

## Investigating the structural and functional implications of PKM2 mutations in cancer

The PKM2 protein is a key player in cancer metabolism acting as a central node in tumor growth and progression. We aimed to study the effect of cancer patient-derived mutations in the PKM2 protein on its structural and functional properties. We deciphered the effect of the mutations on the overall structure of the protein using X-ray crystallography, which revealed subtle structural perturbations in the three dimensional structure of the protein. The structural alterations may play a role in the changes that we observe in the functional characteristics of the protein. The mutations modulate important substrate and ligand binding affinities of the PKM2 protein, particularly affecting its ability to bind to FBP and ADP. The mutations also impair the tetrameric oligomeric state of the protein, favoring a dimeric conformation, which is known to be beneficial for tumor survival. Moreover, the pyruvate kinase activity of the PKM2 enzyme was also hampered which could be a direct functional consequence of the biophysical and biochemical changes induced by the mutations. The C474S and R516C mutants were unresponsive to the FBP mediated change in the oligomeric state of PKM2, while L144P and P403A mutant proteins exhibited FBP mediated allosteric activation, as C474S and R516C mutations directly or indirectly impact the FBP binding site. Furthermore, we also explored the effect of an alkaline pH of cancer cells on the mutant proteins which decreased the kinetic efficiency of the enzymes, possibly by altering the chemistry of catalysis. In addition to this, we found that the PKM2 protein may also play a role in the beneficial effects of hyperthermic oncotherapy via functional disruption of the pyruvate kinase activity of PKM2 enzyme. Overall, our results suggest that cancer-related mutations in the PKM2 protein affect its function and structure, which may support its oncoprotein activity. This could lead to more aggressive forms of cancer in patients compared to those with the wild-type PKM2 enzyme.

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