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Authors: Pawan Kumar Raghav, Ajay Kumar Singh, Gurudutta Gangenahalli



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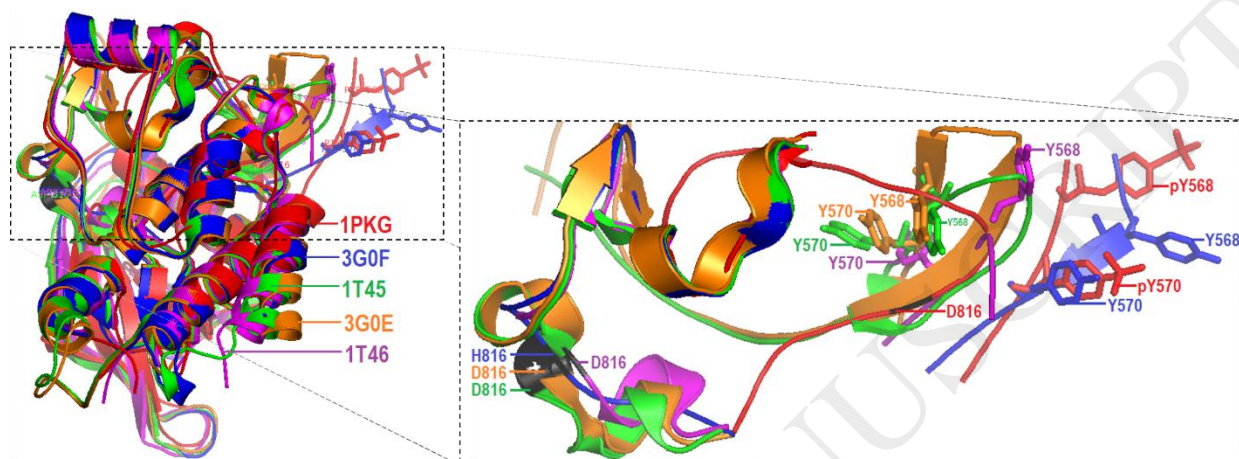
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A change in structural integrity of c-Kit mutant D816V causes constitutive signaling

Pawan Kumar Raghav, Ajay Kumar Singh, and Gurudutta Gangenahalli*

Division of Stem Cell and Gene Therapy Research, Institute of Nuclear Medicine and Allied Sciences (INMAS), Brigadier S. K. Mazumdar Marg, Timarpur, Delhi-110054, India

Graphical Abstract



Highlights

- Describes a comprehensive molecular mechanism of c-Kit mutation (D816V) that identified the SCF, and SHP-1/SHP-2 independent proliferation.
- Elucidation of structural changes occurs after D816V c-Kit mutation.
- Revealed the impact of D816V on the integrity dynamics of the structure responsible for its activity.

*Correspondence: Dr. Gurudutta Gangenahalli, PhD, FICS, FICI, FRACI CC, FRAM, MCIC, FNA Biol Sci's, FRSB, FRSM, FRSC (UK, Cambridge), Scientist 'G', Head, Division of Stem Cell and Gene Therapy Research, Institute of Nuclear Medicine & Allied Sciences (INMAS), Delhi-110054, India; Phone: 91-011-23905144; Fax: 91-011-23919509; E-mail: gugdutta@rediffmail.com

Abstract

Several signaling pathways, ligands, and genes that regulate proliferative and self-renewal properties of the Hematopoietic Stem Cells (HSCs) have been studied meticulously. One of the signaling pathways that play a crucial role in the process of hematopoiesis is the Stem Cell Factor (SCF) mediated c-Kit pathway. The c-Kit is a Receptor Tyrosine Kinase (RTK), which is expressed in the cells including HSCs. It undergoes dimerization upon binding with its cognate ligand SCF. As a result, phosphorylation of the Juxtamembrane (JM) domain of c-Kit takes place at Tyr568 and Tyr570 residues. These phosphorylated residues become the docking sites for protein tyrosine phosphatases (PTPs) namely SHP-1 and SHP-2, which in turn cause dephosphorylation and negative regulation of the downstream signaling responsible for the cell proliferation.

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