Assessment of the inhibitory mechanism of action for a yeast cell-based screening system targeting glycogen synthase kinase-3ß (GSK-3ß)

Abstract

Background and Objective: Glycogen Synthase Kinase-3 (GSK-3) is one of the prior targets for drug discovery due to its involvement in many cell signaling and metabolism. It has been implicated in several critical diseases such as diabetes, Alzheimer's disease, cancer and inflammation. To date, many GSK-3 inhibitors have been identified and classified into different type such as inorganic atom, ATP competitive and non-ATP competitive types. Many laboratories worldwide are still actively screening for bioactive compounds for GSK-3 inhibitory activity using diverse screening systems. This study assessed an assay developed using a yeast cell-based system specifically targeting GSK-3β for preliminary screening and cost effectiveness. **Methodology:** In this study, the GSK-3 homologues in yeast (*MCK1*, *MDS1*, *MRK1* and *YOL128C*) were knocked out and inserted with mammalian GSK-3β. In order to determine the inhibitory mechanism, known GSK-3β inhibitors were tested and evaluated. **Results:** The GSK-3β inhibitor I and staurosporine showed inhibition on GSK-3β activity at a concentration of 1 and 20 µg $disc^{-1}$, respectively. Other known inhibitors, such as indirubin-3'-monoxime, kenpaullone, GSK-3 inhibitor IV and enzastaurin showed no detectable inhibition in this study. **Conclusion:** The GSK-3β inhibitor I and staurosporine interacted with the same **amino acid** on GSK-3β which is Cys199 while other inhibitors have no interactions with Cys199 as reported in docking study. This study suggests that this yeast cell-based system can be used to screen GSK-3β inhibitors that is targeting on Cys199 residue.