Cells control energy metabolism via hedgehog signalling pathway

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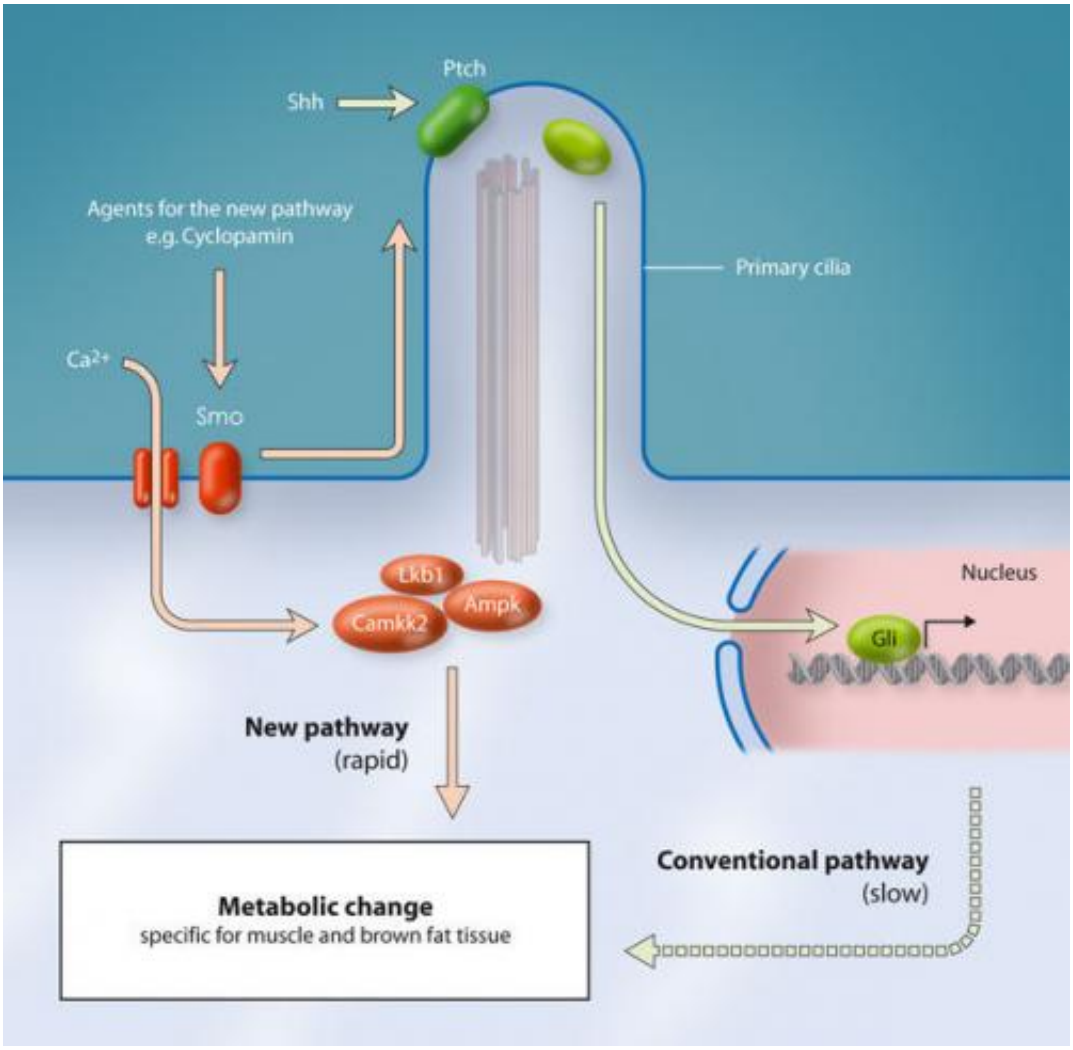

The binding of Sonig Hedgehog (Shh) to its receptor Patched (Ptch) causes the activation of Smo. Credit: Art For Science

Cancer, diabetes, and excess body weight have one thing in common: they alter cellular metabolism. Scientists from the Max Planck Institute of Immunobiology and Epigenetics in Freiburg and the Medical University of Vienna together with an international research team have jointly resolved a new molecular circuit controlling cellular metabolism. The previously unknown signalling pathway, acting downstream of the hedgehog protein enables muscle cells and brown fat cells to absorb sugars without relying on insulin. Substances that selectively activate the signalling pathway could thus be utilized in the treatment of diabetes and obesity. With their results, the researchers are also able to explain why various new anti-cancer agents have induced mysterious pronounced side effects in the clinics.

Hedgehog was initially identified as an important protein for embryonic development across various organisms. Without hedgehog, the physiological partitions of the embryo become indistinct. However, hedgehog also influences replication, migration and specialisation of cells – that is, the processes that also play a role in carcinogenesis. Mutation of genes also occurs concomitantly in various types of cancer, such as pancreatic, gastric or intestinal carcinomas. Above and beyond this, hedgehog inhibits the formation of "bad" white adipose tissue. Brown or "good" fat that serves to control body temperature, however, remains unaffected.

Hedgehog is therefore a very promising target for medications that fight cancer, diabetes and excess body weight. The US Food and Drug Administration (FDA) approved the first hedgehog inhibitor, Vismodegib, for treatment of cancer this year. There are presently at least six further agents being tested in clinical studies. Surprisingly, the first patient cohorts receiving Vismodegib have shown serious side effects, such as weight loss and muscle cramps, to the extent that more than half of the participants in the studies had to discontinue use.

The new research results appear to explain the mysterious cramps and suggest an easy, safe and already available adjunct therapy to resolve the complication. The researchers discovered a new hedgehog signalling pathway that is independent of the activation of transcription factors and genes known thus far. Cells control their primary energy metabolism, including the glucose, fatty acid and amino acid metabolisms, via this pathway.

The membrane protein known as Smo plays an important role here. Smo controls the known signalling pathway through transcription factors, as well as the new pathway via a much faster AMP-kinase enzyme and calcium dependent pathway. Smo is activated if hedgehog binds to a specialised receptor in the cell membrane. In the signalling pathway that has now been discovered, calcium flows through the membrane channels into the cell and activates calcium-dependent enzymes that in turn activate the AMP-kinase. This completely rewires metabolism. The cell can rapidly absorb large quantities of glucose using the AMP-kinase and other enzymes, rebalancing anabolism and catabolism. Further, rather promoting efficient energy metabolism through mitochondria, the new hedgehog signalling pathway prompts much less efficient via lactic acid fermentation – a process with which cancer cells use to acquire their energy without oxygen, for example (Warburg effect).

Even more surprising, the new pathway is stimulated promiscuously by both classical activators and inhibitors of the old, "canonical" hedgehog pathway. This finding potentially flips the interpretation of tens, if not hundreds of research papers in the field. Still not clear, this could be one additional reason why hedgehog inhibitors are so effective, in essence they starve the cancer cells from the inside.

Counterintuitive inhibitor-based activation of the hedgehog and Smo-calcium/AMP-kinase signalling pathways interferes with anabolic metabolism. "Activation of the AMP-kinase and increased catabolism

could explain the exaggerated weight loss of the participants in the clinical studies. More importantly though, the influx of calcium into muscle cells leads to instant contraction, and must be triggering the cramps," explains Andrew Pospisilik from the Max Planck Institute in Freiburg. Importantly, Hedgehog inhibitors do not have to lead to these side effects. "We targeted the Smo protein with various substances and found out that there are inhibitors that do not evoke an increase in calcium or glucose values, and critically, these same inhibitors fail to cause muscle cells to contract in culture. The development of medications such as these, which have minimal side effects, is therefore entirely possible," says Pospisilik.

In addition, again using fat cells, the scientists find that cells dramatically increase the glucose quantity they can absorb – without relying on insulin. Glucose-tolerance tests on mice confirmed the findings. This was accomplished by administering a specific amount of glucose via the food and measuring the blood glucose concentration afterwards. Mice that had previously been treated with the classic hedgehog inhibitor cyclopamine had correspondingly lower blood glucose than untreated animals. Apparently, cyclopamine increases the glucose absorption, but only in the brown adipose tissue and various types of muscle tissue. Thus, researchers measured an increase in body temperature of around one degree – a sign of higher activity in brown adipose tissue.

"Agents that only activate the Smo-calcium/AMP-kinase hedgehog signalling pathway are therefore candidates as medications for treating excess body weight, as well as type-1 and type-2 diabetes. Similar to the broad hedgehog inhibitors, they possess the potential to induce muscle cramps. Thanks to our findings, we now know that a new agent must first be tested on muscle cells before it is used on humans," says Harald Esterbauer from the Medical University of Vienna.

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Sean L. McGee, Andrea Loipetzberger, Timothy Connor, Carsten Jaeger, Bernd Kammerer, Lilli Winter, Gerhard Wiche, Kevin Dalgaard, Madhan Selvaraj, Jeremy Reiter, Michael Gaster, Robert S. Lee-Young, Mark A. Febbraio, Claude Knauf, Patrice D. Cani, Fritz Aberger, Josef M. Penninger, J. Andrew Pospisilik, and Harald Esterbauer, Hedgehog partial agonism drives Warburg-like metabolism in muscle and brown fat, *Cell*, 12 October 2012

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