PKM2 exon-10 mutations drive reduced allostery and increased oncogenicity

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Abstract

Pyruvate kinase M2 (PKM2) that carries the exon-10 region is an alternatively spliced isoform from *PKM*. PKM2, a rate-limiting step in glycolysis, controls the downstream carbon flux. Accumulated evidence has shown that cancer cells often manipulate PKM2's activity via allosteric regulation and posttranslational modification for rapid proliferation. We have previously reported that KDM8, an oncogenic histone demethylase, physically interacts with PKM2 to promote its nuclear translocation, and they work together to facilitate Warburg metabolism. Notably, both PKM2 and KDM8 are highly expressed in breast cancer cells. In this study, we investigated specific PKM2 exon-10 variants and their effects on cancer progression. The cancer-derived (H391Y and G415R) and oncogenic (R399E) PKM2 mutants exhibited reduced allostery in response to fructose-1,6-bisphosphate (FBP) and phenylalanine using kinetic coupling effect evaluation. Crystal structures of H391Y and R399E mutants demonstrate that the intermolecular interactions are disrupted. Moreover, co-immunoprecipitation assay revealed that KDM8 had a higher level of binding affinity with per exon-10 mutant than with WT. We further showed that the PKM2 mutants had a higher degree of nuclear translocation and transactivation activities using confocal microscopic visualization as well as hypoxia response element (HRE)-luciferase-based promoter assay. This effect was even more pronounced in the presence of KDM8. Lastly, each of the PKM2 mutants exhibited a higher degree of cell proliferation and migration than did the wild type PKM2. These results together suggest structure-allostery alterations, increased nuclear translocation and oncogenesis driven by PKM2 exon-10 mutations. Targeting the nuclear PKM2 and KDM8 may provide a new therapeutic intervention.

Keywords – pyruvate kinase, Warburg effect, allosteric regulation.