Glutathione Sensing by PKM2 Allosteric Control Couples Glyco-Redox Signaling to Ferroptosis Vulnerability

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Metabolic adaptation at the malignant and invasive tumor front requires tight coordination between glycolysis and redox homeostasis. Here, we identify reduced glutathione (GSH) as an endogenous allosteric activator that binds the A-A interface of tetrameric PKM2, stabilizing its active conformation and enhancing catalytic flux. Structural and mutational analyses define this pocket as a redox-responsive regulatory node linking glycolytic output to glutathione availability. Integrated transcriptomic profiling of head and neck cancers reveals coordinated upregulation of PKM2, SLC7A11/xCT, glycolysis, and ferroptosis-resistance programs, particularly enriched at invasive regions. Therapeutically, enforced PKM2 activation combined with xCT suppression disrupts the glyco-redox balance, elevates oxidative stress and lipid peroxidation, and drives ferroptotic cell death in PKM2-dependent cancer models, resulting in tumor growth inhibition in vivo. These findings establish a PKM2-centered glyco-redox-ferroptosis axis and support a biomarker-guided strategy to target metabolic vulnerabilities in aggressive tumors.