CLUSTERIZATION OF HUMAN PROTEIN KINASES BASED ON SELECTIVITY OF SUB-MICROMOLAR INHIBITORS.

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Clusterization of human kinases based on selectivity of sub-micromolar inhibitors has been accomplished. Results may be used to rationalize experimental screenings, to identify new targets for existing drugs, to analyze evolutionary biology of protein kinases.

Keywords: kinome, protein kinases, inhibitors, selectivity, networks.

Development of new kinase inhibitors is an area of interests for many scientists from both industry and academia. Such inhibitors may be applied as agents for treatment of wide range of inflammatory and proliferative diseases. However utilization of kinase inhibitors is limited by severe side effects, which are the consequences of low selectivity. Also, it is limited by the acquired resistance to therapy, which is the consequence of high rate of single point mutations in protein kinase genes and dynamic nature of human kinome. This implies that experimental assessment of selectivity of kinase inhibitors at the early stages of drug discovery process is necessary. Since the aim is finding inhibitors, which are characterized by acceptable profile of selectivity, to achieve the balance between efficacy and safety. Applicability of existing protein kinases classification based on similarity of amino-acid sequences of kinase domains to optimize the experimental screening is limited [1]. In our study we created a set of sub-micromolar inhibitors of 270 protein kinases. The network of relationships between protein kinases was built using of this set. The network was clusterized. The derived clusters, relationships inside them and between them represent some kind of “Road Map”, which may be used to plan rational experimental screenings without any additional computations. We will overview the reasons of serious differences between the results of clusterization based on inhibitors selectivity and similarity of amino acid sequences for human protein kinases from the point of view of evolutionary biology.

1. Davis M. I. et al. Comprehensive analysis of kinase inhibitor selectivity //Nature biotechnology. – 2011. – Vol. 29. – №. 11. – P. 1046-1051.