Luba Tchertanov, Drug Des 2017, 6:4(Suppl)
DOI: 10.4172/2169-0138-C1-015

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How conformational dynamics descriptors may help in remodelling of allosteric regulation in proteins

Allostery 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 inter-residue cross-correlations computed from conformational dynamics and a topological description of a protein to build a modular network representation composed of clusters of residues (*dynamic segments)* that are linked together 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 distinguish between the mutation-induced effects that lead to 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 by a pockets search at the proteins surface adjacent to the communication pathway, may constitute valid targets for the development of inhibitors able to modulate the function-related communication properties of a protein. Such communication-inspired and communication-targeted modulation may selectively block several activation or post-transduction processes. We believe that our work will open the way to novel and rational strategies for the definition of targets, and the development of efficient target-specific inhibitors.

Biography

Luba Tchertanov is a Research Director at CNRS-France, and leader of the Bioinformatics, Molecular Dynamics and Modeling team in Centre Mathématiques et leurs Applications (CMLA-CNRS) at the Ecole Normale Supérieure (ENS) de Cachan. She received her MS in Physics, PhD in Crystallography and HDR in the Life Sciences. She has multidisciplinary high-level skills, with extensive experience in structural biology, molecular modelling and numerical simulation of molecular dynamics. She is the author or co-author of more than 100 papers in peer-reviewed journals. Her research topics are focused on exploration of protein structure–dynamics–function relations. In particular, she is working at the mechanisms of the receptors activation, the mechanisms of resistance to inhibitors, the conformational plasticity and dynamics of inter-molecular interactions and molecular recognition.

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