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The Role of the Plasminogen Activation System in Angioedema: novel insights on the pathogenesis

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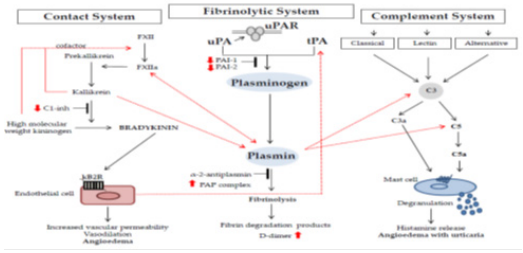
Abstract

The main physiological functions of plasmin, the active form of its pro-enzyme plasminogen, are blood clot fibrinolysis and restoration of normal blood flow. The plasminogen activation (PA) system includes urokinase-type plasminogen activator (uPA), tissue-type PA (tPA), and two types of plasminogen activator inhibitors (PAI-1 and PAI-2). In addition to the regulation of fibrinolysis, the PA system plays an important role in other biological processes, which include degradation of extracellular matrix such as embryogenesis, tissue remodeling, wound healing, angiogenesis, inflammation and immune response.

Recently, the PA system has been related to the pathogenesis of Angioedema. Angioedema is defined as localized and self-limiting edema of subcutaneous and submucosal tissues, mediated by bradykinin and mast cell mediators, including histamine. The disorder may be hereditary or acquired. The molecular alterations are triggered by two events: dysregulation of the kallikrein pathway (also named contact system) and/or inappropriate activation of the complement cascade. The PA system is located at the interface between the kallikrein and the complement systems. The final effect of multiple contacts of the PA system with kallikreins is an auto-amplification loop with abnormal production of bradykinin. On the other hand, plasmin can interact with complement system activating C3a and C5a that drive to mast cells degranulation and histamine release. Recently, we have conducted an exhaustive review of the scientific literature in order to associate a specific dysfunction of the PA system with the specific forms of Angioedema. Interestingly, uPAR acts as an amplifier for bradykinin production by recruitment on the cell surface of prekallikrein and high molecular weight kininogen (HK). HK binding to uPAR could be inhibited by recently discovered small molecules identified in our laboratories.

The intricate cellular and molecular communication underlying Angioedema pathogenesis needs the development of therapeutic agents that disconnect plasminogen activation from production of the disease mediators.



Links between the fibrinolytic system, the contact system and the coagulation system in Angioedema pathogenesis. The red dashed arrows indicate the contacts between the molecular pathways, while the red arrows indicate the increase or decrease of molecules in the plasma from patients affected by angioedema disease

Biography

Dr Filomena Napolitano was born on August 25, 1988, in Avellino, Italy. She graduated in Pharmaceuticals Biotechnology in 2013 at the University of Naples Federico II, Italy; in 2017 she obtained a PhD in Experimental and Clinical Medicine, at the University of Naples Federico II, Italy. She is enrolled in the fourth year of the Specialization School in Clinical Pathology and Clinical Biochemistry, University of Naples Federico II, Italy. Actually, she is postdoctoral fellow at School of Medicine and Surgery, University of Naples Federico II. She has her expertise in the study of the expression and functions of the urokinase receptor (uPAR) and FPRs, a class of innate immunity receptors, in tumor cells and inflammatory cells, being interested in the identification of new inhibitors with anti-cancer activity.

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