ACTIVATOR vs INHIBITOR OF β-ISOFORMS OF AMPK: TOWARDS THE UNDERSTANDING OF ENZYMATIC MECHANISM

Katerina Barmpidi,[1] F. Javier Luque[1,2] and Carolina Estarellas[1]

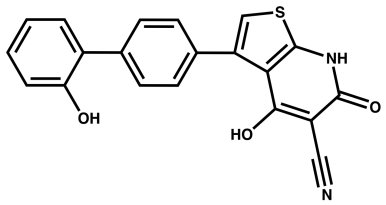
[1]Department of Nutrition, Food Science and Gastronomy, Faculty of Pharmacy and Food Sciences, Institute of Theoretical and Computational Chemistry (IQTCUB), and [2]Institute of Biomedicine (IBUB), University of Barcelona, Av. Prat de la Riba 171, Santa Coloma de Gramenet 08921, Spain.

abarmpba7@alumnes.ub.edu

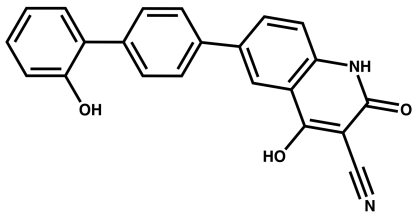
AMPK is a key energy sensor regulating the cell metabolism in response to energy supply and demand. The evolutionary adaptation of AMPK to different tissues is accomplished through the expression of distinct isoforms that can form up to 12 complexes, which exhibit notable differences in the sensitivity to allosteric activators.[1] In our previous studies, we have studied the structural and dynamical properties of β1- and β2-containing AMPK complexes formed with small molecules like A-769662, SC4, PF739 that act as direct activators, in case of A-769662 activating specifically the β1-isoform, whereas in the other two cases these ligands could act as a pan-activators.[2,3] The simulations reveal that the binding of activators to α2β1 promotes the preorganization of the ATP-binding site, acting as a molecular glue between α- and β- subunits. These findings were discussed considering the changes in the residue content of β-subunit isoforms, particularly regarding the β1Asn111--> β2Asp111 substitution, which we hypothesize to be a key factor in modulating the mechanical sensitivity of β1- and β2-containing AMPK complexes. [4,5,6]

Taking advantage of this previous studies, we would like to complete the understanding of the β-isoform selectivity by analyzing an additional modulator, MT47-100, which is able to activate the α2β1 complex, while it inhibits the α2β2. So, will be the β1Asn111--> β2Asp111 substitution still crucial in this different behaviour? Will the MT47-100 molecule, very similar from structural point of view to the A-769662 (selectively activator of β1-isoform), shed more light in the structural factors that dominate the enzymatic mechanism of AMPK? Altogether, our studies will pave the way for the design of selective activators upon specific AMPK heterotrimeric complex.

A-769662



MT47-100



References:

[1] Uhlén, M., et al. *Science*, **2015**, *347*, 1260419.
[2] Xiao, B., et al. *Nat. Commun.*, **2013**, *4*, 3017.
[3] Ngoei, K. R. W., et al. *Cell Chem. Biol.*, **2018**, *25*, 728-737.
[4] Aledavood, E., et al. *J. Chem. Inf. Model.*, **2019**, *59*, 2859–2870.
[5] Aledavood, E., et al. *Comput. Struct. Biotechnol. J.*, **2021**, *19*, 3394–3406.
[6] Aledavood, E., et al. *Front. Mol. Biosci.*, **2021**, *8*, 760026.