Clinical and Translational Medicine
a SpringerOpen Journal

COMMENTARY Open Access

Possible mechanism and clinical potentials of allostery

Peixin Huang[1*] and Elena López Villar[2]

Abstract

Allostery is involved in the dynamic regulation of biological functions in proteins. Advances in allostery research have recently drawn great interest and brought allostery closer to the clinic. The present commentary describes the mechanism by which allostery may involve in from a cell-wide view and its contribution to the discovery of new therapeutics to diseases.

Keywords: Allostery; DNA; Disease; Drug

Background

Allostery is a universal phenomenon whereby an effector molecule combining with a (allosteric) site on the protein surface leads to a functional change through alteration of shape and/or dynamics, to regulate protein activity. Effector perturbations can result from a wide range of biological and physical phenomena, including the binding of a small effector molecule, post-translational modifications, protein binding, temperature changes, and pH changes. Allostery takes place in all dynamic proteins, single chains, and in RNA and DNA polymers.

Main text

Numerous studies demonstrated the importance of the allostery on the protein level, such as MAP kinase, G-protein-coupled receptor (GRCR) kinase, glucokinase (GCK), Hemoglobin S etc. to involve in gene regulation [1-4]. Evolution has exploited allostery as a crucial protein property and optimized it for function [5,6]. Recently, a series of studies reported that the allostery also occurred through RNA and DNA, in addition to the protein level. Three DNA-protein pairs (Cy3B-labled DNA binding domain of glucocorticoid receptor (GRDBD) together with BamHI, Lac repressor (LacR) with EcoRV, or LacR with T7 RNA polymerase) were used to validate and quantitatively characterize the allostery [7-9]. The deformation of the double-helical structure was suggested to be the origin of DNA allostery. However, the altered distance of half a helical turn might affect the evolution with fine-tuning capability of adjusting relative kinetics in regulatory networks. Allostery through DNA was found to be more relative to the placement of regulatory elements such as the transmission of structural influences and switches between canonical structural models.

Discussion

However, people gradually found that the fundamental importance of allostery is not in the protein or DNA level but, rather, on the cells. From a cell-wide view, allosteric changes can function through a number of pathways which are communicated within, across and between cells. Allostery propagates via molecular cooperativeness and recognition specificity, and affects consecutive components in cellular pathways. The main standpoints to descript how allostery works are thermodynamics, free energy landscape of population shift, and structure [10,11]. Allosteric proteins could activate the conformation of different kinase families and may share a similar structure and the same mechanism. Upstream allosteric sites could switch from inactive αC-helix-out state (OFF) to the active αC-helix-in conformation (ON) [12]. It promotes the inter-connection with several signaling pathways and the formation of allostery network linkage. When mutations cause a high population of ON or OFF states, or lead to an irreversible change in active site shape and dynamics, the allosteric diseases occur [13]. Based on such principle, allosteric drugs targeted at those structures and pathways will

* Correspondence: huang.peixin@zs-hospital.sh.cn
[1]Liver Cancer Institute, Pulmonary Department, Fudan University Zhongshan Hospital, Shanghai 200032, China
Full list of author information is available at the end of the article

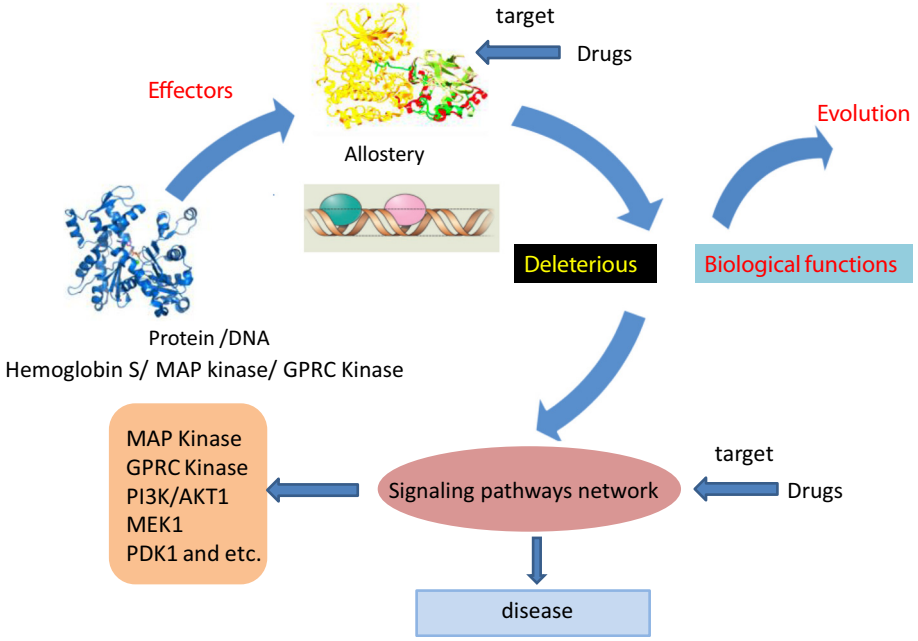

Figure 1 Allostery in gene regulation. Effector molecules bind at the protein's allosteric sites, leading to the changes of protein activity. Allostery of protein or DNA then play their respective biological roles through similar signaling pathways in evolution or deleterious physiological process to cause diseases. Targeting signaling pathways or allosteric sites may provide promising therapeutic choices for new drugs.

provide the possibility of new therapeutics. These pathways may include PI3K/Akt1, MEK1, PDK1 and other protein kinases family pathways [14]. For example, a new model for allosteric regulation of phenylalanine hydroxylase has been studied and ACT interface may be the potential molecule target for therapy [15]. Allosteric ligands bind to protein receptors such as GPCRs also provide the ways for allosteric drugs screening and leading to potential therapeutic benefit [16].

Conclusion

A collection of recently published papers suggest that allostery of protein or DNA play the respective biological roles in evolution or physiological process. The perturbation, such as mutation, phosphorylation and reaction with small molecules at any site in the protein or DNA structure, leads to a shift in the distribution of the conformational states. The irreversible changes in the structure or the abnormality of switch in allostery are the cause of diseases. Those allosteries may share similar signaling pathways and form network regulation in disease development and may provide promising therapeutic choices for new drugs (Figure 1). Therefore, allostery plays a key role in gene regulation and can be a new alternative to develop new therapies for diseases. Effects of allosteric changes in the pathway should gain more special attentions from a comprehensive and dynamic network perspective.

Competing interests
The authors declare that they have no competing interests.

Authors' contributions
PH, ELV collaborated in order to publish this article and to carry out future research studies. Both authors read and approved the final manuscript.

Acknowledgements
The work was supported by Shanghai Health Bureau Research Fund (No. 2010/50), The National Nature Science Foundation of China (91230204, 81270099, 81320108001, 81270131), The Shanghai Committee of Science and Technology (12JC1402200, 12431900207, 11410708600), and Spanish health system "Dr E. Lopez Villar, BOE 2012", ISCIII (PI13/02475FIS "BOE 2013").

Author details
[1]Liver Cancer Institute, Pulmonary Department, Fudan University Zhongshan Hospital, Shanghai 200032, China. [2]Department of Oncohematology of Children, Hospital Universitario Niño Jesús, Avda. Menéndez Pelayo, NO 65, 28009 Madrid, Spain.

Received: 20 February 2014 Accepted: 16 June 2014
Published: 3 July 2014

References

1. Coyle SM, Flores J, Lim WA: **Exploitation of latent allostery enables the evolution of new modes of MAP Kinase regulation.** *Cell* 2013, **154**(4):875–887.
2. Larion M, Salinas RK, Bruschweiler Li L, Miller BG, Bruschweiler R: **Order–disorder transitions govern kinetic cooperativity and allostery of monomeric human glucokinase.** *PLoS Biol* 2012, **10**(12):1001452. 2012-01-20.
3. Liggett SB: **Phosphorylation barcoding as a mechanism of directing GPCR signaling.** *Sci Signal* 2011, **4**(185):e36. 2011-08-09.
4. Weinkam P, Sali A: **Mapping polymerization and allostery of hemoglobin s using point mutations.** *J Phys Chem B* 2013, **117**(42):13058–68. 2013-09-09.
5. Harms MJ, Thornton JW: **Evolutionary biochemistry: revealing the historical and physical causes of protein properties.** *Nat Rev Genet* 2013, **14**(8):559–571. 2013-08-01.

6. De Juan D, Pazos F, Valencia A: **Emerging methods in protein co-evolution.** *Nat Rev Genet* 2013, **14**(4):249–261. 2013-04-01.
7. Kim S, Brostromer E, Xing D, Jin J, Chong S, Ge H, Wang S, Gu C, Yang L, Gao YQ, Su XD, Sun Y, Xie XS: **Probing allostery through DNA.** *Science* 2013, **339**(6121):816–819. 2013-02-15.
8. Chen I: **Allostery through DNA.** *Nat Struct Mol Biol* 2013, **20**(4):410. 2013-04-01.
9. Crothers DM: **Biophysics. Fine tuning gene regulation.** *Science* 2013, **339**(6121):766–767. 2013-02-15.
10. Tsai C, Nussinov R: **A unified view of "How Allostery Works".** *PLoS Comput Biol* 2014, **10**(2):e1003394. 2014-02-06.
11. Motlagh HN, Wrabl JO, Li J, Hilser VJ: **The ensemble nature of allostery.** *Nature* 2014, **508**(7496):331–339. 2014-04-16.
12. Huse M, Kuriyan J: **The conformational plasticity of protein kinases.** *Cell* 2002, **109**(3):275–282. 2002-05-03.
13. Nussinov R, Tsai CJ: **Allostery in disease and in drug discovery.** *Cell* 2013, **153**(2):293–305. 2013-04-11.
14. Lu S, Li S, Zhang J: **Harnessing allostery: a novel approach to drug discovery.** *Med Res Rev* 2014. doi:10.1002/med.21317.[Epub ahead of print].
15. Jaffe EK, Stith L, Lawrence SH, Andrake M, Dunbrack RJ: **A new model for allosteric regulation of phenylalanine hydroxylase: implications for disease and therapeutics.** *Arch Biochem Biophys* 2013, **530**(2):73–82. 2013-02-15.
16. Wootten D, Christopoulos A, Sexton PM: **Emerging paradigms in GPCR allostery: implications for drug discovery.** *Nat Rev Drug Discov* 2013, **12**(8):630–644. 2013-08-02.

doi:10.1186/2001-1326-3-18
Cite this article as: Huang and López Villar: **Possible mechanism and clinical potentials of allostery.** *Clinical and Translational Medicine* 2014 **3**:18.