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Targeting autophagy ULK1 Ser/Thr protein kinase through network analysis and e- pharmacophore modeling, molecular dynamics simulation approach

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Introduction & Aim: A key mechanism that allows eukaryotic cells to survive nutrient starvation is the catabolic process known as autophagy. ULK1/Atg1 is the only serine/threonine kinase in the core autophagy pathway and thus represents an excellent drug target. The role of ULK1/Atg1 kinase in autophagy activation is well established and projected as an important rug target for various diseases. This work aimed to predicted the gene function and identify suitable, high affinity small molecule inhibitor against ULK1/Atg1 using pharmacophore modeling and simulations studies.

Method & Results: In this study, predict the functions of gene and pathway analysis and gene lists using Cytoscape plug-in (GeneMANIA) gene network analysis were carried out. From the gene network analysis we identified genes that were co-expressed and showed genetic and physical interactions. Three pharmacophore were generated and validated using enrichment factor calculation from the available ULK1 cocrystal structures. The validated e-pharmacophore hypothesis (ADDRR) was utilized for screening various commercial chemical databases such as ZINC, CoCoCo and Enamine, which yielded 10,415 hit compounds. These compounds (pharmacophore fitness above 1.0 Å) were further analyzed using structure-based docking in hierarchical filtering approaches of Glide such as HTVS(high-throughput virtual screening), SP (standard precision) and XP (extra precision) precision modes. The docking results show that binding orientations of the inhibitors at active site amino acid residues of serine threonine protein kinase (ULK1). Results from glide XP docking and induced fit docking showed that four leads (lead1, lead2, lead3 and lead4) have good interactions with the target protein in comparison with cocrystal (Quinazoline) ULK1 inhibitor. Molecular Dynamics (MD) simulation for leads bound ULK1 shows better stability. Binding free energetic using MM-GB/SA approaches suggest lead1 and lead2 have comparably favorable binding to that of cocrystal inhibitor.

Conclusion: The serine/threonine kinase ULK1 is important therapeutic drug target for autophagy initiating process. These identified lead compounds have shown better binding affinity to this kinase through molecular docking and molecular dynamics simulation studies. Thus, the proposed leads can provide a framework to design novel ULK1 inhibitor in ULK1 mediated cancer and neuropathy in AD (Alzheimer's disease) therapeutics.

Significance: Autophagy has been associated with number of human health issues, including infectious diseases, neurodegenerative disorders and cancer. Owing to the importance of ULK1 autophagy as reported, in this work, computational efforts are taken to identify suitable inhibitors against this kinase. No drug targeting ULK1 is available until now and so leads identified from this work will be highly appreciated by drug designing community. ULK1 inhibitor leads from this study will help to regulate this highly conserved autophagy kinase in cell biology and in therapeutic possibilities for a wide variety of diseases.

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