**O-GlcNAcylation of PGK1 coordinates glycolysis and TCA cycle**

**to promote tumor growth**

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**Presenter:** Rou-An Hsu **Date/Time:** 2020/03/19 16:10-17:00

**Commentator:** Chuan-Fa Chang, Ph.D. **Location:** Room 601, Med College Building

**Background:**

Warburg effect, the phenomenon which many cancer cells display enhanced glycolysis and suppressed mitochondrial metabolism, is critical for tumor development. O-linked N-acetylglucosamine (O-GlcNAc) is a post-translational modification (PTM) on proteins. O-GlcNAc transferase (OGT) can catalyze the transfer of GlcNAc moiety to the hydroxyl group sidechain of serine or threonine. O-GlcNAc hydrolase (OGA) can remove GlcNAc from serine or threonine. Phosphoglycerate kinase 1 (PGK1), the first ATP-generating enzyme in glycolysis, catalyzes the conversion of 1,3-diphosphoglycerate (1,3-BPG) to 3- phosphoglycerate (3-PG) and produces one molecule of ATP. The previous study indicated that PGK1 can function as a protein kinase in coordinating glycolysis and the tricarboxylic acid (TCA) cycle, which helps cancer metabolism and tumorigenesis. PGK1 expression is also upregulated in liver cancer.

**Objective/Hypothesis:**

In this paper, authors attempted to investigate how cancer cells coordinate glucose metabolism through glycolysis and the mitochondrial tricarboxylic acid (TCA) cycle.

**Results:**

First, the authors investigated the possible role of PGK1 in colon cancer development and progression. Based on PGK1 expression on colon cancer patients and cell lines, the authors made a hypothesis that PGK1 may contribute to the development but not the progression of colon cancers. Second, they tried to investigate whether the function of PGK1 was regulated by O-GlcNAcylation by chemoenzymatic labeling technology. The results indicated that PGK1 was OGlcNAcylated in cells. In addition, the authors tried to identify the site of O-GlcNAcylation on PGK1. They used various site-directed mutants to probe the major site of glycosylation on PGK1 by mass spectrometry analysis. Mutation of T255 on PGK1 significantly reduced the OGlcNAcylation signal suggesting that T255 is the major O-GlcNAcylation site. Finally, O-GlcNAcylation at threonine 255 (T255) activated PGK1 activity to enhance colon cancer cell proliferation and lactate production, as well as induced PGK1 translocation into mitochondria. PGK1 inhibited pyruvate dehydrogenase (PDH) complex to suppress oxidative phosphorylation in mitochondria. Blocking T255 O-GlcNAcylation on PGK1 suppresses the Warburg effect, decreases colon cancer cell proliferation, suppresses glycolysis, enhances the TCA cycle, and inhibits tumor growth in xenograft models of nude mice.

**Conclusion:**

Taken together, this paper showed that O-GlcNAcylation coordinates glycolysis and the TCA cycle to promote tumorigenesis.

**References**:

1. Hu, H. et al. Acetylation of PGK1 promotes liver cancer cell proliferation and tumorigenesis. Hepatology 65, 515–528 (2017).
2. Li, X. et al. Mitochondria-translocated PGK1 functions as a protein kinase to coordinate glycolysis and the TCA Cycle in tumorigenesis. Mol. Cell 61, 705–719 (2016).