Allosteric regulation in drug design

Ashfaq Ur Rehman1,2*, Shah Saud3, Nasir Ahmad4, Abdul Wadood2 and R Hamid5

1State Key Laboratory of Microbial Metabolism, Department of Bioinformatics and Biostatistics, China
2Department of Biochemistry, Abdul Wali Khan University Mardan, Pakistan
3Laboratory of Analytical Biochemistry and Bio separation, Shanghai jiao Tong University, China
4Department of Chemistry, Islama College University Peshawar, Pakistan
5Department of Bioinformatics, Muhammad Ali Jinnah University Islamabad, Pakistan

Submission: May 02, 2017; Published: May 23, 2017

*Corresponding author: Ashfaq Ur Rehman, State Key Laboratory of Microbial Metabolism, Department of Bioinformatics and Biostatistics, Shanghai jiao Tong University, 800 Dongchuan Road, Shanghai 200240, China, Tel: 86-13162094886; Fax: 86-21-34204348; Email: raqsjtu@sjtu.edu.cn

Abstract

Protein and enzymes play significant roles in biological processes of all living organisms; their functions are regulated through allosteric mechanism, which are initiated through attachment of ligand or inhibitors with the protein or enzymes other than active (orthosteric) sites. This mini review involved mechanism, types and importance of allosteric regulations in drug design process.

Keywords: Allosteric, Activator: Drug design

Introduction

For the survival of all organisms the significance of protein function is pivotal. As all the cell processes are under careful control and if not properly controls this leads to the abnormality and ultimately cause disease. While various biological processes expressed the control at different points in life time of protein included regulation of gene expression, translation into protein through control of activity and at last degradation of protein [1].

Figure 1:

(a) When an activator is not bound to the allosteric site, the orthosteric site of the enzyme is unable to bind the substrate and catalyze the formation of product(s), when the activator binds to the enzyme at the allosteric site, the shape of the orthosteric site changes so that it can bind its substrate and catalyze the formation of the product(s). The enzyme will remain activated until the allosteric activator leaves the allosteric site.

(b) In the absence of allosteric inhibitor, the orthosteric site of the enzyme is able to bind the substrate and catalyze the formation of product(s), while in the presence of allosteric inhibitor, the orthosteric site of the enzyme is altered and no substrate can bind to it.
This is a mechanism of protein function, which occurs at one site of protein structure while its impact is on other site of protein. For example, the attachment of the ligand or mutation of amino acid in one allosteric site changes the catalytic activity of another orthosteric site. This is called the action of allosteric regulation. The ligand is called an effector; it may be another protein while its binding site is called an allosteric site.

Allosteric regulation rule in drug discovery

The pharmacological drug design can be developed through deep understanding of mechanism of allostericity. The main reason is when the ligand bind with the allosteric site it completely change function of protein and this site can be used as drug target for novel compounds. The conservation of the allosteric site is common because the evolution has little impact on it and that is the main reason for selective inhibitors across the species [5,6]. In the field of chemical biology and designing of new class of antibiotics the species-specific inhibitors plays important role. The allosteric inhibition has been deeply studied for kinases, G protein-coupled receptors and ligand-gated ion channels [7-10].

Conclusion

The need for drugs with rare side effects cannot be overstressed. Today, most drugs modify the actions of enzymes and other molecules by directly binding to their orthosteric sites. Nevertheless, orthosteric site configuration is similar in several proteins performing related functions and this leads to a lower specificity of a drug for the desired protein. Consequently, such drugs may have adverse side effects. A new basis of drug discovery is emerging based on the binding of the drug molecules to sites away (allosteric) from the orthosteric sites. It is possible to find allosteric sites, which are unique and hence more specific as targets for drug discovery. It is predicted that the drug discovery exploiting allosteric sites will lead to more effective therapeutic agents with rare side effects.

References
