For the article: http://dx.doi.org/10.1038/jid.2008.374
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Progression of *NRAS* and *BRAF* Mutations in Cutaneous Melanoma

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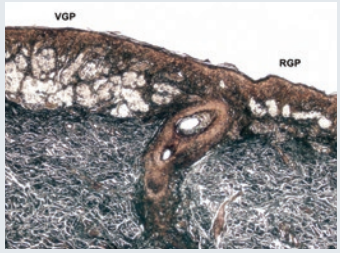

Melanoma, the deadliest of skin cancers, is treatable if caught early, but prognosis worsens with disease progression. Therefore, a better understanding of the mechanisms related to melanoma progression would be of great value. It is thought that melanoma is able to develop, grow, and subsequently spread because of genetic changes in cellular pathways. Mutations important in melanoma development have been found to occur in *NRAS* and *BRAF*, with recent studies reporting a *BRAF* mutation rate of up to 80% in cutaneous melanomas (Davies *et al*., 2002; Goel *et al*., 2006). Smaller, but significant, percentages of melanomas have also been shown to have somatic mutations in *NRAS* (Smalley and Herlyn, 2005).

In contrast to invasive melanomas, *in situ* melanomas carry a lower frequency of *NRAS* and *BRAF* mutations (Dong *et al*., 2003); it is unclear whether advanced tumors have stable genotypes or acquire additional mutations as they progress (Omholt *et al*., 2003; Dong *et al*., 2003). In this issue, Greene and co-workers report an increase in the frequency of *NRAS* and *BRAF* mutations with the histologic transition from the radial (RGP) to the vertical growth phase (VGP).

Greene *et al*. used laser-capture microdissection to examine *in situ* melanomas as well as distinct areas of RGP and VGP of invasive melanomas. *NRAS* exon 2 and *BRAF* exon 15 DNA were amplified by PCR and sequenced. The authors found an increased frequency of mutations in invasive tumors; 75.9% exhibited VGP mutations and 55.2% exhibited RGP mutations. Both were more frequent than mutations found in *in situ* melanomas (40%). In some tumors, VGP mutations but no RGP mutations were detected; in tumors with both RGP and VGP mutations, VGP mutations were more frequent. These findings suggest that melanomas acquire additional genetic alterations with disease progression.

Through the following questions, we examine this paper in greater detail. For brief answers, please refer to http://network.nature.com/group/jidclub.

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QUESTIONS

1. Describe the role of *NRAS* and *BRAF* in melanoma development.
2. What is the hypothesis of the paper?
3. Describe the methods employed.
4. What were the findings of the study?
5. What may be the clinical implications of this study, and what future work could be performed?

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