Homology modeling and docking studies of PRK1 kinase

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Epigenetics is defined as heritable changes in gene expression that are not based on changes in the DNA sequence. Posttranslational modification of histone proteins is a major mechanism of epigenetic regulation. Protein kinase C related kinase (PRK1) is a serine/threonine enzyme. It phosphorylates histone H3 at threonine 11 and is involved in the regulation of androgen receptor (AR) signaling. Recently it was shown that PRK1 is a promising therapeutic target for prostate cancer therapy because of its modulation of AR. [1]

A focused library screening using compound collections of generic kinase inhibitors was carried out to identify PRK1 inhibitors. Four highly potent inhibitors (staurosporine, Ro318220, K252a, and lestaurtinib) of PRK1 could be identified which bind to the enzyme in nanomolar range.

Since the crystal structure of the human PRK1 kinase is not known, a homology model was generated. A BLASTP search was performed for the human PRK1 amino acid sequence. The highest similarity was found for the related kinase PKCtheta. The model was generated using the program Modeller using the coordinates of the PKC-theta X-ray structure (PDB code 2jed) in the active conformation. The stability of the derived homology model and complex with the most active inhibitor staurosporine was examined by means of molecular dynamics (MD) simulations.

Based on the generated 3D model of the PRK1 kinase, the key interactions of known inhibitors with PRK1 were analyzed by means of molecular docking studies. A consensus score using five scoring functions (Chemscore, Goldscore, Glidescore, ParaDockS p-score and DOCK GBSA score) was calculated. The consensus scoring resulted in clear discrimination between the highly active inhibitors and the inactive compounds. Our findings have important implications both for the mechanistic understanding concerning PRK1 inhibitors, as well as for the further development of potent PRK1 inhibitors.

[1] E. Metzger, N. Yin, M. Wissmann, N. Kunowska, K. Fischer, N. Friedrichs, D. Patnaik, J. M. Higgins, N. Potier, K. H. Scheidtmann, R. Buettner, R. Schule, *Nat. Cell. Biol.* **2008**, *10*, 53-60.