Molecular dynamics studies of the STAT3 homodimer:DNA complex: relationships between STAT3 mutations and protein-DNA recognition

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Signal Transducers and Activators of Transcription (STAT) proteins are a group of latent cytoplasmic transcription factors involved in cytokine signalling. STAT3 is a member of the STAT family and is expressed at elevated levels in a large number of diverse human cancers; and is now a validated target for anticancer drug design. Understanding the dynamics of the STAT3 dimer interface, accounting for both protein-DNA and protein-protein interactions, with respect to the dynamics of the latent, unphosphorylated STAT3 monomer, is important for designing potential small-molecule inhibitors of the activated dimer.

Molecular dynamics (MD) simulations have been used to study the activated STAT3 homodimer:DNA complex, the unphosphorylated STAT3 homodimer:DNA complex, and the latent unphosphorylated STAT3 monomer in an explicit water environment. Analysis of the data obtained from MD simulations over a 50 ns time-frame has suggested how the transcription factor interacts with DNA, the nature of the conformational changes, and ways in which function may be affected. Examination of the dimer interface, focusing on the protein-DNA interactions, including involvement of water molecules, has revealed the key residues contributing to the recognition events involved in STAT3 protein-DNA interactions. This has shown that the majority of mutations in the DNA-binding domain are found at the protein-DNA interface. These mutations have been mapped in detail and related to specific protein-DNA contacts. Their structural stability is described, together with an analysis of the model as a starting-point for the discovery of novel small-molecule STAT3 inhibitors.