Researchers discover novel way to inhibit key cancer driver, other mutated genes

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CU Boulder researchers have discovered a new way to inhibit the most commonly mutated gene underlying human tumor growth, opening the door to new therapeutic strategies for cancer and a host of other diseases.

The discovery, published April 5 in the journal Cell Reports, marks an important step forward in the decades-long quest to target transcription factors (TFs), a notoriously hard-to-block class of proteins which, when mutated or dysregulated, can disrupt cell function and drive illness.

"This class of proteins represents one of the most high-impact therapeutic targets in biomedicine," said senior author and biochemistry Professor Dylan Taatjes. "We provide a completely new strategy for blocking transcription factor function that could have broad applications to many diseases, including and beyond cancer."

More than 1,500 transcription factors exist in the human body, each responsible for binding to specific sequences in DNA and transcribing or "decoding" the body's genetic blueprint to instruct a cell what to do.

Different TFs act in different kinds of cells (muscle, skin, blood, etc.), regulating everything from inflammation to cholesterol metabolism to wound healing to controlled cell death, which is key to inhibiting cancer.

When a TF is mutated, those instructions can go awry, turning a beneficial protein into a harmful one "like Jekyll and Hyde," said Taatjes.

For instance, mutations in the p53 transcription factor, the subject of this study, can change its function from a tumor suppressor to a tumor promoter.

For years, scientists have strived to develop methods to inhibit mutated transcription factors. Because they are all molecularly similar in the regions that bind to DNA, targeting one can indirectly target others, disrupting normal cell functions. Transcription factors also contain a section, called an activation domain, that is structurally disordered, making it hard to develop a molecule that will block it.

"Unfortunately, despite the huge potential and years of effort, therapeutic targeting of transcription factors has proven largely intractable," Taatjes said.

A promising workaround

Taatjes and a team of scientists, including Alanna Schepartz, professor of chemistry at the University of California, Berkeley, have spent years developing a workaround.
They set out to selectively inhibit p53, which is present in every kind of cell and plays a critical role in human development and in the body's stress response.

To do so, instead of targeting p53 itself, they targeted a 26-subunit complex aptly named Mediator. Mediator attaches to p53 and other transcription factors, serving as a bridge between them and the enzyme that decodes sections of the body's genetic blueprint. In essence, the transcription factor must click into Mediator, like a key in a lock, which then activates the decoding process.

In laboratory studies of human cancer cells, the researchers found that when they applied a novel peptide, which they designed based upon the p53 activation domain, they could prevent p53 from working. The team showed that the peptide worked by blocking p53 from clicking in to Mediator, much like jamming up the lock before the real key (p53 itself) could be inserted.

"A decades-long goal has been to target drug transcription factors directly," said Taatjes. "Here we have found a way to get the functional equivalent without actually targeting the transcription factor but Mediator instead. And, importantly, this does not negatively affect other transcription factors in the cell."

Taatjes stressed that the work is a proof-of-concept study, and that much more research must be done before such a strategy could become implemented in the clinic.

Ultimately, he said the approach could be applied to many other TFs that have been implicated in disease, opening the door to new treatment strategies for everything from heart disease to neurological disorders.

The unique method they used—using a transcription factor activation domain as a starting point rather than screening thousands of compounds—could also lead to faster, cheaper ways to develop new leads for therapeutics.

"The methods we discuss here could potentially apply to any disease that is driven by aberrant transcription factor function," Taatjes said.


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