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Primary Imatinib Resistance in PDGFRA-mutant GIST

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Abstract

Gastrointestinal stromal tumor (GIST) is the most common sarcoma of the GI tract. The second most common type of GIST is driven by oncogenic mutations in PDGFRA, of which there are 50+ different kinase domain mutations reported. 82% of these occur in the kinase activation loop (AL), with the majority being a single point mutation, D842V. PDGFRA-D842V is notoriously resistant to conventional tyrosine kinase inhibitors approved for GIST, including imatinib. However, it isn't known how GIST with other PDGFRA AL mutations, which include numerous complex indels, would clinically respond to imatinib. From profiling some of these mutations individually, we have observed that one amino acid position, 842, may predict imatinib sensitivity, regardless of other mutations of the activation loop. With D842V, the substitution of a negatively charged residue (aspartate) with a hydrophobic one (valine) confers imatinib resistance. Similarly, we have found that all mutations that result in a hydrophobic residue occupying the 842 position are imatinib resistant, regardless of other deletions or substitutions. Conversely, mutations with a negatively charged residue in the 842 position remain imatinib sensitive. We hypothesize that the residue in the 842 position dictates the conformation of the kinase AL, thus determining the ability of imatinib to bind and inhibit PDGFRA. To test our hypothesis, we examined imatinib response to every amino acid mutation at the 842 position. We expressed these mutations in Ba/F3's and selected with imatinib (IC_{90} concentration). Deep sequencing identified enriched mutations which conferred imatinib resistance. Identified mutants were then validated for imatinib response. Imatinib profiling of these individual mutants has supported our hypothesis and previous observations, showing that hydrophobic residues at the 842 position confer resistance. Our predictions will inform patient care in the clinic, and if imatinib can be used to safely and effectively treat any patients with PDGFRA exon 18 mutations.