

**Src kinase activation:
A switched electrostatic network**

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Src tyrosine kinases are essential in numerous cell signaling pathways, and improper functioning of these enzymes has been implicated in many diseases. The activity of Src kinases is regulated by conformational activation, which involves several structural changes within the catalytic domain (CD): the orientation of two lobes of CD, rearrangement of the activation loop (A-loop), and movement of an important α -helix (α C) into or away from the catalytic cleft. Conformational activation was investigated using biased molecular dynamics to explore the transition pathway between the active and the down-regulated conformation of CD for the Src-kinase family member Lynkinase, and to gain insight into the interdependence of these changes. Lobe opening is observed to be a facile motion, whereas movement of the A-loop motion is more complex requiring secondary structure changes as well as communication with C. A key result is that the conformational transition involves a switch in an electrostatic network of six polar residues between the active and down-regulated conformations. The exchange between interactions links the three main motions of the CD. Kinetic experiments that would demonstrate the contribution of the switched electrostatic network to the enzyme mechanism are proposed. Possible implications for regulation conferred by interdomain interactions are also discussed.

Abbreviations and symbols: CD, catalytic domain; SH2, Src homology domain 2; SH3, Src homology domain 3; CD_{act}, Lyn catalytic domain active conformation; CD_{down}, Lyn catalytic domain downregulated conformation; N-lobe, N-terminal lobe; C-lobe, C-terminal lobe; MD, molecular dynamics; BMD, biased molecular dynamics; MD, molecular dynamics; A-loop, activation loop; α C, α -helix C; RMSD, root mean squared deviation, α , pairwise force constant.