Saudi Journal of Biological Sciences (2017) 24, 379–388

King Saud University

Saudi Journal of Biological Sciences

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REVIEW

Binding of small molecules at interface of protein–protein complex – A newer approach to rational drug design

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Received 8 September 2015; revised 3 November 2015; accepted 3 January 2016
Available online 7 January 2016

KEYWORDS

Hot spots;
Protein interfaces;
Druggability;
Orthosteric inhibitor;
Allosteric inhibitor;
Interfacial binding inhibitor

Abstract Protein–protein interaction is a vital process which drives many important physiological processes in the cell and has also been implicated in several diseases. Though the protein–protein interaction network is quite complex but understanding its interacting partners using both *in silico* as well as molecular biology techniques can provide better insights for targeting such interactions. Targeting protein–protein interaction with small molecules is a challenging task because of druggability issues. Nevertheless, several studies on the kinetics as well as thermodynamic properties of protein–protein interactions have immensely contributed toward better understanding of the affinity of these complexes. But, more recent studies on hot spots and interface residues have opened up new avenues in the drug discovery process. This approach has been used in the design of hot spot based modulators targeting protein–protein interaction with the objective of normalizing such interactions.

Contents

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Peer review under responsibility of King Saud University.

Production and hosting by Elsevier

http://dx.doi.org/10.1016/j.sjbs.2016.01.008

1. Introduction

Protein–protein interaction is an important driving mechanism in many physiological processes in the cell and may also be involved in the pathogenesis of some diseases such as Alzheimer's cervical cancer, bacterial infection and prion diseases (Cohen and Prusiner, 1998; Selkoe, 1998; Loregian et al., 2002). Owing to the diversity of protein–protein interactions there is a need for careful investigation of the nature of the protein interface. The protein interface residues are a determinant of the specificity and stability of protein–protein interaction. The size of the protein interface decides whether the complex will be transient or obligatory. Protein–protein interaction is regulated by environmental conditions such as temperature, pH, ionic strength, etc. and also by cell mechanisms such as enzymes, covalent modification and non-covalent modification ligand binding etc (Furukawa et al., 2002; Eyster, 1998; Klemm et al., 1998; Markus and Benezra, 1999). Depending on their stability, protein complexes can be principally classified into two types: temporary and permanent stable complexes. The temporary complex interfaces have unique properties for each interacting pair of proteins whereas the permanent stable complex interfaces have similar properties on their surfaces as their formation is considered to be a continuation of protein folding (Dmitriev et al., 2002; Tsai et al., 1997).

Prediction of protein–protein interaction is crucial in drug discovery. Many physiological and pathological cellular processes depend on protein–protein interactions which can be influenced by external compounds. The modern drug discovery process involves three main steps-identification of prospective drug target, investigating its properties and designing of a corresponding ligand (Archakov et al., 2003). Therefore, knowledge of protein–protein interaction can be useful in designing modulators that can target the protein complex involved in various diseases. But a number of factors can contribute to the challenge of identifying small molecules that inhibit such interactions. These include the general lack of small-molecule starting points for drug design, the typical flatness of the interface, and the difficulty of distinguishing real from false binding, and the size and character of typical small-molecule libraries (Arkin and Wells, 2004). However, much of these problems have been solved through advancement of molecular biology and computational modeling techniques (Jin et al., 2013; Cheng et al., 2007; Huang and Jacobson, 2010).

2. Protein–protein interfaces: structure, composition and forces

Protein–protein interaction sites are formed by proteins with good shape and electrostatic complementarity (Janin, 1995; Jones and Thornton, 1996; Janin and Chothia, 1990). The standard size for the protein interfaces are 1200–2000 A^2 (Horton and Lewis, 1992). Small protein interfaces of size 1150–1200 A^2 are usually unstable and short-lived (Conte et al., 1999). Large protein interfaces are found in proteases, G-proteins and other proteins of the signal transduction pathways (Janin and Chothia, 1990; Horton and Lewis, 1992).

Protein–protein interfaces are mostly hydrophobic and consist of buried non polar surface area (Young et al., 1994). Thus hydrophobicity is the leading force in protein–protein interactions. The protein–protein complex is stabilized by a large gain in free energy change through increase in entropy, van der waals interactions and desolvation energy (Fernandez and Scheraga, 2003; Dill, 1990). Besides hydrophobic interactions, electrostatic forces also promote complex formation, which in turn defines the lifetime of protein complexes (Nicolini, 1999). It has been found that the average number of hydrogen bonds is proportional to the subunit area surfaces: one bond per 100–200 A° (Jones and Thornton, 1997a,b). Other hydrogen bonds are formed between protein contacts and surrounding water molecules (Laskowski et al., 1996; Vaughan et al., 1999).

It has been found that there is a highly uneven distribution of energetic contribution of individual protein residues across each subunit surface such that only a fraction of key residues contribute to the binding free energy of protein–protein complexes known as hot spots (Janin and Chothia, 1990; Conte et al., 1999). Hot spots have been defined as those sites where alanine mutations cause a significant increase in the binding free energy of at least 2.0 kcal/mol (Thorn and Bogan, 2001). In a protein–protein interface only a subset of the buried amino acids contribute most of the binding affinity which is determined by a change of free energy upon mutation of the residue to an alanine. These hot spots are not only helpful for the study of a single protein–protein dimer but also in the determination of probable binding sites for other binding partners (Thornton, 2001).