Universitat Pompeu Fabra Barcelona | Master in Bioinformatics for Health Sciences

Master project 2021-2022

Personal Information

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Project

Structural bioinformatics

Project Title:

Exploring the molecular basis of the selective activation of specific AMPK isoforms by direct activators

Keywords:

protein dynamics - structure - activation mechanism - MD simulations - interaction networks

Summary:

Up to 30 % of all human proteins could be modified by protein kinases, which are known to regulate most of cellular pathways. The mammalian adenosine monophosphate-activated protein kinase (AMPK) is a Ser/Thr protein kinase that has an important role in cellular energy homeostasis and its activity is tightly regulated by the cellular ratios between AMP, ADP and ATP. AMPK is a 145kDa heterotrimeric complex which consists of a catalytic α subunit and two regulatory subunits, β and γ. Multiple genes in mammals encode all three subunits. The evolutionary adaptation of AMPK to different tissues is accomplished through the expression of distinct isoforms that can form up to 12 αβγ complexes, which exhibit notable differences in the sensitivity to allosteric activators. Due to AMPK central role in energy homeostasis, its activity is susceptible to being regulated by several mechanisms. These are: i) The binding of AMP to the CBS domains in the γ-regulatory subunit promotes the phosphorylation of Thr172 in the activation loop at the kinase domain of the α -subunit by upstream kinases, promoting an allosteric activation. ii) The indirect AMPK activators that act by increasing the cellular AMP concentration, such as metformin, phenformin, or oligomycin. iii) In 2006, Abbott Laboratories reported a novel mechanism of action that involves the first direct activation of AMPK by the thienopyridone drug A-769662. In contrast to adenine nucleotides, A-769662 does not bind to the CBS motifs in the γ-subunit but to a binding site located at the interface between α and β subunits which is called Allosteric Drug and Metabolite binding (ADaM) site. In the last years several direct activators of AMPK were reported. Parts of these activators are specific for certain isoforms of AMPK; some of them can activate both β1 and β2 isoforms while the others can only trigger the activation in one specific isoform. To shed light into the molecular determinants of the allosteric regulation of AMPK, we have already examined the structural and dynamical properties of β1- and β2-containing AMPK complexes formed with A-769662 and SC4 activators trying to dissect the mechanical response leading to active-like enzyme conformations through the analysis of interaction networks between structural domains. The results of these analyses show the mechanical sensitivity of α2β1 complexes in contrast to the large resilience of α2β2. Our results indicate that the binding of the activator to α2β1 promotes the pre-organization of the ATP-binding site, favoring the adoption of the activated form of the enzyme. Moreover, we hypothesize that the change of β1Asn111 to β2Asp111 could be the key factor in modulating the mechanical sensitivity of β1 and β2 containing AMPK complexes. However, still several questions remain to be answered at different levels. Firstly, we have performed the study considering different β isoform, but the same α isoform. So, a needed step is the understanding of the influence of α1 and α2 isoforms over the activation mechanism. Moreover, due to the complexity of the system the AMPK structures crystallized until now are not fully complete, and therefore it has not been simulated the full heterotrimeric complex. So, how the study of the full complex could affect the allosteric mechanism between the different subunits? How could this fact affect the different isoform composition? These questions are key factors that we need to tackle in order to complete the puzzle and shed some light in the drug design for specific isoform complex.

Expected skills::

1) Understanding the protein structure and noncovalent interactions, 2) Use of linux operating system, 3) Preferably: knowledge on visualization programs like pymol, vmd, 4) Preferably: knowledge on MD simulations and some packages to run MD simulations like amber, gromacs, etc

Possibility of funding::

To be discussed

Possible continuity with PhD: :

To be discussed