A new role of uridine diphosphate glucose in dampening tumor metastasis

With the support by the National Natural Science Foundation of China and the Chinese Academy of Sciences (CAS), the research team led by Prof. Yang WeiWei (杨巍维) at the Institute of Biochemistry and Cell Biology, CAS, and Prof. Li GuoHui (李国辉) from the Dalian Institute of Chemical Physics, CAS, revealed a new role of uridine diphosphate glucose (UDP-Glc) in dampening lung cancer metastasis, which was published in *Nature* (2019, 571: 127—131).

Metastasis is defined as the spread of cancer cells from original malignant primary tumor to surrounding tissues and to distant organs. Cancer metastasis is the primary cause of morbidity and mortality, and accounts for up to 95% of cancer deaths. Although surgery and radiation therapy effectively control many primary tumors, the development of metastatic tumors is often companied by a poor prognosis. Chemotherapy, hormonal therapy and radiation serve palliative purposes in the metastatic setting, and some offer a modest but statistically significant extension of survival. It is hoped that a better mechanistic understanding of metastasis will develop new therapies and improve patient outcomes.

Cancer metabolism is one of the core hallmarks of cancer. The characteristic and profound metabolic alteration mainly driven by oncogenic signaling pathways allows cancer cells to accommodate metabolic demands to sustain growth, proliferation, and survival in a nutrient fluctuating environment. Increased uptake of glucose, enhanced rates of glutaminolysis and fatty acids synthesis have been extensively linked to the rapid tumor growth and therapeutic resistance in cancer because of increased energy production and supplies of metabolic intermediates for macromolecules synthesis. However, how altered metabolism contributes to tumor metastasis remains largely unknown.

In this study, they observed that epidermal growth factor receptor activation induces the phosphorylation of UDP-glucose dehydrogenase (UGDH) at tyrosine (Y) 473. UGDH catalyzes the production of UDP-glucuronate (UDP-GlcUA) from UDP-Glc and participates in the biosynthesis of glycosaminoglycan. Phosphorylated UGDH interacts with HuR and converts local UDP-Glc to UDP-GlcUA, thereby attenuating the inhibition of UDP-Glc on the assembly of HuR/*SNAI1* mRNA complex, which consequently stabilizes *SNAI1* mRNA. Increased expression of Snail (encoded by *SNAI1*) in turn initiates the epithelial-mesenchymal transition to promote tumor cell migration and lung cancer metastasis.

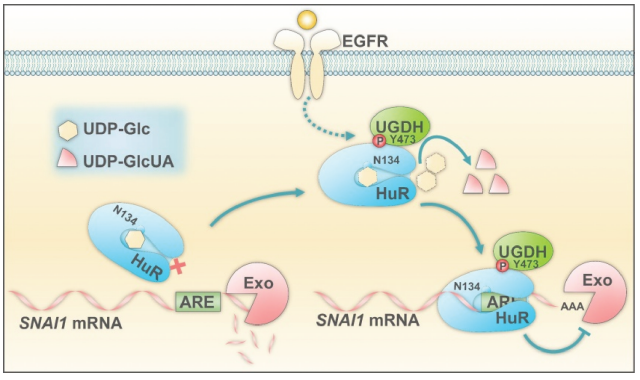

Figure UGDH abrogates UDP-Glc-mediated inhibition of *SNAI1* mRNA stability and promotes tumor metastasis.

Importantly, they found that lower UDP-Glc levels are closely related to the metastasis and recurrence of lung cancer. They observed that UDP-Glc levels in metastatic tumors are much lower than in primary tumors. Moreover, lung cancer patients with distant metastasis had much lower UDP-Glc levels in blood than the patients without metastasis.

The new role of UDP-Glc and underlying mechanism revealed in the *Nature* paper would not only provide a new biomarker for the early detection of lung cancer metastasis, but also help to develop a new strategy to intervene in the metastasis.