A computational protocol to evaluate the effects of protein mutants in the kinase gatekeeper position on the binding of ATP substrate analogues

ID 3765841
Author(s) Romano, Valentina; de Beer, Tjaart A. P.; Schwede, Torsten
Author(s) at UniBasel Schwede, Torsten ; Romano, Valentina ; de Beer, Tjaart ;
Year 2017
Title A computational protocol to evaluate the effects of protein mutants in the kinase gatekeeper position on the binding of ATP substrate analogues
Journal BMC Research Notes
Volume 10
Number 1
Pages / **Article-Number** 104
The determination of specific kinase substrates in vivo is challenging due to the large number of protein kinases in cells, their substrate specificity overlap, and the lack of highly specific inhibitors. In the late 90s, Shokat and coworkers developed a protein engineering-based method addressing the question of identification of substrates of protein kinases. The approach was based on the mutagenesis of the gatekeeper residue within the binding site of a protein kinase to change the co-substrate specificity from ATP to ATP analogues. One of the challenges in applying this method to other kinase systems is to identify the optimal combination of mutation in the enzyme and chemical derivative such that the ATP analogue acts as substrate for the engineered, but not the native kinase enzyme. In this study, we developed a computational protocol for estimating the effect of mutations at the gatekeeper position on the accessibility of ATP analogues within the binding site of engineered kinases.; We tested the protocol on a dataset of tyrosine and serine/threonine protein kinases from the scientific literature where Shokat's method was applied and experimental data were available. Our protocol correctly identified gatekeeper residues as the positions to mutate within the binding site of the studied kinase enzymes. Furthermore, the approach well reproduced the experimental data available in literature.; We have presented a computational protocol that scores how different mutations at the gatekeeper position influence the accommodation of various ATP analogues within the binding site of protein kinases. We have assessed our approach on protein kinases from the scientific literature and have verified the ability of the approach to well reproduce the available experimental data and identify suitable combinations of engineered kinases and ATP analogues.
Publisher BioMed Central
ISSN/ISBN 1756-0500
edoc-URL http://edoc.unibas.ch/54595/
Full Text on edoc No;
Digital Object Identifier DOI 10.1186/s13104-017-2428-9
PubMed ID http://www.ncbi.nlm.nih.gov/pubmed/28219448
ISI-Number MEDLINE:28219448
Document type (ISI) Journal Article