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Melanoma

Major finding: *TERT* promoter mutations are frequent in melanoma and create ETS/TCF binding motifs.

Concept: Promoter variants increase transcriptional activity of the *TERT* promoter in reporter assays.

Impact: Mutations in regulatory regions may be driver events in melanoma as well as in other cancers.

RECURRENT NONCODING MUTATIONS IN *TERT* MAY PROMOTE MELANOMA

Sequencing studies have largely focused on the identification of tumor-associated mutations in protein coding regions, including *BRAF* and *NRAS* mutations in melanoma. However, mutations in noncoding regions of the genome may also contribute to tumorigenesis. To investigate this possibility, Huang and colleagues used a whole-genome sequencing approach and identified 2 somatic, UV-signature mutations in the promoter of *telomerase reverse transcriptase* (*TERT*), which is necessary to maintain telomere length and is frequently activated in cancer, in 71% of melanomas tested. In a complementary study, Horn and colleagues performed linkage analysis followed by high-throughput sequencing of the linked region and found a germline *TERT* promoter variant in affected individuals from a melanoma-prone family. Horn and colleagues also detected recurrent somatic, UV-signature *TERT* promoter mutations in sporadic melanoma, including 74% of cell lines, 33% of primary tumors, and 85% of metastatic tumors. Somatic *TERT* mutations were mutually exclusive and occurred at a higher frequency than those of *BRAF* or *NRAS* mutations, supporting the notion that these may be driver events in melanomagenesis. Furthermore, Huang and colleagues found evidence of *TERT* promoter mutations in bladder and hepatocellular cancer cell lines, suggesting that somatic *TERT* mutations may be a common tumor-promoting mechanism. Intriguingly, both groups showed that each of these nucleotide substitutions generated a consensus binding motif for ETS transcription factors including members of the ternary complex factor (TCF) subgroup, which are activated by MAPK and BRAF signaling. These mutations increased *TERT* promoter activity in *in vitro* reporter assays, suggesting that promoter mutations may enhance *TERT* transcription and lead to telomerase reactivation in tumors. Moreover, these findings show that somatic mutations in regulatory regions of the genome may play a critical role in promoting tumor growth and progression. ■

Huang FW, Hodis E, Xu MJ, Kryukov GV, Chin L, Garraway LA. Highly recurrent TERT *promoter mutations in human melanoma. Science 2013 Jan 24 [Epub ahead of print].*

Horn S, Figl A, Rachakonda PS, Fischer C, Sucker A, Gast A, et al. TERT *promoter mutations in familial and sporadic melanoma. Science 2013 Jan 24 [Epub ahead of print].*

Apoptosis

Major finding: BAX constitutively translocates to and from the mitochondria independently of BH3 proteins.

Clinical relevance: The rate of BAX dissociation from the mitochondria contributes to apoptotic priming.

Impact: BAX "translocation" in response to apoptotic stimuli may in fact be a shift in its equilibrium.

BAX MITOCHONDRIAL TRANSLOCATION IS CONSTITUTIVE AND DYNAMIC

BAX is a proapoptotic BCL-2 family member that commits cells to apoptosis by initiating mitochondrial outer membrane permeabilization. BAX is predominantly cytosolic and is thought to be activated and targeted to the mitochondria by proapoptotic BH3 proteins. However, this model is largely based on data from experimental systems that do not allow real-time analysis of changes in protein localization or signal transduction. Using live-cell spinning-disk confocal imaging, Schellenberg and colleagues evaluated the dynamics of GFP-tagged BAX localization in healthy, nonapoptotic cells. Contrary to existing models of BAX function, BAX constitutively targeted to the mitochondria and inserted into the outer mitochondrial membrane in the absence of apoptotic stimuli and was constantly extracted back to the cytosol to maintain a dynamic equilibrium between these subcellular compartments. In addition, BAX targeting to the outer mitochondrial membrane was unaffected in cells lacking proapoptotic BH3 proteins and did not require prior conversion to its active conformation. In the presence of an apoptotic stimulus, such as detachment from the extracellular matrix, BAX rapidly accumulated on mitochondria, but survival signaling induced by focal adhesion kinase and AKT promoted BAX dissociation from mitochondria. Apoptosis following cell detachment was significantly higher in cells expressing a BAX mutant that dissociates more slowly from the mitochondria, and cells expressing mutant BAX were more sensitive to apoptosis induced by an inhibitor of the antiapoptotic proteins BCL-2 and BCL-XL, suggesting that alterations in the rate of BAX mitochondrial dissociation contribute to apoptotic priming. Collectively, these results suggest that BAX "translocation" to the mitochondria in response to apoptotic stimuli is actually a shift in the equilibrium between the cytosolic and mitochondrial outer membrane fractions that occurs independently of cytosolic BH3 proteins, which raises the possibility that current apoptotic models may need to be updated. ■

Schellenberg B, Wang P, Keeble JA, Rodriguez-Enriquez R, Walker S, Owens TW, et al. Bax exists in a dynamic equilibrium between the cytosol and mitochondria to control apoptotic priming. Mol Cell 2013 Jan 31 [Epub ahead of print].

AACR American Association for Cancer Research

CANCER DISCOVERY

Recurrent Noncoding Mutations in *TERT* May Promote Melanoma

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