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

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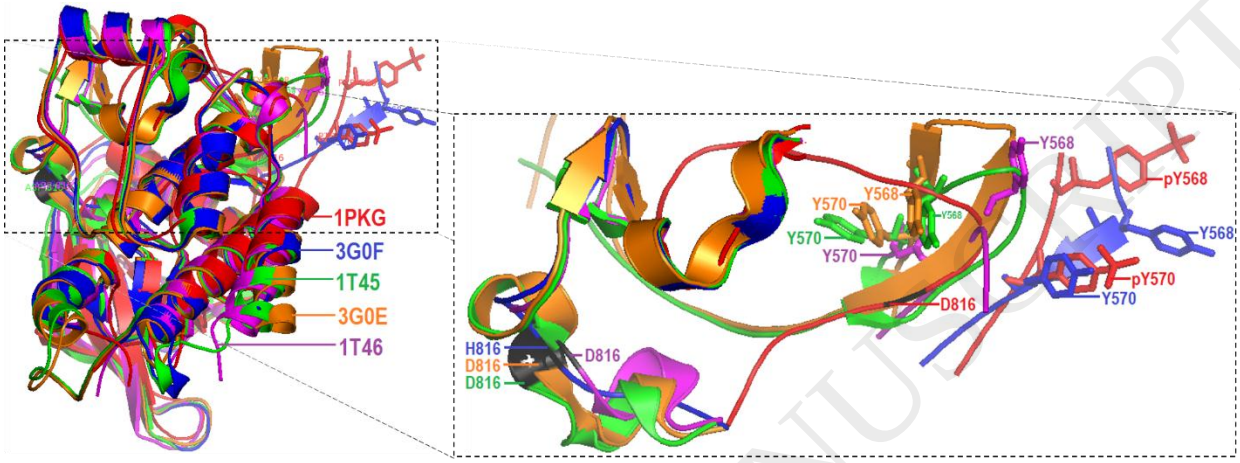
Graphical Abstract



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.

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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.