Glycogen accumulation and phase separation drives liver tumor initiation

Liu, Q. et al. Cell 184, 5559–5576 (2021)

Presenter: Jin Yang Chong **Date/Time:** 2022/10/13, 15:10-16:00

Commentator: Dr. Chi-Wu Chiang **Location:** Room 601, Med College Building

Background:

Glucose is the main nutrient for the growth of cancer cells. In cancer cells, the glucose metabolism is rewired to aerobic glycolysis termed Warburg effect, in which the cancer cells increased glucose uptake and lactate production even in the presence of oxygen and well-functioning mitochondria, resulting in the change of the local immune microenvironment. Among the glucose metabolite, glycogen is the principal storage form of glucose. Mutations in several glycogenolysis enzymes result in various glycogen storage diseases (GSDs) and development of liver cancer. Several studies have shown that glycogen accumulation helps tumor cells to survive under stress condition. However, the role of glycogen metabolism in tumorigenesis remains unknown. Recently, scientists found that biological events in cells are spatiotemporally regulated via the dynamic formation of membraneless biomolecular condensates, called liquid-liquid phase separation (LLPS). Glycogen is a large, branched polymer of glucose which shown to regulate cell cytosolic viscosity. Whether glycogen accumulation is a liquid-liquid phase separation phenomenon and its role in regulating the tumor initiation remain unclear.

Objective/Hypothesis: The authors aim to investigate the role and mechanistic insights of glycogen metabolism in liver tumor initiation.

Results: Through observation of liver cancer induced mice tissues and human liver tumor sections, the authors found that glycogen accumulation is commonly presented in the early stage of liver tumors. By doing RNA sequencing assay with the liver tissues from diethylnitrosamine (DEN)-treated mice, they found that downregulation of glucose-6-phosphatase (G6PC), an enzyme involved in the final step of glycogenolysis, is responsible for the elevated glycogen storage during tumor initiation. Moreover, they discovered the G6PC deficiency-mediated glycogen accumulation blocks Hippo signaling activities, thus activates Yap, which promotes liver enlargement and cancer development. Interestingly, they revealed that the inhibition of Hippo signaling activities were caused by the formation of glycogen-Mst1/2 aggregate foci in cells, and they demonstrated that the glycogen could undergo liquid-liquid phase separation *in vitro* and *in vivo*. Furthermore, they discovered that the LLPS of glycogen causes the assembly of the Laforin-Mst1/2 complex in glycogen condensates and consequently activates Yap for cell survival and transformation by disrupting the Mst1/2-WW45 complex. Lastly, using G6PC and WW45 knockout mice and chemical treatment intervention strategies, they showed that WW45 and repressing glycogen storage signals abrogate liver enlargement and tumorigenesis via regulating Hippo/Mst1/2 signaling. Overall, these findings shed a light on the mechanistic and functional insights of glycogen accumulation in the initiation of liver cancer. Essentially, accumulated glycogen could be the biomarker of early prognosis of liver cancer patients and elimination of glycogen may be a potential therapeutic strategy in the early liver cancer stages.

Conclusion: The authors concluded that tumor-initiating cells possess different glycogen storing mode, which inhibit Hippo signaling through glycogen phase separation to promote tumor incidence.

References:

1. Liu, Q., et al., *Glycogen accumulation and phase separation drives liver tumor initiation.* Cell, 2021. **184**(22): p. 5559-5576 e19.