Melanoma

Major finding: *TP53* mutations accelerate *BRAF*^{V600E}-driven melanoma and are generated by UV exposure.

Clinical relevance: *TP53* is mutated in approximately 20% of human melanomas marked by UV-induced DNA damage.

Impact: These findings provide mechanistic insight into how UV radiation can cause melanomagenesis.

UV RADIATION DRIVES MELANOMA BY INDUCING *TP53* MUTATIONS

Epidemiologic studies have established a link between exposure to UV radiation and cutaneous melanoma, but although UV radiation is known to induce DNA damage, the molecular mechanisms by which UV exposure promotes melanomagenesis remain unclear. Viros and colleagues expressed *BRAF*^{V600E} in the melanocytes of adolescent mice and found that a single dose of UV radiation equivalent to what would cause mild sunburn in humans induced melanocyte proliferation and nevi formation. Whereas *BRAF*^{V600E} expression alone led to tumor formation in approximately 70% of mice with a median latency of just over 1 year, 100% of *BRAF*^{V600E}-expressing mice repeatedly exposed to UV radiation developed melanoma at a median latency of only 5.3 months. Of note, application of sunscreen significantly delayed the onset of UV-driven melanoma in *BRAF*^{V600E} mice, but all mice still developed tumors at a median latency of 7.5 months, providing preclinical evidence that sunscreen can confer partial protection against UV-induced melanoma in susceptible individuals. Whole-exome sequencing revealed a significant increase in single-nucleotide variants in UV-induced tumors compared with unexposed tumors and identified mutations in *Trp53* in 40% of tumors, almost all of which were cytosine-to-thymine transitions at the 3' end of pyrimidine dimers that are indicative of UV-induced DNA damage. Consistent with these findings indicating that *Trp53* is a target of UV radiation in melanoma, *TP53* mutations were significantly more common in human melanomas with a UV-induced mutational signature. Expression of one mutant allele of *Trp53* markedly accelerated melanoma formation in *BRAF*^{V600E} mice, with all mice developing tumors within 3.5 months, suggesting that UV-induced *Trp53* mutations cooperate with *BRAF*^{V600E}. Together, these findings provide evidence that *TP53* mutations play a role in melanoma as well as insight into how UV radiation can promote melanomagenesis. ■

Viros A, Sanchez-Laorden B, Pedersen M, Furney SJ, Rae J, Hogan K, et al. Ultraviolet radiation accelerates BRAF-driven melanomagenesis by targeting TP53. Nature 2014 Jun 11 [Epub ahead of print].

Medulloblastoma

Major finding: *GFI1* and *GFI1B* can be activated by juxtaposition to active enhancers in Group 3 and 4 medulloblastoma.

Concept: Combined expression of GFI1 or GFI1B and MYC can drive medulloblastoma formation in mice.

Impact: Gene activation by rearrangements involving enhancer regions may be a common oncogenic mechanism.

ENHANCER HIJACKING IS AN ONCOGENIC DRIVER IN MEDULLOBLASTOMA

Group 3 and Group 4 medulloblastomas are the most aggressive but least understood medulloblastoma subtypes. Northcott, Lee, Zichner, and colleagues evaluated all detectable chromosomal rearrangements identified by whole-genome sequencing of 137 Group 3 and 4 medulloblastomas and found that 6.6% of cases were distinguished by focal chromosome 9q34 rearrangements. Of the known genes in this region, only growth factor independent 1B (*GFI1B*) was differentially expressed, and analysis of 727 medulloblastomas showed that *GFI1B* overexpression was restricted to Group 3 and 4 tumors, with 10 of 11 *GFI1B*-overexpressing tumors in a validation set harboring 9q34 structural variants. Of note, these rearrangements did not directly affect the *GFI1B* coding region, but resulted in juxtaposition of *GFI1B* to noncoding DNA elements normally hundreds of kilobases upstream, suggesting that "hijacking" of enhancer regulatory elements might activate *GFI1B*. Indeed, chromatin immunoprecipitation sequencing for enhancer-associated histone marks revealed clusters of highly active enhancers, or super-enhancers, overlapping or adjacent to chromosomal breakpoints in *GFI1B*-overexpressing cases. The *GFI1B* paralog *GFI1* was also found to be specifically overexpressed in Group 3 and Group 4 medulloblastomas and similarly rearranged such that the *GFI1* locus becomes proximal to super-enhancers. Overall, mutually exclusive *GFI1* or *GFI1B* activation was observed in 41% of Group 3 tumors and 10% of Group 4 tumors. Neither GFI1, GFI1B, nor MYC expression alone was sufficient to drive transformation of neural stem cells implanted into murine cerebella, but the combination of either GFI family member and MYC drove the rapid formation of aggressive cerebellar tumors that recapitulated features of human Group 3 tumors. In addition to identifying enhancer-driven *GFI1* and *GFI1B* activation as one of the most prevalent driving events in Group 3 and 4 medulloblastomas, these findings suggest that existing cancer sequencing data should be evaluated beyond minimal common regions of amplification or deletion to identify oncogenic mechanisms of gene deregulation. ■

Northcott PA, Lee C, Zichner T, Stütz AM, Erkek S, Kawauchi D, et al. Enhancer hijacking activates GFI1 family oncogenes in medulloblastoma. Nature 2014 Jun 25 [Epub ahead of print].

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