New insights on a common protein could lead to novel cancer treatments

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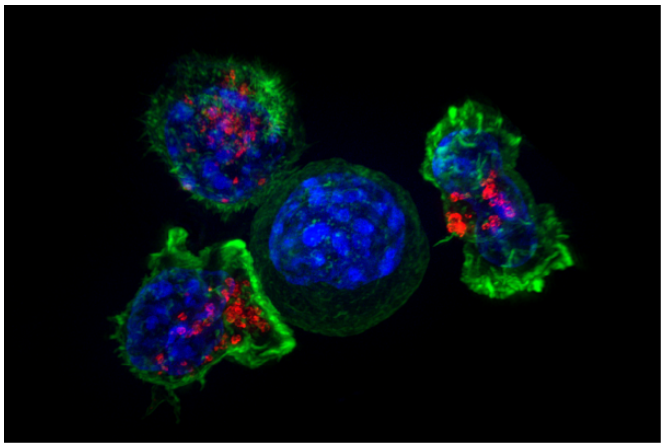

Killer T cells surround a cancer cell. Credit: NIH

A new University of Colorado Boulder-led study sheds light on a protein key to controlling how cells grow, proliferate and function and long implicated in tumor development.

The findings, published this week in the journal *Genes and Development*, could lead not only to new therapies for hard-to-treat cancers, but also inform novel treatments for neurological diseases and rare developmental disorders, the authors say.

"These findings could have broad biomedical application," said lead author Dylan Taatjes, a professor in the Department of Biochemistry.

For decades, scientists have known that the protein Cyclin Dependent Kinase 7 (CDK7) plays an instrumental role in helping all cell types transcribe, or decode, the genetic instructions provided by their DNA.

As Taatjes explains, each cell contains the same vast library, or genome. But a kidney cell may turn to different sections of that library for instructions than, say, a skin cell or a heart cell. Like a librarian, CDK7 helps ensure that each cell accesses the right instructions at the right time, guiding which genes get flipped on and off.

While that's important during human development and for normal cell function, CDK7 can be exploited by cancer cells to drive runaway growth. In recent years, scientists have discovered that the protein can fuel certain cancers to proliferate out of control, including "triple negative" breast cancers, which are more aggressive and don't respond well to common treatments.

That finding has inspired growing interest in the development of so-called "CDK7-inhibitors" but due to a lack of understanding of what the CDK7 does, early clinical trials have been disappointing.

"We wanted to find out exactly how it's really working inside human cells," Taatjes said.

To that end, the Taatjes lab teamed up with scientists from two pharmaceutical companies, Syros and Paraza, as well as colleagues in other CU Boulder labs, the University of Colorado School of Medicine and the BioFrontiers Institute.

Using sophisticated analytical techniques, basic biochemistry and next-generation genetic sequencing, the team identified, for the first time, the hundreds of specific proteins that CDK7 switches on or off, providing unprecedented insight into its role in cells.

The study also revealed that:

- CDK7 plays a role in multiple stages of transcription (decoding the genome), shaping what is known as "transcriptional splicing"—in which unneeded parts of the transcribed genome are pruned away to leave only those necessary for the cellular task at hand. Notably, errors in splicing have been linked to myriad diseases,

including blood cancers.

- CDK7 serves as a "master regulator" of other key enzymes, turning them on to further drive transcriptional programs. Defects in the execution of such programs have been linked to cognitive diseases, including Alzheimer's disease and rare developmental disorders, including head and facial deformities.
- The function of CDK7 is controlled by the company it keeps. When attached to a larger 10-protein complex, known as TFIIH, it is largely inactive. But when it breaks off on its own, its activity ramps way up.

Phase 1 trials are currently underway administering the latest version of CDK7 inhibitors to drug-resistant breast, colorectal, lung, ovarian and pancreatic cancer patients.

The findings of the new study suggest such drugs hold promise, Taatjes said.

"In biology, it is widely recognized that cells will compensate by activating other enzymes if one specific enzyme is inhibited," he said, explaining the mechanism behind drug resistance. "Our results suggest that CDK7 inhibitors could have distinct therapeutic advantages, given that they would not only block CDK7, but would impact the function of other enzymes."

The research could also lead to next-generation therapeutics, which—instead of silencing the protein completely—would target it only in its liberated, most active phase. This could result in more selective inhibitors that would be less damaging to healthy cells, with fewer side effects.

And because of its many roles in shaping how human cells develop and function, other applications may be possible.

"Cancer is an obvious application but it is by no means the only one," Taatjes said.

More information: Jenna K. Rimel et al, Selective inhibition of CDK7 reveals high-confidence targets and new models for TFIIH function in transcription, *Genes & Development* (2020). DOI: 10.1101/gad.341545.120

Provided by University of Colorado at Boulder

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