Computer simulations of kinases - the challenge in resolving enzyme activation

Content

Protein kinases are enzymes that catalyse phosphorylation of Ser, Thr or Tyr residues of substrate proteins. The phosphorylation of a neutral group changes the local electrostatic field close to the phosphorylated residue, which can lead to large structural modifications of the target protein. The phosphorylated target protein can become activated and interact with other proteins in its cellular location. Kinases are thus involved in signalling cascades and are important for proper control of many biological processes. Tight control of the kinases themselves is thus of utmost importance. A typical protein kinase can adopt two states – active and inactive. It must not be constitutively active; when this happens, it might lead to pathologies such as cancer and autoimmune disease. While the end-states structures of many kinases are known, the pathway by which they transform from an inactive state to an active one is generally unresolved. Transient structures along this pathway can teach us on how these enzymes transform and might also serve as drug targets. Using computer simulations, we followed on several kinases of clinical relevance, examined their active and inactive states and managed to follow on the activation pathway of one enzyme, FLT3. In my talk, I will discuss protein kinase dynamics, activation pathway and the importance of discovering hidden structures.

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