PTEN Inactivation Accelerates Lung Cancer Progression

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Small cell lung carcinoma (SCLC) is the most aggressive form of lung cancer, displaying neuroendocrine markers and high rates of metastases. Mutations in both *PTEN* and *PIK3CA* have been found in patients with SCLC; however, because of the high number of smoking-induced mutations in SCLC, it is unclear whether these changes in *PTEN*/*PIK3CA* are functionally relevant. In a recent paper published in *Molecular Cancer Research*, Dr. David MacPherson (Human Biology Division) and collaborators from the Carnegie Institution and Cornell University demonstrate that inactivation of *PTEN* in a mouse model accelerates the progression to cancer, raising the possibility that this pathway may be an effective therapeutic target for some patients with SCLC.

PIK3CA is the catalytic subunit of phosphatidylinositide 3-kinase, a kinase involved in several cellular processes including proliferation and differentiation, and activating mutations of this gene are found in a wide range of cancers. PTEN is a phosphatase that dephosphorylates PIK3CA targets, inhibiting signaling through the AKT pathway, and therefore acting as a potent tumor suppressor. Both *PTEN* inactivating mutations and *PIK3CA* activating mutations have been identified in patients with SCLC (Yokomizo, *et al*., 1998 and Shibata, *et al*., 2009). To determine the significance of these mutations in the progression of SCLC, the researchers generated mice lacking one or both alleles of *PTEN* (*PTEN*$^{-/+}$ and *PTEN*$^{-/-}$, respectively) in a mouse background lacking both the tumor suppressors *p53* and *Rb* (*p53*/*Rb*$^{-/-}$).

Mice with a *p53*/*Rb*$^{-/-}$ genetic background are an established model of SCLC. These animals typically succumb to their tumor burdens after a relatively long period of time (387 +/- 57 days). The tumors that develop display neuroendocrine markers and are highly invasive. When the authors inactivated a single PTEN allele in these animals, tumorigenesis was substantially accelerated (242 +/- 59 days). Histologically, the tumors in these animals were similar to *p53*/*Rb*$^{-/-}$ animals, and 64% of *PTEN*$^{-/+}$ animals also had SCLC liver metastases visible at necropsy. Furthermore, animals that did not express PTEN at all developed tumors extremely rapidly (123 +/- 30 days). However, these animals developed adenocarcinomas that could be differentiated histologically from the SCLC-like tumors that *PTEN*$^{-/+}$ mice developed.

Western blot analysis of the tumors in these mice revealed the complete loss of PTEN protein expression in 4/4 tumors from *PTEN* hemizygous mice, consistent with inactivation of the wildtype *PTEN* allele in these animals. Furthermore, AKT phosphorylation was detected in both $PTEN^{-/+}$ and $PTEN^{-/-}$ tumors, consistent with AKT pathway activation. However, unlike human SCLC, deep DNA sequencing identified a low somatic mutational burden in these mouse tumors, supporting the hypothesis that most mutations in human SCLC are secondary to smoking-induced damage.

The results of this study confirm that *PTEN* inactivating mutations play a substantial role in the progression of SCLC and lung adenocarcinoma. "While there are no targeted therapies yet available for human small cell lung cancer, the strong role shown for PTEN in the mouse model suggests that [inhibitors targeting this pathway] may be effective in subsets of SCLC patients. Moreover, the new mouse models will be ideal tools to test the effectiveness of therapies directed towards vulnerabilities conferred by *PTEN* inactivation," said Dr. David MacPherson.

Cui M, Augert A, Rongione M, Conkrite K, Parazzoli S, Nikitin AY, Ingolia N, Macpherson D. 2014. PTEN is a Potent Suppressor of Small Cell Lung Cancer. *Molecular Cancer Research*. Epub ahead of print. Doi: 10.1158/1541-7786.MCR-13-0554.

See also: Yokomizo A, Tindall DJ, Drabkin H, Gemmill R, Franklin W, Yang P, *et al*. 1998. PTEN/MMAC1 mutations identified in small cell, but not in non-small cell lung cancers. *Oncogene*. 17:475-9.

See also: Shibata T, Kokubu A, Tsuta K, Hirohashi S. 2009. Oncogenic mutation of PIK3CA in small cell lung carcinoma: a potential therapeutic target pathway for chemotherapy resistant lung cancer. *Cancer letters*. 283:203-11.

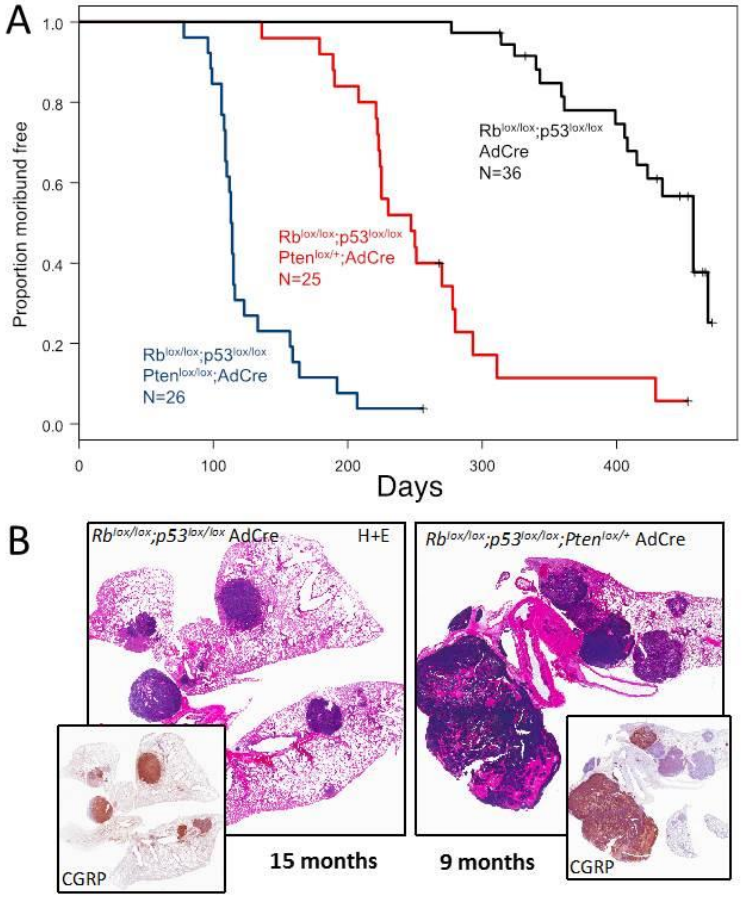

Image courtesy Dr. David MacPherson

Impact of PTEN deletion on cancer progression. A. Animals with active PTEN (black) develop SCLC at a slower rate than animals with either one (red) or both (blue) PTEN alleles inactivated. B. Mice with one inactivated PTEN allele develop more extensive SCLC. These tumors all develop neuroendocrine features similar to human SCLC (inset).