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KIT in Melanoma: Many Shades of Gray

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Abstract

Activating mutations in *KIT* have been identified in melanomas of acral and mucosal types and in those arising in chronically sun-damaged skin. Until now, KIT has been considered an oncogenic driver and a potential therapeutic target. However, data presented by Dhal *et al.* show that in cutaneous melanomas the KIT promoter is a target for hypermethylation, leading to its downregulation. Their observations suggest that signaling pathways downstream of KIT may have distinct and opposing roles in the pathogenesis of melanoma subtypes. This will have important implications for the use of KIT inhibitors in treating melanomas.

KIT (c-kit), a type III receptor tyrosine kinase, and its ligand, stem cell factor (SCF), also known as c-kit ligand, are essential for the development of melanocytes in vertebrates, regulating growth, migration, survival, and differentiation (Wehrle-Haller, 2003). Their importance is highlighted by the development of pigmentation disorders upon loss of function in both mice and humans. The rare autosomal dominant disorder piebaldism, characterized by congenital patchy depigmentation of the skin, is attributed to heterozygous inactivating mutations in the *KIT* gene.

Activation of the KIT receptor is achieved through rapid homodimerization induced by SCF binding, followed by a cascade of auto-inhibitory interactions, transphosphorylation, and recruitment and activation of multiple downstream effectors (reviewed in Lennartsson and Ronnstrand, 2012). Depending on the cellular context in which KIT is activated, downstream effectors include Src family kinases, the p85 subunit of PI3K, phospholipase C-gamma, and MAP kinases. Recently, it has been demonstrated that Y568 and Y570 in the juxtamembrane region of KIT, which are involved in activation of Src, are required for normal pigmentation via regulation of MITF (Phung *et al.*, 2011).

Even though established as a critical mitogen for melanocytes, earlier studies of KIT protein in melanoma suggested that it is lost during disease progression; this was based on its higher expression in benign nevi vs primary and metastatic melanoma (Montone *et al.*, 1997; Isabel Zhu and Fitzpatrick, 2006). Also, early *in vitro* studies indicated that KIT might have a tumor-suppressing role in melanoma because it was lost in the majority of melanoma cell

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CONFLICT OF INTEREST

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lines. In addition, melanoma xenografts with low KIT expression displayed higher metastatic potential, whereas ectopic KIT expression in KIT-deficient lines inhibited growth of these cells *in vivo* (Huang *et al.*, 1996). At the same time, however, KIT was assigned a clear oncogenic role in many other tumor types, including gastrointestinal stromal tumors (GISTs), small-cell lung carcinomas, and acute myeloid leukemia, where activating *KIT* mutations were seen in as many as 70–80% of cases. For this reason, identification of *KIT* amplifications and activating mutations in selected melanoma subtypes generates great excitement in melanoma research and clinical communities as a potential target for therapy.

KIT mutations or amplifications are observed in ~30% of mucosal, 20% of acral, and 20% of melanomas arising in chronically sun-damaged skin (Curtin *et al.*, 2006; Beadling *et al.*, 2008). Although most mutations detected in *BRAF* and *NRAS* genes occur in single codons, V600 and Q61, respectively, *KIT* mutations show heterogeneous distribution thorough the gene, and they are detected most frequently in exon 11 (L576P) and exon 13 (K642E). In early studies, no *KIT* mutations were found in melanomas arising from non-chronically sun-damaged skin. Unfortunately, these were the majority of patients included in the first trials with KIT inhibitors (Ugurel *et al.*, 2005; Wyman *et al.*, 2006; Kim *et al.*, 2008). For this reason, most patients failed to demonstrate significant responses. More recently, however, substantial tumor responses were reported with imatinib mesylate and dasatinib in patients with melanomas harboring *KIT* alterations, including a K642E and L576P mutation as well as a 7-codon duplication of exon 11 (Hodi *et al.*, 2008; Lutzky *et al.*, 2008; Quintas-Cardama *et al.*, 2008; Woodman *et al.*, 2009).

The discrepancies between early and more recent studies reflect the complexity of KIT function in melanoma, suggesting that they vary under specific cellular and microenvironmental conditions. In the current issue of the *Journal of Investigative Dermatology*, Dahl *et al.* focus on the tumor-suppressive functions of KIT. The authors use genome-wide promoter profiling to identify DNA-methylation changes that impact gene expression in melanoma cell lines and uncultured cutaneous melanomas. Their results, verified by using several approaches, show that the *KIT* promoter is highly methylated in melanoma cell lines and that this methylation is a frequent cause of transcriptional silencing of the gene. More importantly, the authors demonstrate that *KIT* hypermethylation is not an *in vitro* artifact but is also observed in uncultured melanomas. It appears that SCF exposure over time can induce epigenetic downregulation of KIT, suggesting the existence of a fine-tuned balance between different consequences of KIT activation. Interestingly, the authors did not find any correlation of KIT activation with well-documented melanoma drivers, including the BRAF and NRAS pathways, even though these have previously been found to be mutually exclusive. Together, these observations suggest that KIT might be mediating its effects via an unidentified and independent molecular pathway.

Their study provides strong support for the previously suggested, but mostly ignored, possibility that KIT has a tumorsuppressive role in melanomas that occur on intermittently sun-exposed skin with frequent *BRAF* and *NRAS* mutations. Co-expression of these two mutations in human melanoma cells is shown to induce senescence (Petti *et al.*, 2006). For this reason and as suggested by Dahl *et al.*, it is possible that downregulation of KIT during

melanoma progression might favor avoidance of hyperstimulation via the ERK1/2 pathway, thereby leading to cell cycle arrest and senescence.

In other cell types, it is well established that KIT ligand SCF acts synergistically with other cytokines, including IL-3, IL-7, and Epo, in part via direct interactions with their respective receptors (reviewed in Lennartsson and Ronnstrand, 2012). Recently, it was shown that activation of the human G protein–coupled melanocortin 1 receptor (MC1R) leads to ERK1/2 phosphorylation by a mechanism involving Srcmediated transphosphorylation of KIT, suggesting crosstalk between these pathways (Herraiz *et al.*, 2011). Whether similar types of interaction could account for KIT's tumor-suppressor functions and whether this is relevant to melanoma, remains to be investigated.

This study provides yet another example of the extraordinary molecular diversity of melanomas, emphasizing the need for careful molecular profiling of these tumors before choosing therapies.

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Clinical Implications

- The functional role of KIT in melanoma development and progression appears to be dependent on melanocyte anatomical location.
- In a subtype of cutaneous melanoma, KIT is frequently lost because of hypermethylation, suggesting that it might have a tumor-suppressive role.
- Clinical KIT inhibitors might have undesirable effects by accelerating the progression of early-stage cutaneous melanomas that are growth inhibited because of intrinsic expression of KIT.
- KIT inhibitors should only be considered for treatment of correctly subtyped and molecularly defined melanomas with confirmed KIT status.