Essential amino acid in humans, methionine, controls cell growth programs

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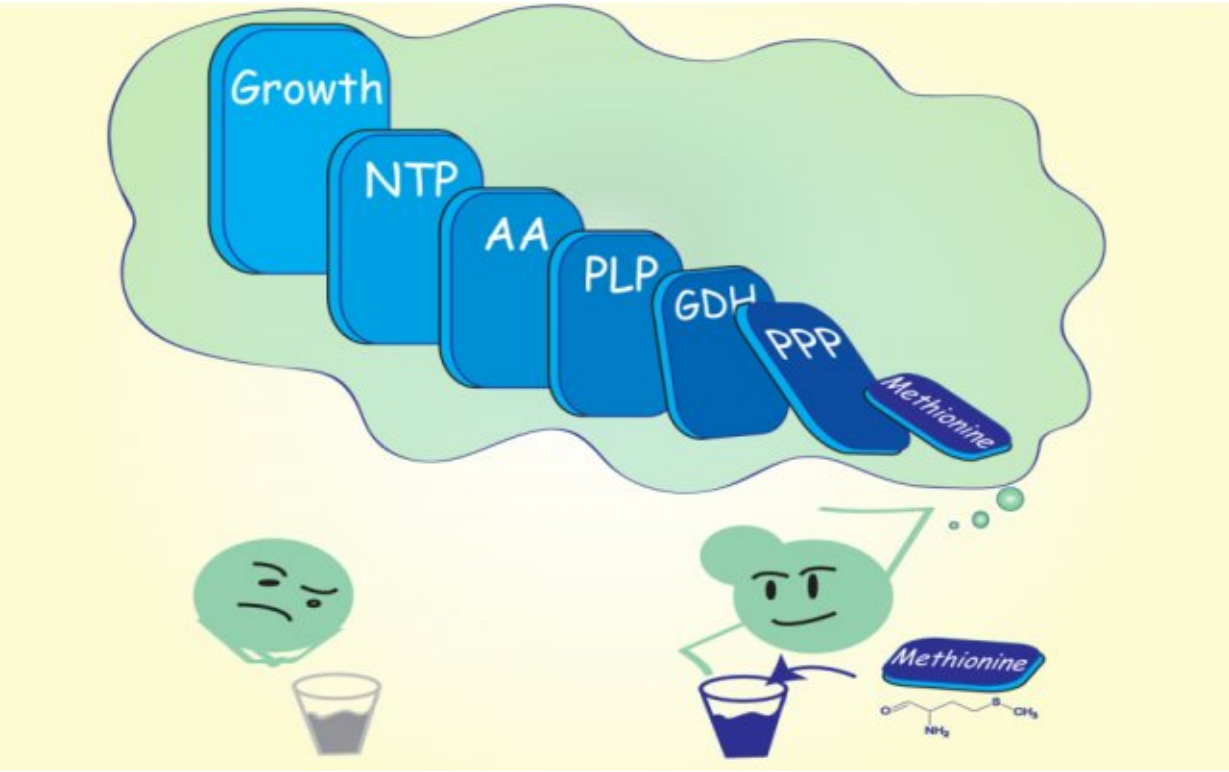

A recent study from the Laxman lab elucidates how a small metabolite and amino acid, methionine, acts as a growth signal for cells, by setting into motion a metabolic program for cell proliferation. Credit: Adhish Walvekar and Sunil Laxman, Institute for Stem Cell Science and Regenerative Medicine (inStem), Bangalore, India

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and amino acid, methionine, acts as a growth signal for cells by setting into motion a metabolic program for cell proliferation.

For cells to grow and then divide, they must be in an anabolic state, where there is sufficient production of all necessary building blocks. It was earlier thought that as long as enough nutrients are present, cells would continue to grow under the control of internal signaling programs. However, recent studies show that many small intermediates and products of biological metabolism commonly termed as metabolites can themselves act as signaling molecules and control cell growth programs.

Several studies, particularly from cancer researchers, have hinted that methionine might be a signaling metabolite. Many cancers appear to be dependent on methionine for growth. However, how methionine controls growth is still a mystery. The researchers used a very simple model system (budding yeast cells), to address how methionine might regulate growth. To understand the logic of such a growth program, they analysed gene expression profiles and measured the new synthesis of necessary building blocks. By piecing together this network, they constructed the organization of a core anabolic program triggered by methionine. This anabolic program relies on a few specific nodes in metabolism and is sufficient to orchestrate an entire cascade of transcriptional and metabolic events that can sustain growth.

When methionine is limited, cells do not grow. On the other hand, when methionine is abundant, it acts as a growth signal and triggers a cascade of biochemical events, ultimately leading to cell growth. Analogous to the butterfly effect, methionine leads to a series of larger metabolic events, controlling an entire cellular program. Methionine activates three key nodes in metabolism: the pentose phosphate pathway, the production of glutamine, and the formation of pyridoxal phosphate (the PPP-GDH-PLP node). These nodes produce a set of critical substrates and co-factors that fuel the production of all other amino acids, as well as make

nucleotides, which are critical for growth. In the cartoon, the dominoes of increasing size show this chain of events and capture how methionine eventually has a significant impact on cell growth.

The study advances the understanding of how some metabolites act as signalling molecules and play a critical role in controlling cell growth. It also provides a long-sought explanation of the role of methionine in sustaining cell growth, and could clarify why cancer cells are "addicted" to methionine for their growth. However, a long-term methionine study could provide strategies to control the growth of many types of cancer.

More information: Adhish S. Walvekar et al, Methionine coordinates a hierarchically organized anabolic program enabling proliferation, *Molecular Biology of the Cell* (2018). DOI: 10.1091/mbc.E18-08-0515

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