Effect of the SH3-SH2 Domain Linker Sequence on the Structure of Hck Kinase

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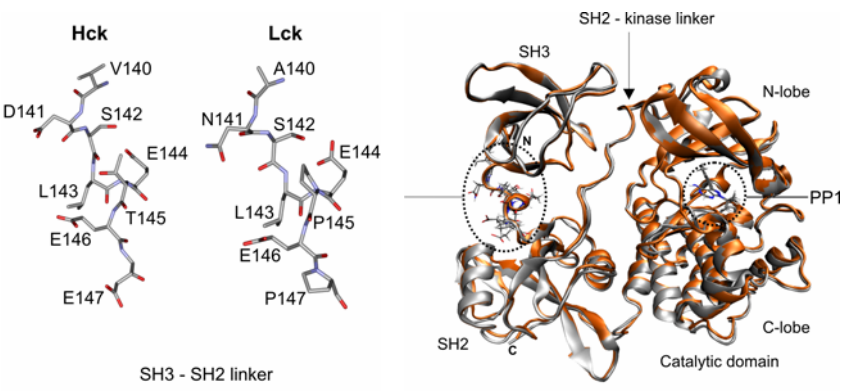
The coordination of activity in biological systems requires the existence of different signal transduction pathways that interact with one another and must be precisely regulated. The Src-family tyrosine kinases, which are found in many signaling pathways, differ in their physiological function despite their high overall structural similarity [1]. In this context, the differences in the SH3-SH2 domain linkers might play a role for differential regulation, but the structural consequences of linker sequence are yet poorly understood.

We have therefore performed comparative molecular dynamics simulations of wildtype Hck and of a mutant Hck, in which the SH3-SH2 domain linker is replaced by the sequence from the homologous kinase Lck. The simulations reveal that linker replacement does not only affect the orientation of the SH3 domain itself, but also leads to an alternative conformation of the activation segment in the Hck kinase domain. The sequence of the SH3-SH2 domain linker thus exerts a remote effect on the active site geometry and might therefore play a role in modulating the structure of the inactive kinase or for the fine-tuning of the activation process itself [2].



[1] MT Brown, JA Cooper, Regulation, substrates and functions of src. *Biochim Biophys Acta*, **1996,** 1287, 121-149.

[2] H. Meiselbach, H. Sticht, Effect of the SH3-SH2 domain linker sequence on the structure of Hck kinase, *J Mol Model*, **2010**, *Epub ahead of print*.