Structural Basis for Tumor Pyruvate Kinase M2 Allosteric Regulation and Catalysis

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Pyruvate Kinase plays catalyzes the last step of the glycolytic cycle, turning over the substrate phosphoenolpyruvate, PEP, into pyruvate, producing one molecule of ATP per reaction. Four isozymes of this enzyme exist in humans: R, L, M_1, and M_2. The R and L isoforms are present in the erythrocytes and liver cells, respectively. Both M_1 and M_2 are encoded by the M gene. The M_1 isoform is found in skeletal muscle and brain tissue. The M_2 isoform is predominately present in fetal tissue and is progressively replaced by the other isoforms after birth. However, the M_2 isoform is again reexpressed in numerous tumor cells.

The overexpression of the M_2 isoform in tumor cells invokes many mechanistic questions regarding the role of $hPKM_2$ in tumorgenesis, as well as offers an intriguing anti-cancer target. Therefore, our structure may be useful as a template for the discovery of novel compounds that may serve as possible anti-cancer drug leads. We cloned, overexpressed, and purified $hPKM_2$ from inclusion bodies in *E.coli* through a unique refolding protocol. The enzyme was crystallized and x-ray data were collected at the APS (Argonne National Labs). The human PKM_2 crystal structure was determined to 2.8 Å resolution. Structural analysis and comparison of structural differences among isozymes is presented here.

Keywords: pyruvate kinase, allosteric, conformational change