Protein complex links cellular metabolism to gene expression

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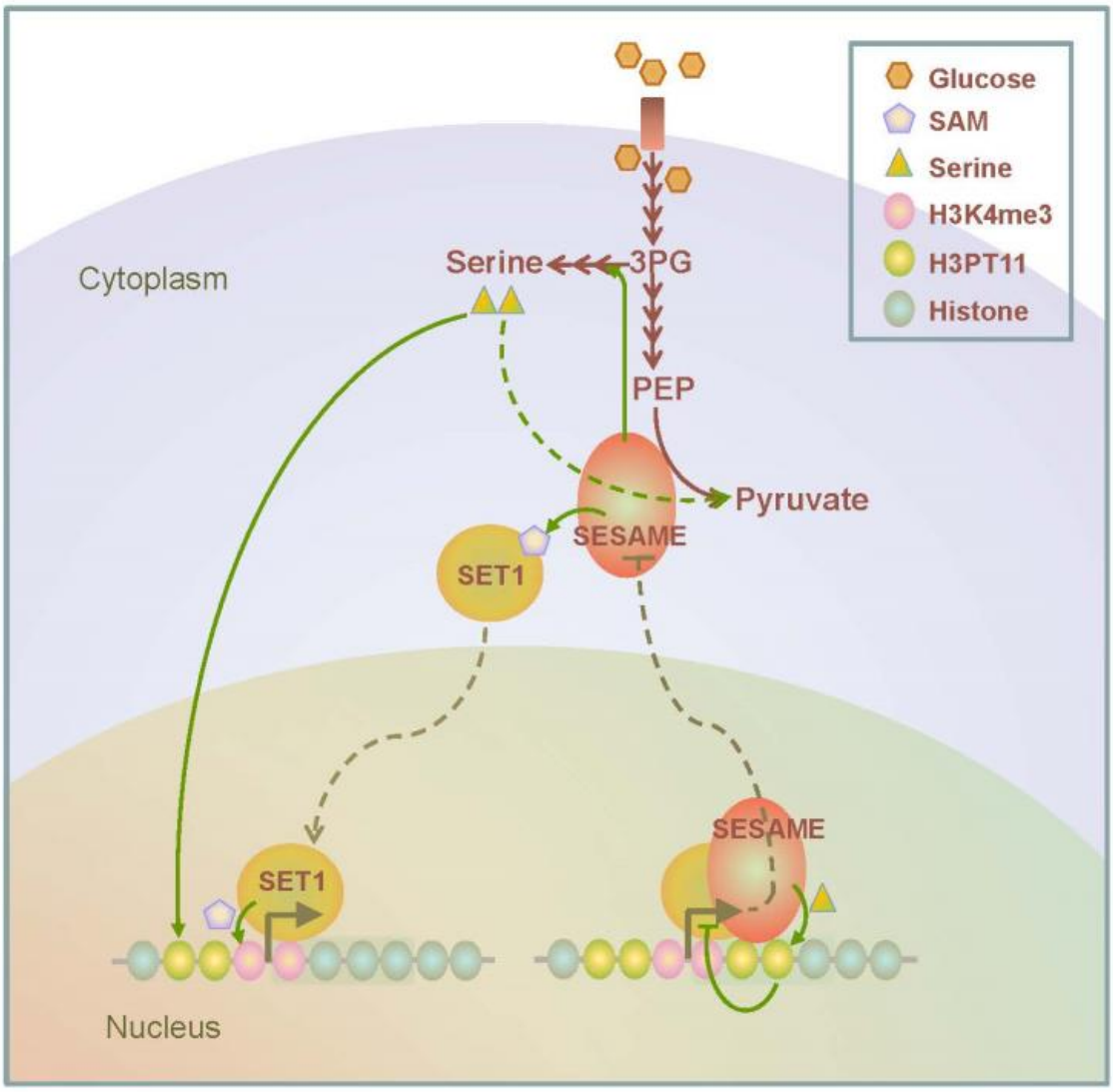
Glucose
SAM
Serine
H3K4me3
H3PT11
Histone
Cytoplasm
Serine
3PG
PEP
Pyruvate
SESAME
SET1
SET1
SESAME
Nucleus

The interaction of SESAME with Set1 complex controls the crosstalk between H3K4me3 and H3pT11 by sensing glycolysis, and glucose-derived serine metabolism drives auto-regulation ofPYK1 expression. Credit: Tamaki Suganuma, Ph.D., Workman Lab

Researchers in the Workman Lab at the Stowers Institute for Medical Research have identified a link between cellular metabolism and gene expression, one with potentially far-reaching implications for cancer risk prediction and treatment.

Although they studied the key protein complex—called Serine-responsive SAM-containing Metabolic Enzyme complex (SESAME)—in yeast, scientists believe a human analogue exists. SAM stands for S-adenosylmethionine, a compound that plays an essential role in histone methylation.

The study was published on Oct. 29 in the online edition of the journal *Molecular Cell*.

"The purpose of our study was to understand more about the pyruvate kinase PKM2, which plays very important roles in tumorigenesis," says lead author and Stowers postdoctoral research associate Shanshan Li, Ph.D. "However, the complexity of mammalian systems makes it difficult to get a clear clue."

"Instead, using yeast as a simple model, we were able to find that the PKM2 homologue in yeast, Pyk1, forms a novel complex with other metabolic enzymes. We called this complex SESAME."

Cancer cells differ from normal cells in that they depend on elevated aerobic glycolysis for rapid growth. One key enzyme for glycolysis is

pyruvate kinase M2 (PKM2). PKM2 catalyzes the chemical reaction that converts phosphoenolpyruvate (PEP), a high-energy phosphate-containing compound, to pyruvate, the final product of glycolysis. It also provides a great deal of energy in the process. PKM2 has an alternative splice variant, PKM1 that, when swapped in, can reverse the aerobic glycolysis that cancer cells rely on and lower the rate of tumorigenesis. Not surprisingly, this fact has made PKM2 an attractive target for anticancer therapy.

But PKM2 doesn't just regulate glycolysis. It also phosphorylates histone H3 threonine 11 (H3T11), a protein that alters chromosomes and affects gene regulation. This raises the question: Is cellular metabolism linked to gene regulation and, if so, what is the connection?

The answer involves a glycolysis-generated amino acid called serine, a yeast homologue of PKM2 called Pyk1 and, of course, SESAME.

According to Li, previous research has revealed that serine metabolic enzymes are "important in cancer cell survival and proliferation, but the underlying mechanism is unknown." Prior work has also uncovered the role serine plays in activating PKM2—and, therefore, in the conversion of PEP to pyruvate during glycolysis, the first phase of cellular respiration.

"It has been suggested that chromatin regulation and gene expression might link to cellular metabolism," says Tamaki Suganuma, Ph.D., a Stowers research scientist who directed the study. "However, the concrete connections have not previously been clarified."

"SESAME is the first example of a protein complex that directly regulates cellular metabolism and chromatin modification by utilizing its own enzyme subunits."

Researchers have found that SESAME links the ability to sense serine (and therefore glycolysis) to the regulation of genetic material (chromosomes) and therefore suggests a potential target for detecting and treating cancers.

Although the study focused on yeast, the same relationship should hold true for humans.

According to Li, "Since most components of SESAME are conserved from yeast to mammals, we think that PKM2 could also form a complex like SESAME, and may shed light on why cancer cells require PKM2 and serine metabolism." Suganuma adds that the processes of glycolysis, and the pathway of glucose-derived serine metabolism, are already used as human cancer therapy targets.

Before such therapies come online, however, researchers must first answer a number of related questions. Do these PKM2-regulating molecules contain mutations in cancer patients? If, as an emerging theory suggests, cancer is a cellular metabolic disease, then does a glycolysis disorder imply tumor formation, and would monitoring histone H3T11 on the PKM2 gene predict the metabolic disorder and tumorigenesis?

If such monitoring proved reliable, says Suganuma, then SESAME enzymes could provide new targets for cancer therapy by promoting the PKM2 feedback loop.

The next step, then, is to identify human SESAME.

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