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Structure guided design of inhibitors for SH3 domain of p47phox subunit of NADPH oxidase 2 implicated in various human disorders

Sripriya Puppala, M. Soumya, Reshma Chowdary, P.Susrutha and D.Sriram and P.Yogeeswari
Department of Pharmacy, Birla Institute of Technology & Science, India

NADPH oxidases (NOX) are a family of transmembrane proteins of which there are seven isoforms. NOX2 is found in the phagocytes. They are involved in the production of ROS which kills the pathogens. However, under pathological conditions, NOX becomes overexpressed, which can cause oxidative stress implicated in various disorders like Diabetic Retinopathy, Alzheimer's disease, and Chronic Granulomatous Disease. NOX2 consists of various subunits which can be classified into membrane bound (cytochrome b_{558}) and cytosolic subunits. $Gp91^{phox}$, $p22^{phox}$ are membrane bound and $p47^{phox}$, $p67^{phox}$, $p40^{phox}$ are the cytosolic subunits. The assembly of all these subunits results in the activation of the complex. The activation mechanism involves series of conformational changes in the various subunits. Initially phosphorylation of the $p47^{phox}$ occurs and thereby causes conformational changes and opening of SH3 domain which binds to $p22^{phox}$ after the assembly of the other cytosolic subunits with $p47^{phox}$. Therefore the SH3 domain binding site of $p47^{phox}$ can be a potential target to prevent activation of NOX2 complex. The present study was done using crystal structure of $p47^{phox}$-$p22^{phox}$ interaction (PDB ID: 1OV3). The protein obtained in its dimer form was subjected to protein preparation and the p22phox fragment was docked into $p47^{phox}$ pocket using Glide of Schrodinger. E-Pharmacophore with 4 features was generated and the possible inhibitors of $p47^{phox}$-$p22^{phox}$ interaction have been screened from a commercial database using Phase module of Schrodinger for novel lead identification. Rational filters like drug-likeliness property and blood brain penetration properties were applied to the hit list to optimize the lead.

Biography

Sripriya Puppala completed her Bachelors in pharmacy from R.G.R Siddhanthi College of Pharmacy affiliated to Jawaharlal Nehru Technological University, Hyderabad. Currently she is pursuing her Masters in pharmacy from BITS-Pilani Hyderabad Campus, Jawahar Nagar, Hyderabad.

puppala.sripriya@gmail.com