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Protein linked with tumor growth could be potential target for cancer-fighting drugs

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As tumors grow, their centers are squeezed of oxygen. And so tumors must flip specific genetic switches to survive in these hypoxic environments. A series of studies funded to do only basic science and published today in the journal *Cell* reports the serendipitous discovery of a druggable target necessary for the survival of tumors in these low-oxygen environments.

"This is a clear example of starting with a basic biology question that now turns out to be relevant to patients," says Joaquin Espinosa, PhD, investigator at the University of Colorado Cancer Center, associate professor in the Department of Molecular, Cellular and Developmental Biology at CU Boulder, and the paper's senior author.

Espinosa along with postdoctoral researcher Matthew Galbraith, PhD, won a National Science Foundation grant to study how gene expression is controlled by a protein complex called Mediator.

"This is an ancient protein complex – conserved in all eukaryotes from yeast to humans," Espinosa says. "But the mechanism of action of Mediator is not well understood."

The purpose of the grant began and ended with increased understanding. Specifically, Espinosa, Galbraith and colleagues focused on an enzyme in Mediator known as CDK8: what is the function of this enzyme? They depleted CDK8 in cancer cells and then grew the cells with and without stressors like low glucose, DNA damage and, of course, low oxygen.

Without CDK8, cells in hypoxic conditions failed to activate the gene expression program that could help them survive hypoxic conditions.

"Low and behold, it turns out CDK8 has a major role in controlling gene expression in conditions of low oxygen. A few hundred genes go up to allow the cell to adapt to these conditions, but not without CDK8," Espinosa says.

In itself, this is a fairly major finding in basic biology. But it was Espinosa's connection with the cancer research community that allowed the next step:

"See, we've known that the transcription factor HIF1A is a master regulator of a cell's response to hypoxia. It turns survival genes up when oxygen goes down," Espinosa says. "HIF1A has been known as a major factor in tumor development, but as a transcription factor it's notoriously hard to drug."

The group wondered if CDK8 and HIF1A might work together to regulate genetic response to hypoxic conditions. By now you see where this is going: it turns out that HIF1A necessarily works through CDK8 to help tumors respond to the hypoxic environment. And while it's difficult to drug the transcription factor HIF1A, the class of drugs known as kinase inhibitors are designed to specifically target enzymes similar in function to CDK8.

"From the start, it was a very mechanistic question: how do cells use the Mediator complexes to turn genes on and off? Now we find this same system is important for tumor hypoxia. We entered from the CDK8 angle, landed right on the known oncogene HIF1A, and are back to CDK8, now with very real clinical potential," Espinosa says.