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Targeting Mitochondrial ADP/ATP Carriers: Virtual screening of chemical libraries highlights new small molecules with potential therapeutic applications

Mitochondrial carriers (MCs) are proteins that transport a wide range of metabolites, nucleotides, and coenzymes across the inner mitochondrial membrane [1]. Among them, the mitochondrial ADP/ATP carriers (AACs) are specifically responsible for the import of cytosolic ADP, and the export of matrix ATP, by switching between cytoplasmic-open (c-conformation) and matrix-open states (m-conformation) [2]. This process is essential for energy production, maintaining cell viability and regulating the mitochondrial permeability transition pore [1],[2]. Remarkably, the dysregulation of AAC expression/function was observed in aggressive tumors, whereas mutations affecting AACs were associated to the onset of rare diseases. Thanks to the existence of a few crystallized carrier structures, it was possible to create 3D comparative models of the four human AAC members to perform virtual screening of chemical libraries to identify new small molecules with high affinity for the investigated mitochondrial carriers. Notably, AACs were crystallized in complex with two well-known inhibitors, namely the pro-apoptotic Carboxyatractyloside (CXT), stabilizing AACs in c-conformation, or the anti-apoptotic Bongkrekic acid (BKA), stabilizing AACs in the m-conformation. Starting from the re-docking of the two face-selective AAC-inhibitors, it is possible to search for high-affinity ligands structurally related to the characterized inhibitors searching for pro-apoptotic or anti-apoptotic small molecules able to regulate mitochondrial permeability transition pore (mPTP) opening and AAC function. The constructed 3D models of human AACs in c- and m-conformation were used to perform a virtual screening of 17248 selected compounds extracted from the KEGG Compound library (10839 compounds), the SelleckChem library (716 mitochondrial targeted compounds), the KEGG-drug library (3703 compounds) and the Diversity library (1990 compounds). Among the top-scoring compounds, resulting from the analysis of all the investigated chemical library, a few molecules displayed strong predicted binding affinities. i.e., Flavoxanthin and Momordin, known for their anti-inflammatory and pro-apoptotic activities, show a binding energy between -11.47 and -13.94 kcal/mol. This may suggest a possible role of negatively charged carboxylates (observed in Flavoxanthin, like those observed in CXT) or insaturations (observed in Momordin, similar to those observed in BKA) in stabilizing interactions within the AAC binding cavity. Other promising small molecules included sennoside, amaranth, gomphrenin-I, prebetanin, esmeraldin B, GDPhexose, and atractyloside, a well-known mitochondrial ADP/ATP carrier inhibitor. In vitro validation of the predicted high affinity small molecules is ongoing by using proteoliposomes and isothermal titration calorimetry.

Primary author(s) : Dr. SCAGLIONE, Valeria; Prof. PIERRI, Ciro Leonardo; Prof. VOLPICELLA, Mariateresa

Co-author(s) : Dr. SPADONE, Serena; Dr. TODISCO, Sabino; Dr. FRANCAVILLA, Anna Lucia; Dr. DE LUCA, Danila I.; Dr. MASTROPIRRO, Federica; Dr. SGOBBA, Noemi Maria; Dr. PERRONE, Giulia C.M; Prof. GUERRA, Lorenzo; Prof. DE GRASSI, Anna

Presenter(s) : Dr. SCAGLIONE, Valeria