Impact of Intracellular Ionic Strength on Dimer Binding in the NF-kB Inducing Kinase

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Impact of Intracellular Ionic Strength on Dimer Binding in the NF-kB Inducing Kinase

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Abstract

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 the signaling pathways are known, how these molecular mechanisms respond to changes in the intracellular microenvironment such as pH, ionic strength, and temperature, remains elusive. Molecular dynamics simulations were employed to differentiate the structural dynamics of the NF-kB Inducing Kinase (NIK), a protein kinase responsible for invoking the non-canonical NF-κB pathway, in its native and mutant form, and in the absence and presence of salt concentration in efforts to probe whether changes in the ionic environment stabilize or destabilize the NIK dimer. Analyses of structure-activity and conformational-activity relationships indicate that the protein-protein interactions are sensitive to changes in the ionic strength. Ligand binding pockets as well as regions between the oligomer interface either compress or expand, affecting both local and distal intermolecular interactions that result in stabilization or destabilization in the protein assembly.

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Keywords