J Cancer Sci Ther 2017, 9:7 (Suppl)
DOI: 10.4172/1948-5956-C1-109

Bi-allelic loss of *CDKN2A* initiates melanoma invasion via RB-BRN2 axis

Robert Judson
University of California, USA

CDKN2A acts as a critical tumor suppressor in melanoma, as evidenced by frequent loss of function mutations and deletions. Loss of *CDKN2A* is believed to permit escape from senescent pre-neoplastic cell populations through relief of a cell cycle block mediated by its two gene products. We performed a comprehensive analysis of *CDKN2A* gene status and mRNA and protein expression levels of *CDKN2A* gene products in a cohort of melanomas and their adjacent pre-neoplastic lesions. We observed that bi-allelic *CDKN2A* loss coincides with the progression stage when primary melanomas become invasive. In melanoma lines, $p16^{INK4A}$, one of the protein products of the *CDKN2A* locus, is a potent barrier to metastasis, independent of its known role inhibiting cell proliferation. We genetically engineered primary human melanocytes to harbor *CDKN2A* deletions and/or BRAF V600E mutation at their endogenous BRAF locus. Using this physiologic model for the early phases of neoplastic transformation, we found no evidence for BRAF-induced senescence, rather observing that $p16^{INK4A}$ loss activates a master regulator of melanoma invasion, BRN2, through phospho-state specific binding of Rb to MITF. These results demonstrate that one of the most frequently altered genes across human cancers, *CDKN2A*, has an unexpected role in inhibiting cellular invasion through direct binding to lineage specific transcription factors and acts as an essential gatekeeper of early metastatic dissemination.

Robert.Judson@ucsf.edu