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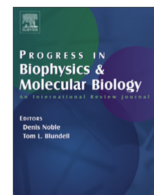

Review

In silico design of low molecular weight protein–protein interaction inhibitors: Overall concept and recent advances

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Protein–protein interactions (PPIs) are carrying out diverse functions in living systems and are playing a major role in the health and disease states. Low molecular weight (LMW) "drug-like" inhibitors of PPIs would be very valuable not only to enhance our understanding over physiological processes but also for drug discovery endeavors. However, PPIs were deemed intractable by LMW chemicals during many years. But today, with the new experimental and in silico technologies that have been developed, about 50 PPIs have already been inhibited by LMW molecules. Here, we first focus on general concepts about protein–protein interactions, present a consensual view about ligandable pockets at the protein interfaces and the possibilities of using fast and cost effective structure-based virtual screening methods to identify PPI hits. We then discuss the design of compound collections dedicated to PPIs. Recent financial analyses of the field suggest that LMW PPI modulators could be gaining momentum over biologics in the coming years supporting further research in this area.

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1. Introduction

About 20–30 years ago, it was generally considered that protein–protein interactions (PPIs) could not be inhibited by low molecular weight (LMW) "drug-like" compounds. This was in part due to the fact that protein–protein interfaces were perceived as flat, large and apparently lacking tractable cavities that could accommodate small chemical compounds and also because, in general, protein interfaces are not known to bind LMW molecules as compared to enzymes or GPCRs (Arkin and Wells, 2004). The lack of clear binding pockets at the interfaces and the lack of endogenous ligands or substrates to start the design process together with the difficulty of developing experimental assays further accentuated this opinion. This view was also supported as, in general, very low hit rates (or no hits) were obtained after high throughput screening (HTS) experiments (Arkin and Wells, 2004; Macarron et al., 2011). As such, modulators of PPIs were essentially proteins (e.g., antibodies) and peptides (or modified peptides), yet these

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molecules are still difficult (or impossible) to administrate orally (the preferred mode of administration for both the clinicians and the patients), may not reach intra-cellular targets and are usually very expensive to develop (the costs still do not go down as expected some years ago) (Kinch, 2014a, 2014b). Starting around the years 2000 and up to now, although this traditional view is still dominating text books and many recent reviews in drug discovery, numerous investigations suggest a new emerging view: PPIs can be modulated by biologics AND by LMW "drug-like" compounds (see for instance several reviews reported in 2014 (Arkin et al., 2014; Cierpicki and Grembecka, 2015; Falchi et al., 2014; Jin et al., 2014; Johnsson, 2014; Lage, 2014; Milroy et al., 2014; Nero et al., 2014; Petrey and Honig, 2014; Rognan, 2015; Villoutreix et al., 2014; Watkins and Arora, in press; Zhang et al., 2014a)). With regard to LMW inhibitors (the focus of this review), it is known that they can act via one or several mechanisms: for example orthosteric inhibitions (here understood as a small molecule binding at the interface) or allosteric inhibitions (the small molecule binds some distance away from the interface and induces structural and/or dynamic changes over the target) (Jin et al., 2014; Szilagyi et al., 2013; Wells and McClendon, 2007). We decided to comment here binding pockets (for orthosteric LMW compounds) at the protein interfaces and in silico methods that can help to predict these special regions of the molecular surface. We then discuss recent reports describing the design of "smart" compound libraries dedicated to the direct inhibition of protein–protein interactions (i.e., we do not discuss peptides, small chemical fragments and allosteric molecules, readers can find valuable information in several recent studies like for instance (Baaden and Marrink, 2013; Chen and Tou, 2013; Craik et al., 2013; Fayne, 2013; Kaspar and Reichert, 2013; Khan et al., 2013; London et al., 2013; Ma and Nussinov, 2014; Morley et al., 2013; Nussinov and Tsai, 2015; Petrey and Honig, 2014; Pevzner et al., 2014; Rognan, 2015; Schon et al., 2011; Szilagyi et al., 2013; Thevenet et al., 2015; van Westen et al., 2014; Wang et al., 2012)). In addition, while LMW inhibitors of PPIs are valuable for therapeutic interventions, stabilizers can obviously be of importance. Stabilizers are outside the scope of the current review but interested readers can for instance find information in two recent reports (Giordanetto et al., 2014; Zhang et al., 2014b).

2. Protein–protein interfaces and ligandable pockets

General principles about protein–protein interactions at the atomic levels (e.g., for transient complexes) have been proposed some 20 years ago (Bogan and Thorn, 1998; Janin et al., 2008; Janin and Chothia, 1990; Jones and Thornton, 1996; Nooren and Thornton, 2003) and have been recently revisited and/or reviewed (see for instance (Andreani and Guerois, 2014; Chen et al., 2013b; Cukuroglu et al., 2014; Higueruelo et al., 2013a; Jubb et al., 2012, 2015; Kastritis and Bonvin, 2013; Levy, 2010; Makley and Gestwicki, 2013; Smith and Gestwicki, 2012; Sudha et al., 2014; Surade and Blundell, 2012; Winter et al., 2012)). Analysis of several hundreds of transient PPIs gave a general trend about interactions and showed that the minimum protein surface that must be buried to form a functional complex is in the order of 900 Å^2 (about 500 Å^2 provided by each partner) with about 12 residues involved on each partner (Janin et al., 2008). A large majority of atoms in transient protein–protein interfaces are usually still accessible to the solvent. Relative to the accessible protein surface, the interfaces of such protein complexes are generally depleted in Glu, Asp and Lys and enriched in Met, Tyr and Trp (Janin et al., 2008). From these initial observations about protein–protein interactions, several additional structural, biochemical and computational investigations were performed and suggested, as seen below, that it should be possible to use LMW molecules to modulate such biological systems.

Protein interfaces can be divided into a core region and a rim region (Janin et al., 2008). The rim is made of residues in which none of the atoms are fully buried and has an amino acid composition close to the protein accessible surface, the rim regions by definition, are located around the core region. The core comprises buried atoms and about 55% of all interface residues. This core region is enriched in aromatic residues and to a lesser extent, in aliphatic residues but Arg residues can be present in both the core and the rim regions. Another region was also recently described, the so-called support zone that seems similar in composition to the protein interior (Levy, 2010). A related way to model protein recognition is based on the concept of hotspots. Hotspots in this context were first proposed after site directed mutagenesis (alanine scanning) experiments (see for instance (Clackson and Wells, 1995)). Analysis of these experiments suggested that the binding energy was not equally distributed among all amino acids present at the interfaces, some residues were directly responsible for the stabilization of the complex and conferred most of the binding energy. Indeed, in the investigation of the human growth hormone (HGH)/HGH receptor system by Clackson and Wells, 31 interface residues were mutated on the receptor, but only 11 mutants showed a significant loss of affinity for the hormone. Hotspot residues in the context of protein–protein interactions are typically defined as those amino acids contributing to about 2 kcal/mol to the total binding energy of the complex (Clackson and Wells, 1995). Hotspots tend to occur in clusters and are generally located on both protein partners, these regions can be in contact with each other in the complex and form a network of interactions that is often called hot region (Keskin et al., 2008). As mentioned above, hotspot regions can be identified experimentally using alanine scanning but a number of computational approaches can also be used, with as input, the amino acid sequence alone or the 3D structures (experimental or homology models) of each individual partner (e.g., by docking, see for instance a protein docking computation guided by site directed mutagenesis data which predicted an overall contact area between the two protein partners that is partially confirmed by X-ray crystallography (Autin et al., 2006; Pomowski et al., 2014)) or the macromolecular complex (Fernandez-Recio, 2011; Sudha et al., 2014; Thangudu et al., 2012; Villoutreix et al., 2014, 2013). Hotspot residues (among the most conserved amino acids) are generally located around the center of the interface, and are protected from bulk solvent by energetically less important residues forming a hydrophobic O-ring (Bogan and Thorn, 1998). This view is indeed very similar to the core–rim-support model reported above and support further the concept of direct LMW modulators. Tryptophan (21%), arginine (13.3%) and tyrosine (12.3%) are often hotspot residues (i.e., thus hotspot regions would tend to be hydrophobic and aromatic) whereas leucine, serine, threonine and valine tend to be disfavored (Bogan and Thorn, 1998; Fernandez-Recio, 2011; Moreira et al., 2013). The surface area of a region containing some hotspot residues is around 600 Å^2, a size that is compatible with a small molecule (NB: traditional protein–small ligand interaction ~300–1000 Å^2 and the solvent accessible surface of many small molecule drugs usually ranges from 150 to 500 Å^2), and much smaller than a typical protein–protein interface (e.g., 1000 to 2000 to well over 3000 Å^2) (Janin et al., 2008). Also, it is important to note that the term hotspot can have a different meaning in drug design and be considered as a site on a therapeutic target that has high propensity for (small) ligand binding. In such case, investigation of these regions can be performed experimentally with for instance investigation of fragment binding using NMR or X-ray approaches (Hajduk et al., 2005a, 2005b). Another important observation suggesting that small compounds binding at

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