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Cellular and biophysical pipeline for peroxisome proliferator-activated receptor (PPAR) delta agonist screening

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Peroxisome Proliferator Activated Receptors delta (PPARδ) has been associated with pathophysiological processes, such as inflammation, obesity, dyslipidemia, diabetes, cancer, and cardiovascular diseases, being considered as new therapeutic targets for these processes. Here, we developed and set up one way to perform a screening to drive PPARδ agonists. We use methodologies capable of identify new molecules from compound libraries, which may work as this receptor's ligand. The first step in this screening pipeline is a valid cellular transactivation assay, as the primary search for potential compounds. We developed one assay based on a cellular transactivation reporter gene technology, performed on a 96-well microplate with support of automated pipette. The applied validation methodology was a combination of a thermal shift assay, used to check if the compounds or extract components selected in the transactivation assay stabilize PPARδ tertiary structure; coupled with a ANS quenching assay, which checks if the compound binds to the hydrophobic ligand binding pocket of PPARδ. Furthermore, the quality of the cellular high-throughput screening (HTS) in stability and reliability was evaluated by the Z-factor, and a natural extract library was used to validate the developed method. The results suggested that we developed a pipeline capable to search compounds or extracts feasible and robust enough to measure PPARδ activation, tertiary structure stabilization and ligand binding. As example, we could find one plant extract that contains interesting molecules, capable to binding and activate PPARδ. In conclusion, this pipeline presented more efficacy in comparison to the single activation screening, because it can exclude false-positives that may promote indirect PPARδ activation, without physical interaction with the receptor. Finally, this approach may improve the effectiveness of screening agonists targeting PPARδ for drug development.

Figure 1 : Screening Pipeline for PPARδ agonists with 3 steps: Cellular Transactivation Assay, Thermal Shift Assay and ANS Quenching Assay .

Biography

Natalia Bernardi Videira is a PhD student from Brazilian Biosciences National Laboratory (LNBio). LNBio is a laboratory dedicated to cutting-edge research and innovation focused on biotechnology and drugs development. Her PhD project deals with the development of a screening pipeline for PPAR delta agonists. She is currently in Switzerland for a 1-year research internship in the Center of Integrative Genomics, University of Lausanne. There she will study PPAR-dependent regulations of skin cell responses to environmental insults under supervision of Dr. Michalik.

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