GENETICS

Novel mutations explain secondary resistance to imatinib

A possible mechanism of secondary resistance to imatinib in gastrointestinal stromal tumors (GIST) has been delineated in a new study. Chun-Meng Wang and colleagues identified novel *KIT* mutations in exon 13 or exon 17 in patients with GIST who acquired resistance to imatinib therapy.

The tyrosine kinase inhibitor imatinib, which targets the KIT receptor, illicits a favorable response in most patients with GIST. However, resistance to therapy eventually occurs with a median time to progression of 2 years.

Although *KIT* mutations have been implicated in a large proportion of GIST, the molecular response of KIT inhibition by imatinib is poorly understood. Thus, Wang *et al*. evaluated *KIT* mutations and downstream signaling profiles in 32 patients with GIST who had been treated with imatinib and surgical resection.

Activating mutations in *KIT* were observed in 26 patients. Furthermore, of the 14 patients who acquired secondary imatinib resistance, 11 had secondary *KIT* mutations, of which nine were in exon 17 and two in exon 13. The expression levels of KIT and AKT were higher in GIST with secondary *KIT* mutations and acquired imatinib resistance compared with imatinib-responsive GIST with primary *KIT* mutations.

In conclusion, the novel *KIT* mutations in exon 13 or exon 17 are involved in the molecular mechanism of secondary resistance to imatinib. Furthermore, the PI3K/AKT pathway might be important in these patients, notes Wang Chun Meng. "We should pay more attention to the signal transduction pathway in the imatinib-resistant GIST," he adds.

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