A NEW PIPELINE FOR SCREENING OF PPAR DELTA AGONISTS

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The Peroxisome Proliferator-activated Receptor beta/delta (PPAR delta) is a lipid-activated transcription factor member of the nuclear receptors superfamily. PPAR delta is expressed ubiquitously in the human body and is associated with numerous biological processes, like lipid and glucose metabolism, cell differentiation, proliferation, wound healing and immune regulation. Furthermore, this protein is related with pathophysiological processes such as inflammation, obesity, dyslipidemia, diabetes, cancer, cardiovascular diseases and skin disorders. Therefore, due to this significance, it is important to find molecules that could work as PPAR delta agonists/antagonists helping the treatment of these disorders. The aim of this work is to develop methodologies for identification of molecules or plant extracts from some compound libraries that may work as PPAR delta’s agonists. The first methodology is a valid cellular transactivation assay for the primary screening of potential compounds. This methodology is based on a cellular transactivation reporter gene assay performed on a 96-well microplate with support of automated pipettes. The validation methodology is a Thermal Shift assay to check if the compound or extract component found in the Transactivation assay binds to the PPAR delta and stabilizes its tertiary structure. In this technique the heterologous PPAR delta’s ligand binding domain has its stability analyzed in vitro with a hydrophobic probe. Our results showed that these methodologies constitute a valid, useful and fast pipeline for screening and validation of potential agonists for PPAR Delta. After using these methodologies, the HITs found in our assays will be better evaluated by biophysical and structural biology methodologies. Acknowledgments: FAPESP and LQPN/CNPEM. Key Words: PPAR Delta, Screening, Transactivation.