Medical Xpress

Quick-and-dirty DNA repair sets the stage for smoking-related lung cancer

January 26 2017

The stem cells that proliferate the most in response to damage caused by cigarette smoke repair their DNA using a process prone to errors, setting the stage for lung cancer, according to a study publishing January 26, 2017 in the open-access journal *PLOS Biolog*y by Marie-Liesse Asselin-Labat and her team of the Walter and Eliza hall Institute of Medical Research, Australia.

Smoking is a strong risk factor for squamous cell carcinoma, the second most common form of lung cancer, but the relative contributions to carcinogenesis of two types of lung stem cells (basal cells and alveolar progenitor cells) —and the molecular reasons for accumulation of the DNA damage that leads to cancer—have not been clear. To explore these issues, the authors isolated both types of cells from the lungs of heavy smokers and compared the activity of their genes, their rates of cell division, and their ability to repair their DNA in response to damage.

They found that carcinoma cells from smokers carried the "transcriptional fingerprint" (i.e. the pattern of genes that were switched on or off) of basal cells, suggesting that the tumors may originate from this type of cell. They showed that basal cells were much more efficient at repairing DNA damage, allowing them to survive and reproduce following exposure to chemicals or radiation that damaged the DNA. However, the principal repair pathway used by basal cells, called "non-homologous end joining," introduced many errors into the DNA. The combination of rapid but error-prone repair, the authors suggest, leads basal cells to accumulate a high burden of mutations that ultimately leads

to carcinoma.

"Our results indicate that targeting DNA repair processes may be a promising approach to preventing and treating this form of lung cancer," said Asselin-Labat.

More information: Weeden CE, Chen Y, Ma SB, Hu Y, Ramm G, Sutherland KD, et al. (2017) Lung Basal Stem Cells Rapidly Repair DNA Damage Using the Error-Prone Nonhomologous End-Joining Pathway. *PLoS Biol* 15(1): e2000731. DOI: 10.1371/journal.pbio.2000731

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Citation: Quick-and-dirty DNA repair sets the stage for smoking-related lung cancer (2017, January 26) retrieved 18 April 2024 from https://medicalxpress.com/news/2017-01-quick-and-dirty-dna-stage-smoking-related-lung.html

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