List of Publications


Patent

1. Introduction

Activation of plasminogen (Pg) to plasmin (Pm) is a key event in fibrinolysis. Two bacterial Pg activators, staphylokinase (SAK) and streptokinase (SK), initiate fibrinolysis in humans by forming a cofactor-enzyme complex with Pm or Pg and results in conformational expression of new catalytic active site that specifically leaves the Arg561-Val562 activation bond in the catalytic domain of Pg to form Pm [1–3]. Thus, both SAK and SK serve as cofactors that alter the substrate specificity of Pm from the cleavage of fibrin to the cleavage of Pg. In contrast with SK–Pg complex, the SAK–Pg complex remains inactive and requires conversion into SAK–Pm form to exhibit high specificity for the Pg activation [4]. Understanding of structural and molecular basis of this “specificity switch” in Pm after complex formation with the SAK is crucial to unravel the molecular mechanism of Pg activation by SAK. SAK is a 15.5 kDa single domain molecule and three times smaller than SK that carries three independently folded domain (α, β and γ). Although α and β domains of SK exhibit close structural similarity with SAK [5–9], Pg activation ability of individual SK domain is highly attenuated unlike single domain SAK which is fully functional as a Pg activator. Therefore, being the smallest and single domainPg activator, SAK provides an ideal molecule to delineate the mechanism of cofactor mediated specificity switch in Pm that may be helpful in design and development of new thrombolytic molecules.

During Pg activation by SAK–Pm bimolecular complex, the heterotrimer formed between one SAK and two Pg/Pm molecules, generates several intermolecular interactions that are crucial for altering the geometry of the active site for changing the specificity of Pm towards the activation loop of substrate Pg. Thus, SAK residues, interacting and lining the active site cleft of Pm, may be functionally important for contributing to its cofactor function. The crucial region of SAK that remains in close vicinity of active site of Pm spans from Gly36 to Glu46 and participates in generating a network of salt-bridges and hydrogen bonding (e.g. SAKGlu38-PmLys101; SAKSer41-PmGln177; SAKGlu46-PmArg175) at the interface. The importance of Arg175 of Pm in modulating the Pg activator activity of SAK [6,7,10], suggests that a part of this activator interacts with the partner Pm in a manner similar to SK. The interface of the SAK–Pm enzyme complex displays existence of a pair of basic and aromatic residues (His43, Tyr44) in SAK that protrude into the active site cleft of the partner Pm [7] but do not show direct interaction with the partner Pm, thus, a clear picture of their role in modulating the Pg activator activity of SAK–Pm complex is lacking.