Researchers discover novel role of specific histone deacetylase in non-small cell lung cancer

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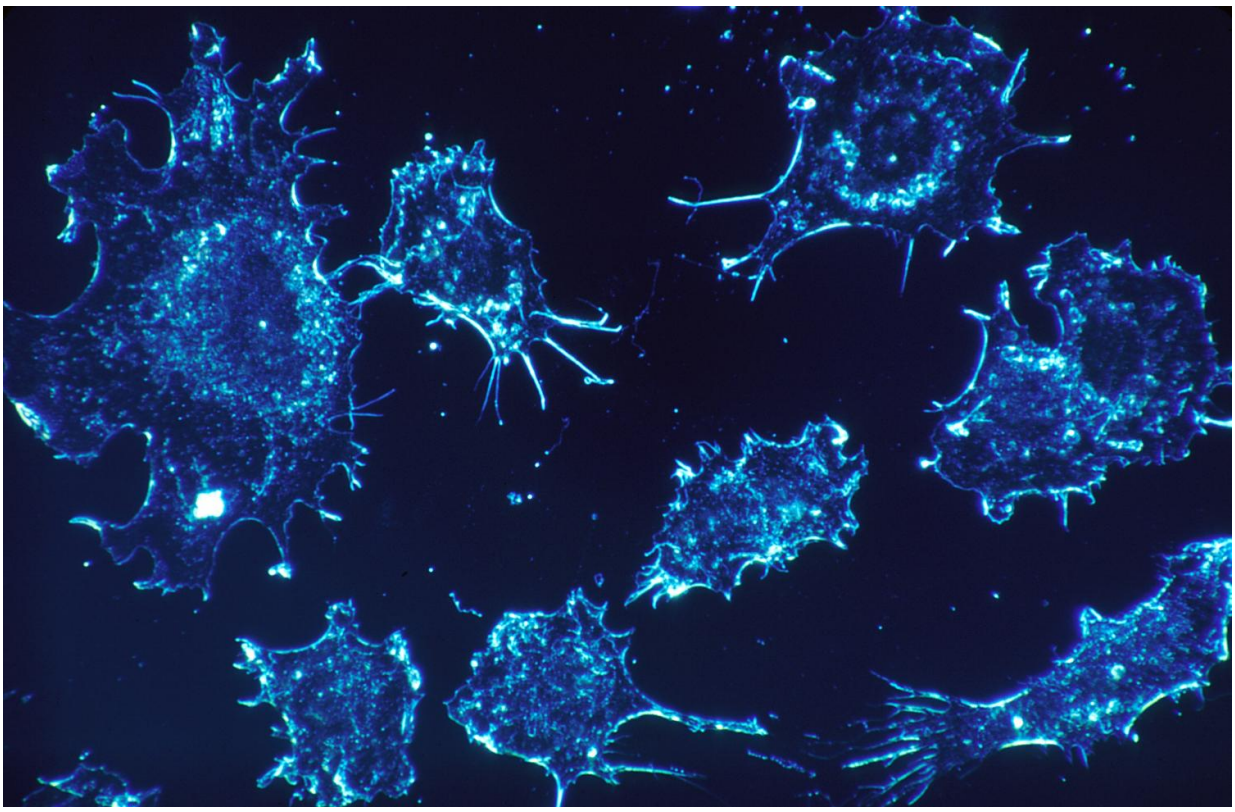

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The survival rates for patients with non-small cell lung cancer (NSCLC) have improved greatly over the past decade thanks to several new

targeted treatment options for patients. However, lung cancer still remains the number one cause of cancer-related morality, leading to approximately 154,000 deaths each year in the United States. Many patients do not respond to these new targeted therapies or they may develop drug resistance. Researchers at Moffitt Cancer Center are trying to identify alternative strategies to treat this disease. In a new article published online in *Scientific Reports*, they highlight how targeting the histone deacetylase HDAC11 may be a novel therapeutic strategy for NSCLC.

Histone deacetylases (HDACs) are proteins that regulate the expression and activity of genes by altering DNA compaction and modifying proteins. HDACs are often deregulated in different types of cancer and several drugs that inhibit HDACs have been approved to treat these diseases. HDAC11 is one of the newest HDACs to be identified, but its role in cancer is not yet known.

Moffitt researchers conducted a series of preclinical studies to investigate the role of HDAC11 in NSCLC. They discovered that high levels of HDAC11 are found in samples from patients with NSCLC and that these high levels are associated with poor survival. The research team wanted to further delineate the potential role of HDAC11 in NSCLC development. They focused their studies on cancer stem cells (CSCs), which are slowly dividing cells that can undergo self-renewal. CSCs are known to contribute to tumor development and progression and are also highly resistant to chemotherapy and targeted drug treatments.

"It has been suggested that drugs that can eliminate CSCs would be effective as anti-cancer agents and could potentially overcome drug resistance," said Srikumar Chellappan, Ph.D., chair of the Department of Tumor Biology at Moffitt.

Chellappan and his team discovered that HDAC11 is found at high levels in CSCs and is associated with expression of the protein Sox2—a gene that is highly important for the self-renewal of CSCs. When the researchers targeted HDAC11 in NSCLC with specific inhibitors, they observed that the ability of CSCs to undergo self-renewal and expression of Sox2 were greatly reduced. Given the importance of CSCs to lung cancer growth and development, these observations suggest that targeting HDAC11 may be a potential strategy to block the self-renewal process of CSCs and inhibit NSCLC progression.

In additional studies, the research team found that these specific HDAC11 inhibitors impacted several processes associated with cancer development, including the formation of vascular networks, anchorage independent growth and cell motility. The HDAC11 inhibitors also reduced the growth of lung cancer cells that were resistant to other targeted therapies and inhibited the growth of lung cancer cells grown in the presence of other cells that contribute to drug resistance.

"This study presents a mechanistic basis for the role of HDAC11 in lung adenocarcinoma and suggests that once the parameters for in vivo studies and efficacy are met, they would be of immense potential in combating NSCLC," said Chellappan.

More information: Namrata Bora-Singhal et al, Novel HDAC11 inhibitors suppress lung adenocarcinoma stem cell self-renewal and overcome drug resistance by suppressing Sox2, *Scientific Reports* (2020). DOI: 10.1038/s41598-020-61295-6

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