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Scientists provide new insight on how to stop transcription of cancer cells

New UCLA research identifies TAF12 as a potential cancer drug target

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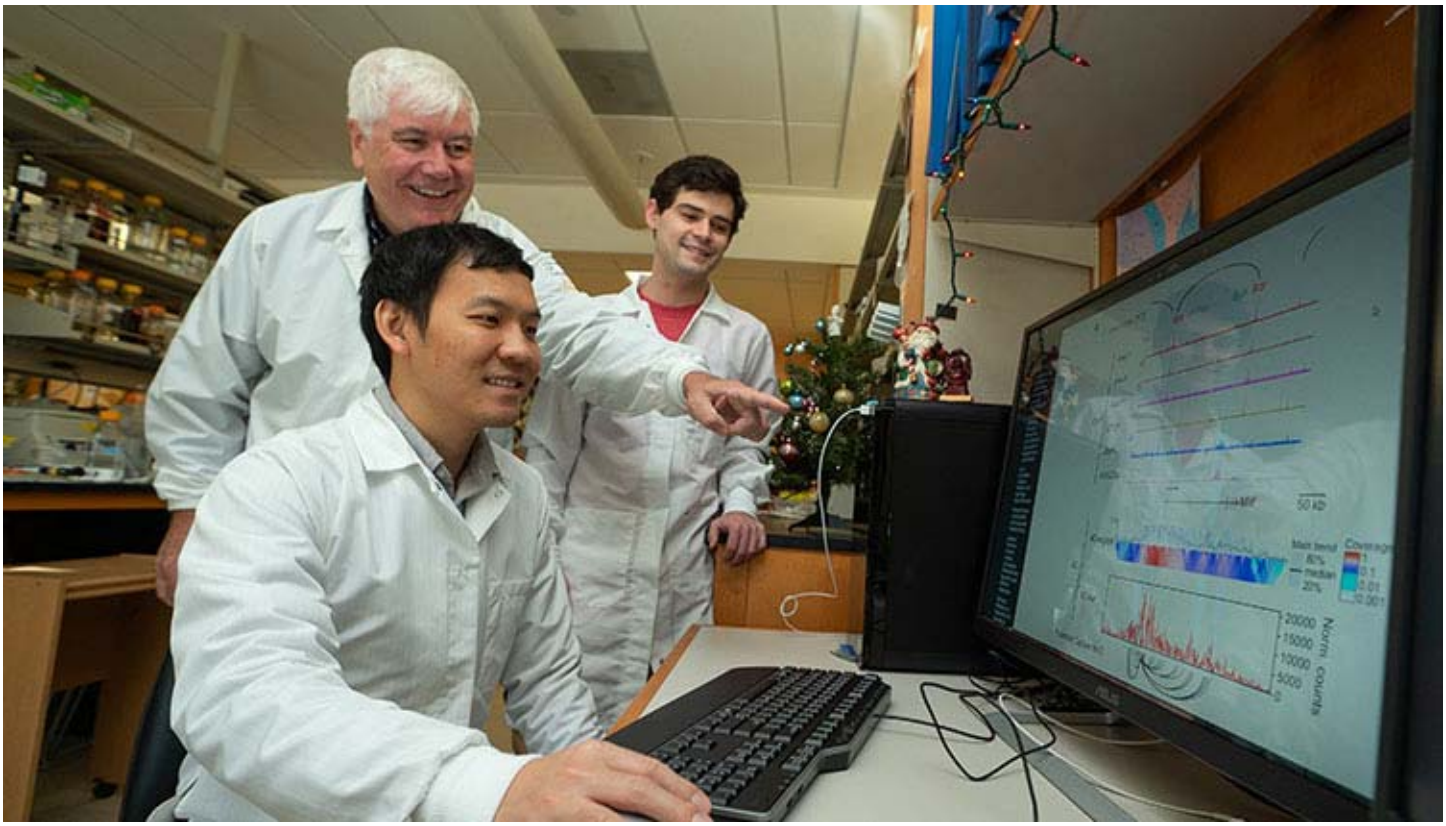
FACULTY Michael Carey



UCLA researcher Michael Carey (middle) guides his team in the lab

Scientists from the UCLA Jonsson Comprehensive Cancer Center have identified a key protein, transcription factor TAF12, that plays a critical role in the formation of a preinitiation complex, which consists of over one hundred proteins that are necessary for the transcription of protein-coding genes. The team found by eliminating TAF12, the entire preinitiation complex is destroyed and the genome-wide transcription is downregulated drastically.

The findings could help pave the way for cancer therapies that target TAF12, potentially stopping transcription in cancer cells and helping decrease the growth of cancerous tumors. TAF12 had previously been shown by others to be essential for growth of acute myeloid leukemia in mouse models.

“Identifying TAF12 as the cornerstone of the preinitiation complex allowed us to eliminate preinitiation

complexes in the cell, and that has not been done before," said senior author Michael Carey, PhD, professor of Biological Chemistry and director of the Gene Regulation Program at the Jonsson Cancer Center.

BACKGROUND

There have been significant advancements in the last couple of decades in principles about how the genome is organized and understanding the structures of transcription factors. However, the precise details of how enhancers communicate with promoters — genetic elements that control transcription in human and mouse genomes — to turn on genes is still not completely understood.

Efficient transcription, a basic and fundamental biological process that plays an important role in making proteins, requires the formation of a preinitiation complex that has over one hundred transcription factors including two major complexes termed co-activators. Understanding how these major co-activators function in cells is crucial in determining the precise mechanisms of gene activation. In this study, UCLA investigators looked to identify the key proteins in the co-activators to see if this knowledge of gene regulation and transcription could be eventually be applied to cancer therapeutics.

METHOD

The researchers conducted an shRNA knockdown screen to identify key proteins in gene transcription in mouse embryonic stem cells. A technique termed auxin-inducible degradation was employed by the researchers to rapidly remove the identified transcription factor to determine the effects on formation of preinitiation complexes throughout the genome.

AUTHORS

Senior author is Dr. Carey, who is also a member of the UCLA Eli and Edythe Broad Center of Regenerative Medicine and Stem Cell Research. The first author is Fei Sun, a postdoc of Biological Chemistry and the David Geffen School of Medicine at UCLA. Other authors include Terrence Sun, Michael Kronenberg and Xianglong Tan from UCLA, and Chengyang Huang from Shantou University Medical College.

JOURNAL

The study was published in the journal Genes & Development.

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