Cancer Science-2013
OMICS Group Conferences
Accelerating Scientific Discovery
3rd World Congress on
Cancer Science & Therapy
October 21-23, 2013 DoubleTree by Hilton Hotel San Francisco Airport, USA

Mouse models as drivers in defining new targets for therapies – Examples from prostate cancer melanoma studies

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Abstract

Prostate adenocarcinomas (PCa) with neuroendocrine (NE) phenotype and NE prostate tumors are associated with poor prognosis and androgen independence. Using a *TRAMP::Siah2*$^{-/-}$ genetic mouse model we found that formation of NE tumors and metastasis of PCa requires the ubiquitin ligase Siah2. Siah2 enables cooperation between HIF-1□ and the NE-specific transcription factor FoxA2. Genes induced by HIF-1□/FoxA2 cooperation are expressed in NE lesions and in metastatic human PCa and are required for formation of the NE phenotype, for metastasis of human PCa as for the development of NE tumors. Inhibition of Siah2 ligases or partial attenuation of HIF1a, or its cooperation with FoxA2, offers new therapeutic modalities for these more aggressive forms of PCa.

Using a genetic *Braf*^{V600E}*::Pten*$^{-/-}$ melanoma model, we recently established the importance of phosphoinositide-dependent kinase-1 (PDK-1) for melanoma development and metastasis. PDK-1 is a serine/threonine protein kinase that phosphorylates members of the conserved AGC kinase superfamily, including AKT and PKC. Selective inactivation of *Pdk1* in the melanocytes of *Braf*^{V600E}*::Pten*$^{-/-}$ or *Braf*^{V600E}*::Cdkn2a*$^{-/-}$*::Pten*$^{-/-}$ mice delayed the development of pigmented lesions and melanoma induced by systemic or local administration of 4-HT. Melanoma invasion and metastasis were significantly reduced or completely prevented by *Pdk1* deletion. PDK-1 inhibitor GSK2334470 (PDKi) effectively delayed melanomagenesis and metastasis.These studies provide direct genetic evidence for the importance of PDK1in melanoma development and progression and the rationale for targeting this pathway with corresponding inhibitors.

Biography

Ze'ev Ronai graduated (PhD, tumor immunology) from the Hebrew University in Jerusalem Israel, followed by postdoctoral training at Columbia University NYC. In 2004, his laboratory moved from Mount Sinai School of Medicine (NYC) to the Sanford-Burnham Medical Research Institute (La Jolla, CA), where he is the Scientific Director of the La Jolla Campus and the Deputy Director for the NCI-designated Cancer Center. Dr. Ronai authored over 250 peer-reviewed papers in the field of signal transduction pathways that underlie melanoma and prostate cancer development. Dr. Ronai has been studying ubiquitin ligases (Siah, RNF5), kinases (JNK, PDK1) and the transcription factor ATF2.