Photoswitchable Wnt Pathway Agonists: Molecular Docking and Dynamics Reveal Selective Binding of cis-Isomer to Frizzled Receptors

Said Byadi
Hokkaido University

Photoswitchable small molecules allow us to control biological signals more precisely, improving drug selectivity and timing through the use of light. In this study, we looked at how N4-(1,3-benzodioxol-5-ylmethyl)-6-(3-methoxyphenyl)pyrimidine-2,4-diamine (BML-284) and its light-sensitive (photoswitchable) azo-analogues interact with Wnt signaling receptors. Using molecular docking with AutoDock 4.2.6 and molecular dynamics simulations with GROMACS 2024.5, we first tested their binding with tubulin (PDB: 7CEK). We found that only the cis-form of the photoswitchable compound (cis-1) binds in a similar way to BML-284. Further simulations showed higher stability of complexes with cis-1 than the trans-form (trans-1). We then extended our study to all ten Frizzled receptors (FZD1 to FZD10) and discovered ththe preferential binding of cis-1 to FZD5 and FZD7. More simulations confirmed that both cis-1 and BML-284 form stable complexes with these receptors, while trans-1 showed weaker binding. These results suggest that the cis-form is likely to be a potent photoswitchable analogue of BML-284 for binding to FZD5 and FZD7 and give the opprtunity of designing light-controlable ligands for Wnt signaling.