Yale study finds some aggressive tumors silence genes that fight cancer

By Vicky Agnew

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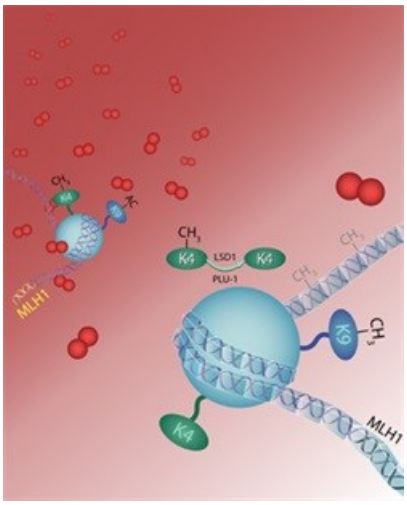
A study led by Yale Cancer Center may provide clues to how some aggressive cancers turn off, or silence, genes critical to suppressing tumors. The findings, published in the journal Cell Reports, suggest that this gene silencing process could be interrupted to increase the chances that aggressive tumors will respond to treatment.



When oxygen levels (shown as red balls) are low, DNA (shown in light blue) is frozen — and its gene expression, including that of tumor suppressors, is silenced.

As cancer develops, it often outstrips its blood supply and receives less oxygen than normal tissue. This low-oxygen environment, called hypoxia, is associated with aggressive tumors of all types that are more likely to progress despite chemotherapy and radiation therapy.

The study, which used colon cancer tissue, found that hypoxia also triggers the silencing of a critical tumor-suppressing gene called MLH1.

The team also identified an enzyme, LSD1 (lysine specific demethylase), associated with MLH1 that could be a target to reverse or block the silencing process. Since LSDI is an enzyme, it is possible to target it with small molecules to inhibit its activity.

"We've long known that hypoxic tumors are associated with worse prognoses, but the idea that hypoxic tumors could

silence genes was an unexpected finding," said senior author Dr. Peter M. Glazer, the Robert H. Hunter Professor and chair of therapeutic radiology, and professor of genetics at Yale School of Medicine. "Now that we know how big a role hypoxia plays, we have a new and clinically-relevant path to explore in terms of circumventing this process. The next step is to determine how hypoxia affects other tumor-suppressing genes."

Other authors were first author Yuhong Lu, and Narendra Wajapeyee of Yale School of Medicine; and Mitchell Turker of Oregon Health & Science University.

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