Molecular Dynamics Simulations of the NF-kB Inducing Kinase in Disease Prevention: The Structure-Function Relationship of the NIK protein and Its Effect on Cancer

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Improper signaling of the nuclear factor-κB (NF-κB) pathway plays a critical role in many inflammatory disease states, including cancer, stroke, and viral infections. Although a majority of the signaling pathways are known, how these molecular mechanisms respond to changes in the intracellular microenvironment (i.e., pH, ionic strength, temperature) remains elusive. In this study, molecular dynamics simulations were employed to determine how changes to the intracellular ionic strength alter the structure-property relationships of the NF-κB Inducing Kinase (NIK), a protein kinase responsible for invoking the non-canonical NF-κB pathway. Two different states of NIK were tested; an active state containing an introduced phosphomimetic mutation on its 549th amino acid residue (S549D) and an inactive state resembling the wild-type (WT), native, NIK structure. The results from this study indicate that the introduced phopshomimetic mutation induced changes in the flexibility of the catalytic domains in NIK's structure. These structural fluctuations not only cause NIK to alter its phosphorylating behavior but also made NIK more sensitive intracellular to ionic changes. Further analyses of NIK's structure-activity and conformational-activity relationships suggest that changes in ionic concentrations also have a direct impact on its structure and behavior. The presence of ions, in this case sodium, served to increase NIK's structural flexibility and disrupted its ability to form a stable conformation. The results from this research reveal new insight into NIK's structure-behavioral functions that can be used to develop therapeutics and drug-delivery mechanisms to prevent cancers and diseases.

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