX. Plasmin activation provides a broad spectrum of reactions including proteolytic activity, cell migration and signaling pathway activation, which are involved in both physiologic and pathologic processes such as inflammation, thrombosis and cancer. These feedback mechanisms ensure the balance between the fibrinolytic and the coagulation system. Plasmin can be activated either on a fibrin-containing thrombus or on cells.

In addition, PLG can be trapped at the cell surface by PLG receptors, like low-density lipoprotein receptor-related protein-1 (LRP-1) or annexin A2 (Fig. 2). Annexin A2 is expressed on various cell types, including endothelial cells, monocytes, macrophages and cancer cells. Plasmin/PLG binds to monocytes via its receptors annexin A2 and PLG-R_{KT} [5]. Studies with the annexin A2-deficient mouse have suggested important functions for annexin A2 and the heterotetramer in fibrinolysis, in the regulation of the LDL receptor and in cellular redox regulation (Fig. 2). Annexin A2 is a pleiotrophic calcium- and anionic phospholipid-binding protein that exists as a monomer and as a heterotetrameric complex with the PLG receptor protein, S100A10, also known as p11 [6]. P11 binding to PLG mediates the activation of uPA or tPA as this binding facilitates the conversion of PLG to plasmin [7].

Aside from the activation of uPA due to its binding to fibrin, uPA activation can also be achieved after the binding of the pro-uPA molecule to the uPA receptor (uPAR; CD87) on the cell surface under physiological conditions [8] (Figs. 1, 2). The binding of single chain uPA to uPAR strongly enhances PLG cleavage to generate active plasmin. A positive feedback is produced since plasmin, by a proteolytic cleavage of the Lys158-Ile159 peptide bond, converts latent single chain-uPA to an active two-chain uPA [9].

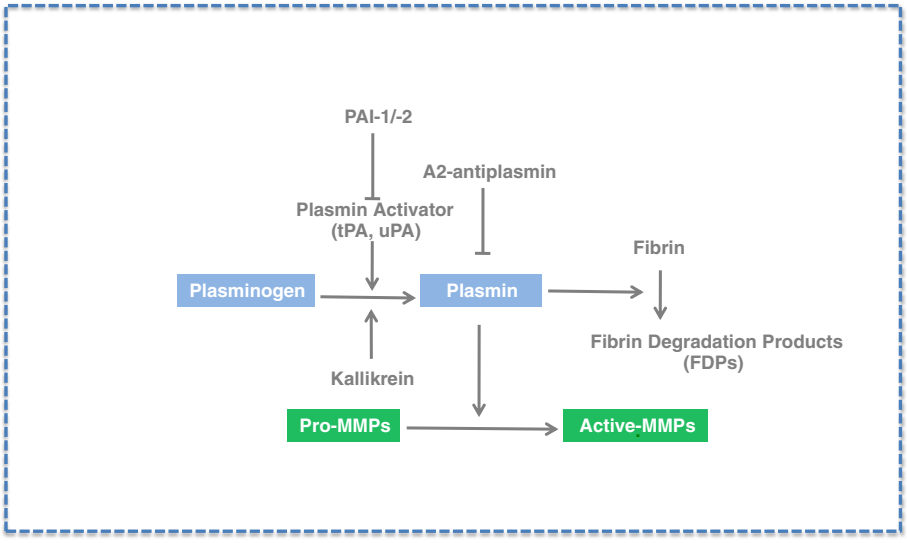

Fig. 1. The proteolytic environment induced by fibrinolytic factors. PLG can be converted to its active form plasmin by both tPA and by uPA or kallikrein. Plasmin can degrade fibrin into fibrin degradation products. Plasmin activates pro-MMPs into active MMPs and can activate pro-uPA into uPA. Plasmin activation is regulated by inhibitors of PLG activation, such as PAI-1, -2, and by inhibitors of plasmin itself, such as a2-antiplasmin or a2-macroglobulin.