# Revisiting the Warburg Effect: Linking Hydrogen Sulfide to Central Metabolic Regulation

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Most cancer cells reprogram their glucose metabolism from oxidative phosphorylation in mitochondria to aerobic glycolysis, a phenomenon known as the Warburg effect. This metabolic shift facilitates rapid proliferation by increasing glycolytic intermediates for macromolecule synthesis while reducing reliance on mitochondrial respiration. A key regulator in this process is pyruvate kinase M2 (PKM2), whose reduced enzymatic activity enables cancer cells to divert glycolytic metabolites toward biosynthetic pathways. In our current study, we reveal that hydrogen sulfide ($H_2S$) destabilizes the PKM2 tetramer into its monomeric and dimeric forms through sulfhydration, particularly at cysteine 326 (C326). This post-translational modification decreases PKM2 enzyme activity while enhancing its transcriptional regulatory functions that support glycolytic reprogramming. Notably, blocking sulfhydration at C326 via a PKM2-C326S mutation stabilizes the tetrameric form of PKM2, as confirmed by crystal structure analysis. Importantly, expression of PKM2-C326S in cancer cells redirects glucose metabolism from glycolysis back to mitochondrial oxidative phosphorylation, restoring mitochondrial respiratory activity and significantly suppressing tumor growth. Our findings suggest that $H_2S$-mediated sulfhydration of PKM2 promotes tumorigenesis by sustaining glycolytic metabolism and repressing mitochondrial function, and that targeting this modification may offer a novel therapeutic strategy to reprogram cancer metabolism.