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Predicting imatinib responses in exon 18 PDGFRA-mutant GIST

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Abstract

The majority of gastrointestinal stromal tumor (GIST) are driven by mutations in KIT or platelet derived growth factor receptor alpha (PDGFRA) receptor tyrosine kinases. Imatinib, a type II KIT/PDGFRA tyrosine kinase inhibitor (TKI), is the first-line treatment for advanced GIST. However, the most common PDGFRA mutation, exon 18 D842V, is strongly resistant to imatinib and other type II TKIs. Over 80% of unique PDGFRA mutations in GIST occur in exon 18, and they include many complexities such as in/dels and additional point mutations. It is largely unknown how these mutations respond to imatinib, but many are assumed to be resistant, like D842V. Contrary to these assumptions, we have shown in our in vitro models that some of these clinically observed exon 18 mutations were imatinib sensitive. Imatinib sensitivity also seemed to be dependent on the characteristics of the amino acid at the 842 position, which led us to hypothesize that sensitivity is largely determined by this residue.

To test this hypothesis, we cloned and expressed every possible variant at the 842 position in Ba/F3 cells and determined imatinib sensitivity via immunoblotting. To date, we tested at least 1 mutation from each amino acid class. Similar to D842V, all hydrophobic amino acid mutations tested were resistant to imatinib, as defined by an IC_{50} much greater than 100nM. Furthermore, all mutant kinases without a hydrophobic 842 residue were sensitive to imatinib, with IC_{50s} less than 100nM. Based on these data, we debunked the belief that all PDGFRA exon 18 mutations are imatinib resistant. Our work demonstrates the importance of understanding the biochemical properties of mutations to predict treatment outcomes. While avapritinib was recently approved for first-line treatment for all PDGFRA exon 18 mutant GIST, identifying which mutations respond to imatinib would provide a much safer and more tolerable treatment for patients.