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Drug Design 2020: How conformational dynamics descriptors may help in re-modelling of allosteric regulation in proteins - Luba Tchertanov - CNRS

Luba Tchertanov[1]

[1]CNRS, France

Abstract:

Allostery is a universal phenomenon that couples the knowledge induced by an area perturbation (effector) during a protein to spatially regulated sites which are distant. Such an occasion are often described in terms of an outsized scale transmission of data (communication) through a dynamic coupling between structurally rigid (minimally frustrated) and plastic (locally frustrated) clusters of residues. To elaborate the method of allosteric coupling, we propose an approach of ingenious method - MOdular NETwork Analysis (MONETA) - which supports the analysis of inter-residue dynamical correlations to estimate the point of propagation of both structural and dynamical effects of a perturbation throughout a protein structure. MONETA uses inter-residual cross-correlations and commute times which are computed from topological description and molecular dynamics simulations of a protein to create a modular network representation composed of clusters of residues (dynamic segments) linked together by chains of residues which are called as communication pathways. MONETA provides a fresh direct and straightforward visualization of protein allosteric communication. A GEPHI module implemented within the MONETA package allows the generation of 2D graphs of the communication network. An PyMOL plugin interaction permits enhancing of the communication pathways between chosen protein fragments or residues on a 3D representation. MONETA may be a powerful tool for on-the-fly display of communication networks in proteins. We applied MONETA for the analysis of communication pathways (i) between the main regulatory fragments of receptors tyrosine kinases (RTKs), KIT and CSF-1R, in the native and mutated states and (ii) in proteins STAT5 (STAT5a and STAT5b) within the phosphorylated and therefore the unphosphorylated forms. The physical support for allosteric coupling by MONETA leads a comparison of the mechanisms of (a) allosteric regulation within the activated and non-activated STAT5 proteinsand (b) constitutive activation induced by equivalent mutations in two RTKs. Our theoretical prediction supported results obtained with MONETA was validated for KIT by in vitro experiments. MONETA may be a versatile analytical and visualization tool entirely dedicated to the understanding of the functioning/malfunctioning of allosteric regulation in proteins - an important basis to guide the invention of next-generation allosteric drugs.

Control of regulation of enzymes allosteric nature is required to drive metabolic flux at desired levels. Although many enzyme-ligand complexes with three-dimensional (3D) structures are available, it is still difficult to rationally engineer an allosterically regulatable enzyme without decreasing the activity of catalyst. Here, we describe an effective strategy to deregulate the inhibition of nature of allostericity of enzymes supported the physicochemical and molecular evolution characteristics of allosteric ligand-binding sites. We found that allosteric sites are evolutionarily comprised and variable of more residues of hydrophobic ares than catalytic sites. We applied our findings to style mutations in selected target residues that deregulate the allosteric activity of fructose-1,6-bisphosphatase (FBPase). Specifically, amino acids which are charged at less conserved positions were substituted with neutral or hydrophobic amino acids with similar sizes. The engineered proteins successfully diminished the allosteric inhibition of E. coli FBPase without affecting its catalytic efficiency. We estimate that our method will aid the rational design of allosteric enzyme regulation strategies and enables facilitation of control of metabolic flux.

Allosteric controls nearly all biological processes, and as a consequence it has been declared by Jacques Monod to be “the second secrete of life” after the genome. This universal phenomenon in nature represents a target perturbation using an effector (a non-covalent binding of small and large molecules, covalent modifications, environmental changes, or a point mutation) leading to a functional change at the target’s binding site(s) through alteration of the structure and/or dynamics. Such an event can be described in terms of a large-scale transmission of information (communication), which takes place through a dynamic coupling between residues. This concept is the cornerstone of the Modular Network Analysis (MONETA), a method that delivers descriptor encoding of the communication network in a protein. MONETA uses interresidual cross links computed from a topological description and conformational dynamics and of a protein to create a modular network presentation composed of clusters of residues (dynamic segments) that are linked closely by chains of residues (communication pathways). Using MONETA, we were able to describe the allosteric regulation of several proteins involved in cell signalling. First, we focused on the receptors tyrosine kinases (RTKs), KIT and CSF-1R, and their numerous clinically-relevant mutants. We showed that the allosteric communications between the major regulating fragments (A-loop, juxta-membrane region and Cα-helix) in the native proteins were disrupted by the gain-of-function mutations. The diverging impact of equivalent mutations on communication in these homologue RTKs permits us to differentiate between the mutation induced effects that cause the constitutive activation of KIT (an oncogenic event) and the mutation-induced effects promoted by resistance to Imatinib in CSF-1R (resistance phenomenon). Secondly, the study of STAT5s (STAT5a and STAT5b), RTK downstream signalling proteins, showed the sequence-dependent asymmetry in the STAT5s’ communications and their different responses to phosphorylation of specific tyrosine residue. We established a branched allosteric coupling within the STAT5 DNA macromolecular complex. Finally, our recent study provided a fascinating illustration of how the binding of agonist ligands controls intrinsic conformational dynamics in human NMDA receptors that stabilize the channel opening. The allosteric binding sites, which were identified as a pockets at the proteins surface located adjacent to the communication pathway, also may constitute valid

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targets for the inhibitor development which may have ability to modulate the function-related communication properties of a protein. Such communication-targeted and communication-inspired modulation may selectively block several post-transduction processes or activation.

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