



Genetically engineered and domain-exchanged streptokinase molecules with enhanced kinetics of fibrin-dependent proteolytic activity and resistance to α 2-antiplasmin

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Abstract:

Streptokinase (SK), a heterogeneous plasminogen activator (PA) protein from groups A, C, and G streptococci (GAS, GCS, GGS, respectively) contains three structural domains (SK₁, SK₂, and SK₃). Based on the variable region of SK₁, GAS-SK (ska) are clustered as SK1 and SK2 (including SK2a & SK2b). We report the first α -domain exchange study for skcg and cluster 2₁ska alleles to elucidate the contribution of SK₁ for a broad range of functional characteristic including kinetics of specific/ proteolytic activity, fibrinogen-bound Pg activation and α 2-antiplasmin resistance. Results pointed to the 'minor to determining' contribution of SK₁ in these functionalities which might be potentially accompanied by a few critical residues substitutions. Our findings indicated minor contribution of the SK₁ for highly different SA* between co-clustered skcg₁ and SK2a₁ variants but major role of the SK₁ on enhancement of proteolytic activity between skcg₁/SK and SK2b. Using computational approaches, SKC₁· μ Pm complex with/without residual substitutions that contributed to the changes in PA properties were modelled. Results of molecular dynamics (MD) simulations and residue interaction networks (RINs) analyses showed generally enhanced structural flexibility of SK but more stabilization of the catalytic complex by residual substitutions. These in silico results were confirmed in vivo by production of the E.coli-derived residual-substituted SKs (via site-directed mutagenesis) with higher proteolytic activities and higher levels of fibrinogen-bound Pg activation.



Biography:

Farzin Roohvand received his Ph.D in Biotechnology (Middle East Tech Univ; Ankara-Turkey) in 1999. In 2002, he did Post-doc in Pasteur Institute of Paris. In 2004, he served as a guest scientist in the same institute and in 2008 as Principal investigator for ANRS (France). Since 2012, he served as principal investigator in Pasteur Institute of Iran. He is author of more than 60 international articles and served as invited speaker for presenting keynote lectures in several international symposiums. He serves as Editorial Board in several scientific Journals.

Recent Publications:

1. Farzin Roohvand, et al Iran Biomed J, 2020.
2. Farzin Roohvand, et al Iran Biomed J, 2020.
3. Farzin Roohvand, et al Protein Pept Lett, 2019.
4. Farzin Roohvand, et al Curr Pharm Biotechnol, 2019.
5. Farzin Roohvand, et al Mol Immunol, 2019.
6. Farzin Roohvand, et al J Immunol Res, 2018.

Webinar on Pharmaceutical Chemistry | May 22, 2020 | Paris, France

Citation: Farzin Roohvand; Genetically engineered and domain-exchanged streptokinase molecules with enhanced kinetics of fibrin-dependent proteolytic activity and resistance to α 2-antiplasmin; Pharmaceutical Chemistry 2020; May 22, 2020; Paris, France