Computer-aided drug design for oncogenic mutant proteins using HPC resources

Zoe Cournia[1]

[1]Biomedical Research Foundation of the Academy of Athens

Cancer may result from alterations (mutations) in critical regulatory genes that control cell proliferation, differentiation, and survival. Mutated genes, called oncogenes, are expressed into mutated proteins, which often bear only a single mutation, i.e. the replacement of an amino acid into another on the structure of the protein. One of the most commonly mutated proteins in human cancers is phosphoinositide 3-kinase alpha (PI3Kα). 80% of PI3Kα mutations result in amino acid replacements located in two hotspots: (a) in the helical domain of PI3Kα the glutamic acid at position 545 is replaced by lysine E545K), (b) in the kinase domain, a histidine is changed to arginine at position 1047 (H1047R). These mutations result in loss of regulation and constitutive PI3Kα activity, which can then lead to oncogenesis. A key challenge in inhibiting the action of mutated proteins such as PI3Kα with small molecules, is to selectively target only the mutated protein and leave the normal protein (called wild-type, WT) unaffected, thus avoiding undesirable side effects. One of the problems with selective targeting of mutant proteins with small molecules is that the mutation occurs far from the functional (active) site of the protein at a distant location, where druggable cavities are not characterized. In this work, we investigate the mechanism of over-activation of the two hotspots mutations of PI3Kα using extensive Molecular Dynamics simulations using PRACE resources to examine conformational changes differing between the WT and mutant proteins as they occur in microsecond simulations. We find that the two mutations have a completely different mechanism of over-activating PI3Kα. In E545K, the mutation causes a spontaneous detachment of the nSH2 PI3Kα domain (regulatory subunit, p85α) from the helical domain (catalytic subunit, p110α), which results in significant loss of communication between the regulatory and catalytic subunits and abrogation of PI3Kα regulation [1]. The H1047R mutant instead affects the conformation of PI3Kα regulatory elements such as the C-terminus, and also alters the protein interaction with the cell membrane [2]. The allosteric networks of the WT, E545K, H1047R PI3Kα proteins were constructed [1] and show residues important in delivering communication signals between the catalytic and regulatory subunits. Following that, allosteric cavities specific for E545K, H1047R PI3Kα have been identified in terms of their communication with the active site [3]. In these cavities, computer-aided drug design has been performed and novel, mutant-selective allosteric PI3Kα inhibitors were identified and submitted as a patent application [4]. Allosteric small molecules typically bind to less conserved sites compared to the active site of an enzyme, and thus they may confer greater specificity in protein regulation. These could be promising leads for effectively inhibiting PI3Kα oncogenic mutants that could result in treatments for cancer patients bearing these mutations.

References

1. Leontiadou H, Galdadas I, Athanasiou C, Cournia Z. Insights into the mechanism of the PIK3CA E545K activating mutation using MD simulations, Sci Rep, Sci Rep, 2018, 8(1):15544.

2. Gkeka P, Evangelidis T, Pavlaki M, Lazani V, Christoforidis S, Agianian B, Cournia Z. Investigating the Structure and Dynamics of the PIK3CA Wild-Type and H1047R Oncogenic Mutant. PLoS Comput Biol. 2014, 10 (10):e1003895.

3. Gkeka P, Papafotika A, Christoforidis S, Cournia Z. Exploring a Non-ATP Pocket for Potential Allosteric Modulation of PI3Kα. J Phys Chem B. 2015, 119 (3), pp. 1002-1016.

4. Z. Cournia, S Christoforidis, A Kapela, E Couladouros, A Efstratiadis, "Method of preparation and use of phosphoinositide 3-kinase inhibitors in treating cancer". OBI Patent Application number 20180100392.