Upsurge of the Glycolytic Pathway in Cancer: A Dynamic Network Analysis of Oncogenic Mutations in Phosphofructokinase-1

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Phosphofructokinase-1 (PFK-1) is an allosteric enzyme in glycolysis that regulates the ATP-dependent phosphorylation of fructose 6-phosphate (F6P) into fructose 1,6-bisphosphate (FBP). In cancer, PFK-1 has shown to be upregulated in an uncontrolled glycolytic pathway to fuel nutrient metabolism for different tumors. To investigate how cancer can lead to unregulated glycolysis, we used molecular dynamics simulations and computational models to create network analyses based on the atomic motion correlation between the regulatory and catalytic sites on wild-type and oncogenic R210H-mutated PFK-1. It has been believed that oncogenic PFK-1 exhibits a complete breakdown of connections between receptor sites for ADP ligands and the F6P and FBP catalytic sites. However, our research shows the molecular dynamic network is rather enhanced to ensure efficient communication between the 2 domains. The number of atomic node residues present on the F6P domain of the mutated enzyme is significantly greater than that of the wild-type, potentially showing a higher ability for cancer-afflicted PFK-1 to phosphorylate F6P. The average shortest distance between the regulatory and catalytic domains of the mutant PFK-1 is significantly smaller than that of the wild-type, correlating to stronger internal communication with greater ADP sensitivity. The oncogenic PFK-1 exhibits a greater number of connections in its optimal path, resulting in efficient and more diversified communication pathways. The number of paths between the catalytic and ADP-regulatory domains is also significantly greater for oncogenic PFK-1, providing evidence that the number of possibilities for the catalytic and regulatory domains to establish connections is actually increased in cancer.