PTEN Inactivation Accelerates Lung Cancer Progression

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G Brennan

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 phosphatidylinositol 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.


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).