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Defining the role of NRAS in melanoma maintenance

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Defining the Role of NRAS in Melanoma Maintenance

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Malignancies is the most rapidly increasing malignancy among young people in the U.S.
• The incidence of melanoma has increased by more than 600 percent over the last 30 years.
  (ACS statistics www.cancer.org)
• Melanoma is the leading cause of cancer death in women aged 25-29.
• 5-year survival for advanced stages of the disease is ~20%.

**Goal:** to generate an in vivo model of melanoma that is resistant to inhibition of MAPK signaling in the context of mutant NRAS.

**Hypothesis:** resistant tumors will develop that are no longer dependent on NRAS for continued growth.

**Methods:** to use a novel mouse model of melanoma, generated through the somatic introduction of NRAS-encoding avian retroviruses in transgenic mice expressing the avian retroviral receptor, TVA, specifically in melanocytes to induce melanoma in vivo. The MAPK pathway will be inhibited genetically by doxycycline-mediated suppression of NRAS expression to select for resistant tumors.

**Long-term goal:** to identify additional targets for rational combination therapy for advanced melanoma.

**Results and Conclusions:**
• SHH (+) and 3.36 are resistant to doxycycline (DCT-TEA) or Cre induction.
• Delivery of a dCas9/SAHA to mice expressing P-ERK resulted in a loss of tumor maintenance in nearly all NRAS-regulated tumors.
• Tumor burden from primary tumors established and were significantly defected from the DCT-TEA/Dox/Cre treated mice.

**Future Directions:**
• Preservation and evaluation of samples to identify the mechanisms of resistance to other genetic or pharmacological inhibitors of the MAPK pathway.
• Development of resistant tumor samples to assess expression of the delivered NRAS expression by both DCT-TEA and Cre and by Western blot analysis of established cell lines.

**Acknowledgements:**

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