How chronic obstructive pulmonary disease increases risk of lung cancer

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In addition to the well-known risk factor of smoking, chronic obstructive pulmonary disease (COPD) increases lung cancer risk.

A University of Colorado Cancer Center study published in the journal Cancer Prevention Research details one novel mechanism of this risk: long-term oxygen depletion stimulates signals that promote tumor growth. In addition, this early study – performed in animal models – shows that tumors fueled by these COPD-induced signals may be especially susceptible to prevention or perhaps even treatment with drugs that turn off these same signals, namely VEGFR-2 and EGFR inhibitors.

"At least in animal models, this study shows an important pathway activated in lung tumors arising in poorly oxygenated regions of the lung that isn't activated to nearly the same degree in other lung cancers," says York Miller, MD, investigator at the CU Cancer Center and professor in the Department of Pulmonary Sciences and Critical Care Medicine at the University of Colorado School of Medicine and Denver Veterans Affairs Medical Center, the paper's senior author.

"There are probably other mechanisms driving lung cancer in COPD as well – for example, inflammation is also very likely playing in – but this paper shows that the hypoxic sensing pathway is specifically activated in these COPD lung cancer models and that this sensing pathway is to a large degree driving tumor growth," Miller says.

Specifically, his study used animal models designed to develop cancer,

which the group placed in high altitude chambers set to mimic the chronic oxygen depletion of found in parts of the lung affected by COPD. Mice in the hypoxic condition developed larger tumors than mice given normal oxygen, but, according to Miller, what was especially striking is the reason for this tumor growth.

"We saw that tumor growth in the hypoxic environment – which mimics that of COPD conditions including chronic bronchitis and emphysema – is due to signaling by HIF-2a. This HIF-2a in turn activates cancer growth promoting mechanisms including VEGF and the EGFR ligand, TGFa, which are growth factors involved in stimulating cell proliferation and the development of new blood vessels," Miller says.

Likewise, just as tumors that arise in hypoxic conditions do so through turning on pathways that lead to the over-production of VEGF and TGFa, so too are these tumors especially susceptible to cancer therapies that block these growth factors. Sure enough, animal models given the drug vandetanib – a combined VEGFR/EGFR inhibitor – failed to develop cancer under hypoxic conditions.

"Chemoprevention hasn't been done successfully for lung cancer," Miller says, "but this approach of VEGF/EGFR inhibitors for patients with COPD and extreme lung cancer risk may be something that should be explored further."

Miller imagines the next step is a review of patient records to discover if COPD lung cancer patients who happened to be treated with VEGF/EGFR inhibitors, in fact, had better tumor response than patients with normal lung function and similar tumors.

"Right now it's not a treatment," Miller says, "but it's an exciting line of inquiry."