# Regulation of the Hippo-YAP pathway by glucose sensor O-GlcNAcylation

With the support by the National Natural Science Foundation of China, a collaborative study by the research groups led by Prof. Pei HuaDong (裴华东) and Prof. Qin WeiJie from the State Key Laboratory of Proteomics, Beijing Proteome Research Center, National Center for Protein Sciences (Beijing), Beijing Institute of Lifeomics reported that glucose sensor O-GlcNAcylation regulates the Hippo-YAP pathway and tumorigenesis, which was published in *Molecular Cell* (2017, 68(3): 591—604).

The Hippo pathway is crucial in organ size control and tissue homeostasis, with deregulation leading to cancer. Cell growth is an energy-consuming process and must be coordinated with cellular energy status. An extracellular nutrition signal, such as glucose, regulates the Hippo pathway activation. Glucose stress can regulate the Hippo pathway by activating AMPK, but in AMPK-deficient cells, YAP activity still can be regulated by 2-DG. These results indicate that there are AMPK-independent mechanisms in the regulation of the Hippo pathway in response to nutrition stress. However, the mechanisms are still not clear.

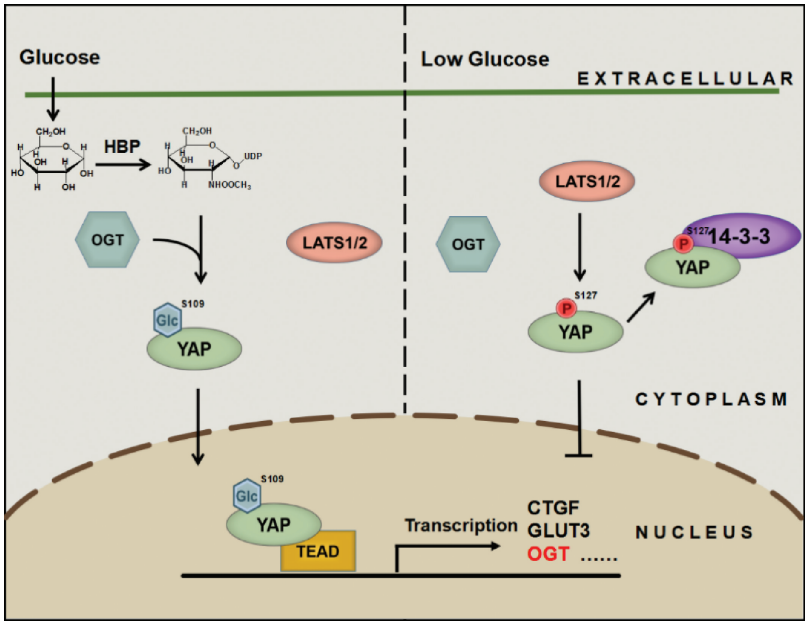


**Figure** Regulatory model of OGT-mediated O-GlcNAcylation in activation of Hippo Pathway.

They found that the Hippo pathway is directly regulated by the hexosamine biosynthesis pathway (HBP) in response to metabolic nutrients. Mechanistically, the core component of Hippo pathway (YAP) is O-GlcNAcylated by O-GlcNAc transferase (OGT) at serine 109. The O-GlcNAcylation at YAPserine 109 and its "cross-talk" with phosphorylation at serine 109 and 127 was confirmed by high-resolution mass spectrometry with EThcD fragmentation. YAP O-GlcNAcylation disrupts its interaction with upstream kinase LATS1, prevents its phosphorylation, and activates its transcriptional activity. And this activation is not dependent on AMPK. They also identified OGT as a YAP-regulated gene that forms a feedback loop. Finally, they confirmed that glucose-induced YAP O-GlcNAcylation and activation promoted tumorigenesis.

Together, these findings establish a molecular mechanism and functional significance of the HBP in directly linking extracellular glucose signal to the Hippo-YAP pathway and tumorigenesis. However, more studies are needed to completely understand YAP O-GlcNAcylation physiological functions *in vivo*.