Probing Dynamics of 14-3-3: A Potential Remedy for Pancreatic Cancer

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Introduction: Pancreatic cancer is the third-most-common cause of cancer-related deaths in the U.S. Drug development for pancreatic cancer has greatly advanced over the past decade. However, chemoresistance exacerbates challenges in improving the efficacy of the current treatment regimens. 14-3-3 is a small, homo-dimeric, regulatory protein, mostly expressed in epithelial cells. It promotes cancer metastasis, confers resistance to anticancer drugs and radiation, and increases cell cycle arrest upon DNA damage. Overexpression of 14-3-3 is correlated with a poor survival rate among pancreatic cancer patients. 14-3-3, therefore, is a potential anticancer target for the treatment of pancreatic cancer. It belongs to the 14-3-3-protein family with other six isoforms involved in diverse cellular pathways. The discovery and development of 14-3-3-isoform-selective inhibitors are indispensable because of the pan-inhibitory nature of currently available inhibitors of 14-3-3 isoforms.

Methods: Molecular Dynamics Simulation and Biological Small-angle X-ray scattering were used to study protein dynamics of 14-3-3- isoforms.

Results: We found potential differences in conformational states between 14-3-3-isoforms when unbound by a ligand and similarities in bound states. Unbound 14-3-3 displayed unique, wide-open conformation i.e. significant flexibility, in comparison to other unbound isoforms. Principal Component Analysis captured a highly, flexible loop region between Helices 3 and 4 which could play an important role in regulating the open-close conformational change in 14-3-3-isoforms.

Conclusion: Our study revealed that the dynamics are not conserved among 14-3-3 isoforms and this promising finding could lead to the development and discovery of 14-3-3-isoform-selective inhibitors for pancreatic cancer.

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