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**Topic Category:** 4081-ASIP Lung - cancer**First Author:** Yi-Chieh Yang

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**First Author is a:** Graduate Student**First Author is a member of:** American Society for Investigative Pathology**First Author Degree:** PhD, DSc, or equivalent**Presentation Preference:** Oral**Sponsor:** Michael Hsiao**Sponsor Phone:** 886227871243

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**Sponsor's Society:** Pathology - American Society for Investigative Pathology (ASIP) - Host Society**Keywords:** 1. pyruvate kinase M2 2. cancer stem cell

## Glucose limited enhance the cancer stem cell population through PKM2/AMPK-dependent signaling

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### Background

Solid tumor cells encounter stress from oxygen and glucose limitation as tumors continue to grow. This kind of metabolic stress in the solid tumor interiors affects cancer stem cell (CSC) formation. However, the mechanisms of how cancer stem cells are affected by glucose, a key nutrient in the microenvironment, exist many controversial reports and it still remain largely elusive.

### Design

The enhancement of cancer stem cell population were detecting by the ability of sphere formation, percentage of CD133<sup>+</sup> positive cells, and expression of cancer stem cell markers under glucose limitation condition. We investigated the detailed mechanism of nuclear translocation of PKM2 and AMP2 under glucose limited condition by Western blot and immunoprecipitation. We also assessed the effects of nuclear PKM2 in vitro and in vivo.

### Results and Conclusion

In response to glucose limited, we found that nuclear translocation of the glycolic key enzyme, pyruvate kinase M2 (PKM2), helps cancer cells survive under metabolic stress. We demonstrate here that limited of glucose concentration stimulates AMPK activation, resulting in co-translocation of AMPK and PKM2 through Ran-mediated nuclear transport. Translocated PKM2 subsequently binds with OCT4 to promote expression of cancer stemness-related genes. In this way, nuclear PKM2 is able to enrich a cancer stem cell population under metabolic stress. Nuclear PKM2 is also shown to promote cancer metastasis in an orthotopic xenograft model. In conclusion, our work not only reveals the critical role of nuclear PKM2 in CSC formation, but also identifies a detailed mechanism of PKM2 nuclear translocation, which cooperates with the cytosolic nutrient sensor AMPK, under a glucose limited environment. These details suggest the possibility of finding new targets for therapeutic intervention.

### Support or Funding Information

Ministry of Science and Technology (ROC): MOST 105-2320-B-038-058-MY3, MOST 106-0210-01-15-02