**New Epigenetic Target for Lung Cancer Identified**

A player in epigenetic gene regulation, the histone demethylase KDM2A, is overexpressed in poor prognosis, non-small cell lung cancers (NSCLC), according to a recent[study](http://www.jci.org/articles/view/68642?key=c85b37ed02f837ee5ede) in the Journal of Clinical Investigation.

The revelation means KDM2A may be a druggable target. This is a potentially key development given that lung cancer is by far the leading cause of cancer death, killing more people than breast, prostate and colon cancers combined.

“A very interesting study,” says Philip Tsichlis, who is director of the Tufts University-New England Medical Center Cancer Center and was not involved with the study. “It makes a convincing case for the amplification and overexpression of KDM2A in NSCLC. Also, I found it interesting that the analysis of clinical samples confirmed that this pathway is not only active in NSCLC but that it also represents an independent unfavorable prognostic marker.”

The group not only found that KDM2A is overexpressed in a subset of NSCLC, but that it is “indispensable for tumorigenicity and invasiveness of KDM2A overexpressing NSCLC cells,” wrote the authors. “Our mechanistic results indicate that KDM2A overexpression activates ERK1/2 (a common cancer pathway) by repressing DUSP3’s transcription. Thus, these findings provide insights into how the dysregulation of an epigenetic enzyme is coupled to kinase signaling in NSCLC and also reveal the clinical importance of KDM2A in NSCLC.”

Tsichlis, however, cautions: “Regarding the mechanistic experiments in the paper, I would like to point out that the rescue of cell proliferation” in cells where KDM2A and DUSP3 have been silenced “is rather poor despite the fact that ERK phosphorylation is essentially restored.” This suggests, says Tsichlis, “perhaps DUSP3 is not the only biologically relevant target of KDM2A.”

Furthermore, he says, the fact that no tumors were observed when KDM2A knockdown cells were injected via IV into mice, “may suggest that knocking down KDM2A depletes the culture of tumor initiating cells (cancer stem cells), a point not made by the authors. If this is the case, the mechanism has not been addressed in this paper.”

But in addition to providing lung cancer researchers with a new target, “in this paper there is a lot more information that confirms beyond doubt that the functional activities of KDM2A and (its sister histone demethylase) KDM2B significantly diverge,” says Tsichlis, who has extensively [studied](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3505602/) the role of histone demethylases in cancer.

He adds that KDM2B and KDM2A are also known as NDY1 and NDY2, or “Not Dead Yet” 1 and 2, as they are similar in their ability to immortalize mouse embryonic fibroblasts in culture.

Indeed, Tsichlis is soon submitting research that finds KDM2B plays a role in a different major cancer. “It would be interesting to find out by direct comparison where KDM2A and KDM2B do overlap.”

“The majority of NSCLC patients do not have well-defined drug targets,” the MD Anderson group wrote. “It is also challenging that most of NSCLC patients who receive targeted therapies (e.g., the EGFR inhibitor erlotinib) eventually acquire drug resistance. Therefore, the identification of new drug targets may provide better therapeutic options for NSCLC patients.”