Oncogenic Kit receptor signaling and targeted molecular therapies – in mouse models of gastrointestinal stromal tumor.

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The KIT receptor tyrosine kinase has critical roles in several distinct cell systems including hematopoiesis, the pigmentary system, gametogenesis, and in pacemaker cells of the gastrointestinal tract. Normal Kit receptor mediated functions include cell proliferation, cell survival, cell adhesion, cell migration, secretory responses and differentiation. In human neoplasia oncogenic activation of Kit has roles in gastrointestinal stromal tumors (GIST), mastocytosis, acute myelogenous leukemia, and subsets of melanomas and germ cell tumors. Kit receptor functions are mediated by kinase activation, receptor auto-phosphorylation and association with various signaling molecules and signaling cascades. How do receptor tyrosine kinases such as Kit mediate distinct cellular responses in different cell types during embryonic development and in the postnatal animal, and what are the requirements for oncogenic transformation in different cell types to produce cancer? We have produced mice containing knock-in point mutations, loss of function and gain of function mutations in the Kit receptor gene in mice which block distinct signaling cascades or which provide for oncogenic activation of Kit in distinct cell types and driving oncogenesis. These mice have distinctly different phenotypes in gametogenesis and hematopoiesis, demonstrating the critical importance of the cellular context of *in vivo* signaling.

Most gastrointestinal stromal tumors express KIT. The principal genetic events responsible for the pathogenesis of GIST are thought to be gain-of-function mutations in the *KIT* gene and oncogenic KIT signaling drives GIST tumorigenesis. Interestingly patients with familial GIST syndrome carry a germline *KIT* gain-of-function mutation. We have used a knock-in strategy to introduce the V558 deletion mutation observed in a familial GIST case into the mouse genome. Remarkably, $Kit^{V558\Delta}/+$ mice provide a faithful model for human familial GIST, and demonstrated that constitutive KIT signaling is necessary and sufficient for induction of GIST. These GIST mice provide an excellent tool to study mechanisms of oncogenic KIT receptor signaling in vivo and for studies of targeted pharmacological intervention. A majority of oncogenic Kit mutations are sensitive to inhibition by the tyrosine kinase inhibitor imatinib mesylate, and thus GISTs have become a prototype for targeted therapy of cancer. However, many patients who initially benefited from imatinib treatment eventually develop drug resistance. Because of the clinical importance of imatinib resistance the development of new strategies for the treatment of GIST is highly relevant.