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Peptidomimetics: A Synthetic Tool for Inhibiting Protein–Protein Interactions in Cancer

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Abstract
Protein–protein interactions (PPI) are vital in modulating biochemical pathways in many biological processes. Inhibiting PPI is a tremendously important diagnostic and therapeutic strategy in averting pathophysiological cues and disease progression. Targeting PPI as a smart drug discovery tool has been largely overlooked over the years due to their highly dynamic and expansive interfacial areas. However in recent years, researchers have developed new technologies that have the potential to move this approach up the technology development curve and enable the regular discovery of PPI-focused smart drugs. Few drugs are already on the market and some potential drug-like candidates are in clinical trials. In this study we review the application of peptidomimetics as a valuable tool in PPI inhibition in cancer. First, we describe PPI and the general properties of the PPI interface. Next, we discuss the classification of peptidomimetics. Lastly, we focus on the application of peptidomimetics on targeted PPI in cancer pathways.

Keywords Protein–protein interactions · Peptidomimetics · Proteomimetics · Mimicries · Cancer

Introduction

Protein–protein interactions (PPI) are well recognised mediators in biological processes and are vitally important in the progression of many disease states (Du et al. 2018; Robertson and Spring 2018; Zhang et al. 2018). About 650,000 disease-relevant PPI have been so far reported in the human interactome (Bonetta 2010; Gonzalez and Kann 2012). Of which 98% of these interactions remain elusive and underexplored. Over the years PPI were regarded as prototypically "intractable" and "undruggable" due to their highly dynamic and expansive interfacial areas (flat, featureless and relatively large) (Robertson and Spring 2018; Zhang et al. 2018). However due to the improving technology expertise, PPI have now come to the spotlight as significant drug development targets. The PPI-focused drug technology presents an emerging field for drug discovery. This review will focus on the application of synthetic mimicries to target PPI in cancer diagnostics and therapeutics.

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General Properties of PPI

PPI occur over a relatively large protein contact surface area of approximately 1000 to 4000 Å^2. The area is relatively larger as compared to the average contact area needed for inhibition by small molecule binding (300 to 1000 Å^2) (Jones and Thornton 1996; Conte et al. 1999). PPI contact surface area harbor certain hydrophobic regions called "hot spots". Hot spots regions contribute to the binding affinity and help to hold the two interacting proteins together (Clackson and Wells 1995; Jochim and Arora 2010). They are rich in Tyr, Trp, Leu, Ile, Phe and Arg. The amino acids Trp, Arg and Tyr are hydrophobic and form hydrogen bonds which contribute to π-interactions and the binding free energy (Bogan and Thorn 1998). In addition to that, systematic alanine scanning mutagenesis has revealed that the substitution of an amino acid residue by alanine in these hot spot regions lowers the binding affinity by at least 2 kcal/mol (Bogan and Thorn 1998).

Hot spots regions consist of two segments, a core region and a rim region (shown in Fig. 1). The rim region has an amino acid composition similar to that of the rest of the protein contact surface area. The core region consists of aromatic residues (Chakrabarti and Janin 2002; DeLano 2002; Chene 2006).

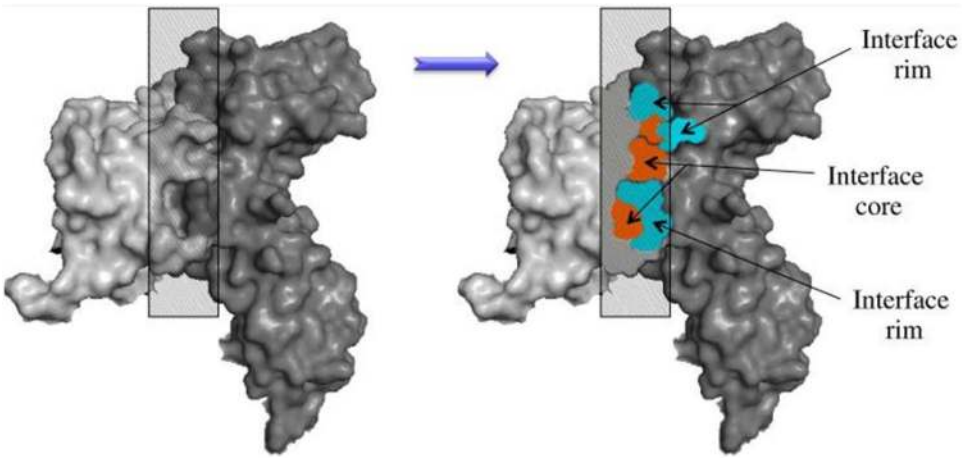

Fig. 1 Schematic diagram of core and rim interface regions. Highlighted is a cross-sectional view of a protein–protein interface. Interacting proteins are presented in light and dark gray, respectively. The interface core is presented in orange and the rim is presented in blue (David and Sternberg 2015). (Color figure online)

Many hot spots core regions are associated with the α-helix, β-sheet and β-turn protein secondary structure motifs. And of these the α-helix has been on the spotlight because they comprise more than 50% of all secondary structures in protein complexes. The α-helix actively binds into the grooves of binding partners and modulates the functioning of a large number of therapeutically relevant PPI. Of which more than 50% bind to one face of the helix (Jochim and Arora 2010; Raj et al. 2013). Peptidomimetics that mimic more than one face of an α-helix have also been reported (Lanning and Fletcher 2015; Robertson and Spring 2018). A majority of these helices contain hot spot residues on one helical face while the rest project critical functionality residues for recognition.

Helix mimicry has become a promising avenue for discovery of potent PPI inhibitors. They have been classified into two categories vizly topographical helix mimics and stabilized helices. Topographical helix mimics contain a non-peptidic scaffold which mimic more than one face of the helix to orient protein-like side chains into proper vectors and mimic the projection of side chains on α-helices. This kind of helix mimicry generally harbors low molecular weight compounds that mimic a single helix face (Bullock et al. 2011; Azzarito et al. 2013; Grossmann et al. 2015). Other than the first developed aromatic scaffold many different topographical helix mimetic scaffolds have been described to afford compounds that are less hydrophobic than the original designs (Orner et al. 2001). And these can target more than one face of a helix (Bullock et al. 2011; Lao et al. 2014a, b; Lanning and Fletcher 2015).

Stabilized helices (foldamers) often mimic 2 to 3 faces of the helix depending on the stabilization technique (Henchey et al. 2008). The side chain staples consist of lactams, thiols, triazole linkages and hydrocarbons which allows two faces for recognition and one for stabilization (Bullock et al. 2011; Azzarito et al. 2013; Grossmann et al. 2015). Both hydrogen bond surrogate (HBS) helices with peptide backbone stabilisation as well as foldamers comprised of judiciously placed α- and β-amino acids mimic proteins that require three faces for recognition (Bullock et al. 2011; Sawada and Gellman 2011; Azzarito et al. 2013; Grossmann et al. 2015). Most of the these dual faced helix peptidomimetics have been developed from single faced bis-benzamide scaffolds (Marimganti et al. 2009; Thompson et al. 2012), an amphiphilic α-helix mimetic based on a benzoylurea scaffold (Thompson and Hamilton 2012) and two-faced amphipathic α-helix mimetics based on a triazine-piperazine-triazine scaffold (Lee et al. 2016). These mimics have been successful in modulating PPI. Recent advances in helix mimicry have been extensively reviewed, and we refer the reader to these excellent reports (Azzarito et al. 2013; Milroy et al. 2014). Other drug-like proteo-mimetics based on a purine scaffold have also been reported (Lanning et al. 2015).

Despite the fundamental role of strands and sheets at protein–protein interfaces, application of β-strand or β-sheet mimics as modulators of PPI is limited. Strand designs are challenging because mimics with appropriately placed hydrogen-bonding groups tend to aggregate (Spiegel et al. 2012). An analysis of the PDB for β-strands found at PPI interfaces reveals that β-strands interact with protein partners in multiple ways: as a lone strand or a sheet, side chain recognition, and with or without engagement of backbone hydrogen bonding (Watkins and Arora 2014). A number of scaffolds for each type of these structures have been designed (Angelo and Arora 2005; Robinson 2008).

The PPI hot spots regions have been on the spotlight as potential drug targets since majority of the binding energy that contributes to interactions localises in these areas (Du et al. 2018; Robertson and Spring 2018; Bogan and Thorn 1998). The disruption of PPI targeting hot spots regions using small molecule or peptide inhibitors both diagnostic and therapeutic significance (Robertson and Spring 2018). It stirs high expectations for the development of smart drugs. Such an observation has successfully challenged the

traditional thought that PPI are "intractable and undruggable". New small molecule or peptide PPI inhibitors are already on the market and some are still in clinical trials (Whitby and Boger 2012; Grossmann et al. 2015; Robertson and Spring 2018). Several strategies and new techniques which aid in the discovery of new PPI and facilitate the discovery of small molecules and peptides inhibitors exist. And these include phage display (Ting et al. 2018), high throughput screening (Taylor et al. 2018), computational studies (Melagraki et al. 2017), crosslinking (Suchanek et al. 2005) and structural based design techniques (for an insightful review see Meireles and Mustata 2011).

Classification of Peptidomimetics

The efficient mimicking of peptides in their bioactive conformation is a long-standing goal in the design of PPI inhibitors. Advances in PPI-focused technology have facilitated a display of side chain functionalities in analogy to peptide secondary structures, yielding molecules that are generally referred to as peptidomimetics (Grossmann et al. 2015). Peptidomimetics are compounds whose essential elements (pharmacophore) mimic a natural peptide or protein in 3D space and which retain the ability to interact with the biological target and produce the same biological effect (Vagna et al. 2009). Over the years peptidomimetics have been traditionally divided into three subtypes; Types I to III. Type I mimetics were defined as short peptides which mimic the secondary structure landscape of the antecedent peptide with minor alterations to the peptide sequence. Type II mimetics were defined as non-peptidic functional molecules based on a scaffold that does not mimic the peptide secondary structure. Type III mimetics were also defined as non-peptidic molecules which match the spatial topology of key interaction motifs of the antecedent peptide (Ripka and Rich 1998; Azzarito 2013; Grossmann et al. 2015; Robertson and Spring 2018). However, these categories have been recently revised and subdivided into four different classes: Classes A–D, where Class A mimetics are the most identical to the antecedent peptide and Class D mimetics show the least similarities (Grossmann et al. 2015).

Class A mimetics, like Type I mimetics, are peptides with minimal alterations to the peptide side chains and backbone. They consist mainly of the antecedent peptide amino acid sequence with a limited number of modified amino acids incorporated to stabilize the bioactive conformation. The backbone and side chains align closely with the bioactive conformation of the antecedent peptide (Grossmann et al. 2015). Class B mimetics are modified class A mimetics with different unnatural amino acids, isolated small-molecule building blocks or major backbone alterations. While still peptidic in nature, Class B mimetics include much more dramatic backbone and side chain alterations (e.g., peptoids, β-peptides and α/β-mixed peptides). Foldamers (β- and α/β-peptides as well as peptoids) with side chains aligning topologically identical to the antecedent peptide also form part of this class (Grossmann et al. 2015).

Class C mimetics consists of highly modified structures that completely replace the entire peptide backbone with small molecule character (Grossmann et al. 2015; Robertson and Spring 2018). The central scaffold displays the substituents in comparison to the orientation of the key residues (for example hot spots) in the bioactive conformation of the antecedent peptide (Grossmann et al. 2015). The replacement of the entire peptide backbone result in molecules with improved oral bio-availability and pharmacokinetic properties. The resulting bioactive compounds are more likely to follow Lipinski's rule of five, thus rendering them promising candidates in drug development (Spiegel et al. 2012).

Class D mimetics are small molecule drugs used in the classical medicinal chemistry that mimic the mode of action of a bioactive peptide without a direct link to its side chain functionalities. The small molecule drugs bind either into the active site of a protein or at an allosteric position. However as mentioned earlier on, PPI are large and remain a challenging to target with small molecules. Nevertheless, few small molecule PPI inhibitors have been successfully developed on a "one compound at a time'' basis (Bunnage 2011; Stockwell 2011) through affinity optimization of class C molecules and screenings of compound/virtual libraries (Grossmann et al. 2015). Small molecule drugs are already on the market and some are in clinical trials (Grossmann et al. 2015).

Targeted Protein–Protein Interactions

Peptidomimetics are designed for a broad range of targets in cancer diagnostics and therapeutics. Their applicability has been tested on different protein model systems that include apoptosis regulators, transmembrane receptors, small GTPases and transcriptional regulators. Here we will discuss the application of class A–C mimetics for these cancer model systems. This section does not present all the examples of peptidomimetics comprehensively, but focuses on major target classes and recent contributions.

Apoptosis Regulation

MDM2 and MDMX

In response to cellular stress the transcription factor p53 mediates the expression of genes involved in protective processes such as DNA repair, cell cycle arrest and apoptosis (Vogelstein et al. 2000; Chene 2003). Binding of MDM2

and MDMX (also known as MDM4 and HDM4/ HDMX) to the N-terminal transactivation domain of p53 blocks the normative function of this so called "guardian of the genome". MDM2 and MDMX downregulate the tumor suppressor p53 either by acting as a direct antagonist to p53 or by mediating the ubiquitylation of p53 leading to its degradation in proteasome-dependent manner (Kubbutat et al. 1997; Toledo et al. 2006). An upregulation of MDM2 and MDMX has been detected in different types of cancers and the interactions between these proteins and p53 have become prime targets for anticancer strategies. Crystal structures of the p53-MDM2 and p53–MDMX complexes reveal an α-helical conformation of the p53 interaction domain when bound to MDM2 (Fig. 2a) (Popowicz et al. 2007). The p53 hot-spot comprise of the amino acid residues Phe19, Trp23 and Leu26 (Kussie et al. 1996). This structural information together with the crystallographic data have been vital as the starting point for a rational design of the corresponding peptidomimetics.

For some peptidomimetics, helical peptides derived from phage-display selections served as alternative starting points. For example pDi (Phan et al. 2010) and PMI (Pazgier et al. 2009). These peptides exhibit dual inhibitory effects for both the p53–MDM2 and p53–MDMX complexes. A commendable feature for efficient anticancer activity (Phan et al. 2010; Pazgier et al. 2009). For other peptidomimetics, mirror-image phage-display (MIPD) techniques coupled with native chemical ligation have provided proteolytically more-resistant D-peptide inhibitors of the p53–MDM2 interaction. However, these peptides do not feature sufficient cell permeability (Liu et al. 2010a, b, b; Zhan et al. 2012). Finally, though mRNA display has facilitated the selection of larger libraries of peptides, the proteolytic instability and/or poor cellular uptake of these peptides remain major limitations of these approaches (Shiheido et al. 2011). A variety of peptidomimetics were designed based on these peptide binders.

A modified octapeptide comprising four unnatural amino acids is an early example of a class A peptidomimetic that binds HDM2 in vitro with nanomolar affinities (Bottger et al. 1996; Garca-Echeverra et al. 2000; Sakurai et al. 2006). This peptide promotes apoptosis by mediating the accumulation of p53 in cancer cells (Chene et al. 2000). Poor cellular uptake and high proteolytic instability remain the drawbacks of this peptide. Later, Robinson and co-workers grafted the crucial residues of the p53 helix onto a cyclic β-hairpin and stabilized the β-sheet structure using the head-to-tail macrocyclization and the d-Pro-l-Pro (p-P) turn mimetic. The mimetic displayed good affinity and binds HDM2 at the p53 binding site (Fasan et al. 2004). Sequence optimization by the introduction of unnatural amino acids yielded class B mimetics with improved affinities (Fasan et al. 2006). Remarkably, this innovative approach impressively illustrates the interchangeability of secondary structures and represents one of the few examples of a stabilized β-sheet structure used as a PPI inhibitor.

The generation of class A helix mimetics for MDM2 and MDMX using the peptide-stapling technique and thiol- and triazole-based cross-links observed a prominent increase of

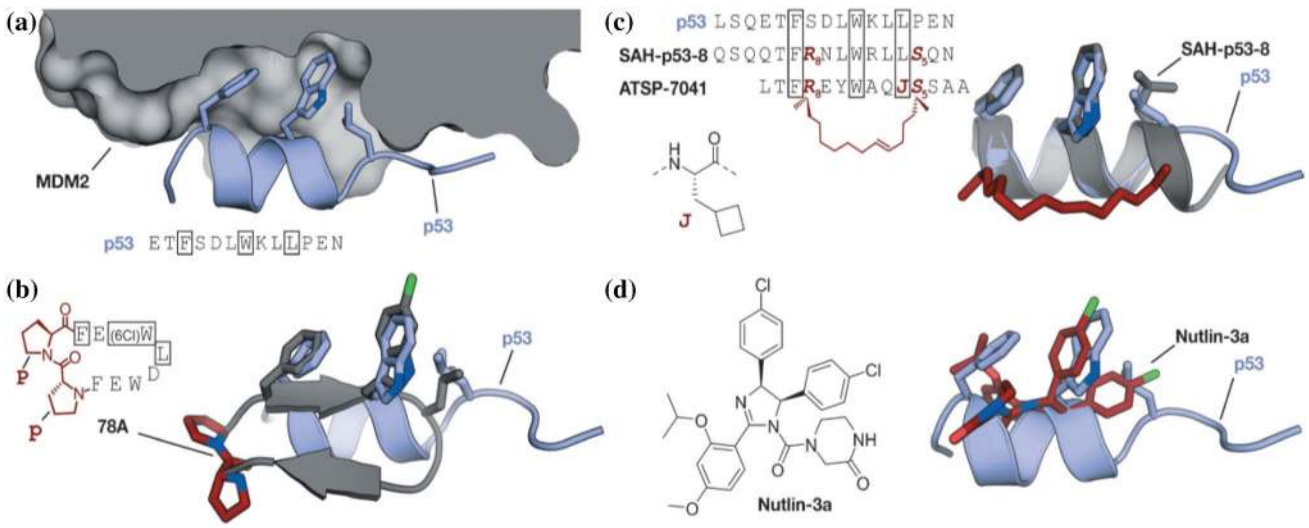

Fig. 2 MDM2–p53 interaction: **a** Crystal structures of MDM2 (gray) with the transactivation domain of p53 (blue, PDB 1YCR) (Kussie et al. 1996). **b** Superimposed crystal structures of p53 (blue, PDB 1YCR) and cyclic b-hairpin peptide 78A (gray/red, PDB 2AXI). The d-Pro-l-Pro (p-P) crosslink is highlighted in red (Fasan et al. 2004). **c** Sequences of stapled peptides (left). Superimposed crystal structures (right) of p53 (blue, PDB 1YCR) and SAHp53-8 (gray/red, PDB 3V3B). The cross-link is highlighted in red (side chains of amino acids in boxes are shown explicitly in the crystal structures) (Baek et al. 2012). **d** Superimposed crystal structures of p53 (blue, PDB 1YCR) and Nutlin-3a (red, PDB 4HG7) (Anil et al. 2013) All superimposed structures were obtained from structures of complexes with MDM2 or MDMX. (Color figure online)

cellular uptake, thus alleviating the challenges regarding cellular permeability and proteolytic instability (Madden et al. 2011). The incorporation of a bisaryl cross-link at positions i and i + 7 of the pDi sequence enhances the α-helicity and bioactivity of the class A mimetics. A cross-linking based on addition of photo induced 1, 3-dipolar cyclo produced high affinities peptides for MDM2 and MDMX. The peptides displayed dual inhibitory activity and improved cellular uptake after the incorporation of positively charged amino acids (Madden et al. 2011). A D,L-dicysteine-linked 6,6′bis(bromomethyl)-3 3′-bipyridine (Bpy) crosslink observed additional MDMX contacts allowing more affine binders (Muppidi et al. 2011). A double triazole tethering approach based on a single p53-derived sequence enables the synthesis of several cross-linked peptides using a set of modified linkers. The resulting cross-linked peptides observed improved proteolytic stability and affinities. And the subsequent incorporation of Arg moieties in the linker resulted in cell penetrating peptides, thus eliminating the need for additional sequence variations (Lau et al. 2014a, b). Metallopeptides and HBS stabilized helices also produced MDM2 affine binders (Henchey et al. 2010a, b; Zaykov and Ball 2011).

Stapled α-helical p53-derived peptides (SAHp53, Fig. 2c) with i and i + 7 cross-linking positions showed increased α-helicity and improved binding affinity for MDM2. The peptides observed enhanced proteolytic stability as compared to the wild-type p53 peptide. Neutral and positively charged stapled peptides following the substitution of negatively charged amino acids induced apoptosis, cell permeability and suppressed tumor growth features in vivo (Bernal et al. 2007, 2010). The direct involvement of the hydrocarbon cross-link in MDM2 binding following the incorporation of a staple explains the increase in the binding affinity (Baek et al. 2012). Furthermore, Aileron Therapeutics reported another series of stapled peptides based on phage-display-derived peptide pDi which include ATSP-7041-peptides and another candidate currently in clinical trials (Chang et al. 2013). The ATSP-7041-peptides observed improved pharmacokinetic properties with high specificity and affinity for both MDMX and MDM2. They bind to mutated forms of MDM2 that are inaccessible for small-molecule p53–MDM2 inhibitors of the Nutlin family (Fig. 2c) (Brown et al. 2013; Wei et al. 2013).

The development of class B mimetics using foldamers as validated scaffolds proved useful for the generation of p53–MDM2 inhibitors. The p53-MDM2 interactions active residues (Phe19, Trp23, and Leu26) were integrated into the recognition face of a 14-helix β-peptide. The helical structure was coerced using the electrostatic macrodipole strategy to proffer micromolar binders. (Kritzer et al. 2005). Several techniques to synthesize and evaluate β-peptides targeting MDM2 have been reported however their relatively poor binding affinities suggest that the 14-helix may not reproduce the p53–MDM2 interaction suitably (Murray et al. 2005). Non-natural side chains were introduced into these β-peptides and moderate improvements were observed in the biological activity (Michel et al. 2009). The cellular uptake of these β-peptides was increased by conjugation to cell-penetrating peptides (Hintersteiner et al. 2009) and by the introduction of side chain to side chain cross-links or β-homoarginines (Bautista et al. 2010). HBS α/β-peptides harboring the ααβ pattern and α-amino acids hot spots yielded affine MDM2 binders with improved conformational rigidity (Patgiri et al. 2012). And rationally designed achiral peptoids with high conformational flexibility observed moderate inhibitory activity of the p53–MDM2 complex (Hara et al. 2006).

Class C structural mimetics were used to inhibit the interaction between p53 and MDM2. Hamilton and group developed a series of trisubstituted terphenyls scaffolds (3,2′,2″-terphenyl compounds) that mimic an α-helix face in order to target PPI. The terphenyls' aryl cores adopt a wobbled dihedral conformation (59.1° and 120.7°) to mimic the helix residues (i, i + 3, i + 4 and i + 7) through the ortho positions of the scaffold (Orner et al. 2001). The Hamilton group also developed other extended α-helix scaffolds such as terephthalamides (Yin et al. 2005), 4,4′-dicarboxamines (Rodriguez et al. 2009), 5-6-5-imidazole-phenylthiazoles (Cummings et al. 2009), trispyridylamines (Ernst et al. 2003) and enaminones (Adler et al. 2012). Sterically enforced terphenyls (27) with large aromatic substituents at the central position and aliphatic groups at the termini were used to mimic the binding epitope of p53. These mimetics proved to be active in cell-based assays and exhibit highest affinity for MDM2 Notably, these compounds also and the best selectivity when binding between MMD2 and BCL-2 family proteins (Yin et al. 2005; Chen et al. 2005). Wilson and group described a solid-phase synthesis for an α-helix mimetic with N-alkylated oligobenzamides as well as hybrids which act as inhibitors of p53-HDM2 complex in vitro (Campbell et al. 2010; Long et al. 2013; Barnard et al. 2014, 2015; Azzarito et al. 2015). Notably, the same group reported an orthogonal chemical functionalisation of non-peptidic helix mimetics using a copper-mediated 'click' technique (Barnard et al. 2014).

Spiroligomers disrupted the p53–HDM2 complex and trigger HDM2 accumulation in cells assumably by preventing proteolytic degradation (Brown et al. 2012). Covalently constrained OHMs were also able to bind MDM2 in vitro (Lao et al. 2014a, b). Furthermore, cell permeable pyrrolopyrimidines were also utilised to disrupt both the p53–MDM2 and the p53–MDMX complexes, thereby facilitating p53-dependent apoptosis in cultured cancer cells (Lee et al. 2011). The other groups have developed scaffolds to mimic amino acid side chains

on α-helices. And these include phenyl-piperazine-triazines (Moon et al. 2014), pyrazines (Van Mileghem et al. 2017), 2-O-alkylated picolinamides (Yap et al. 2012), 3-O-alkylated oligobenzamides (Plante et al. 2009; Prabhakaran et al. 2013) and pyridazines (Biros et al. 2007; Londregan et al. 2016). Although less formidable, the hydrogen-bond-guided mimetics also act as inhibitors of p53-HDM2 complex in vitro (Barnard et al. 2015).

Class D peptidomimetics are small molecule p53–MDM2 inhibitors developed from lead structures obtained from high-throughput screening of synthetic chemical libraries (Wade et al. 2013). The benzodiazapinediones (Johnson and Johnson Pharmaceuticals) along with the Nutlin family of small molecule compounds (Hoffmann-La Roche) inhibit the p53/mDM2 PPI in the initiation of cancer (Vassilev et al. 2004; Grasberger et al. 2005). Nutlins bind to MDM2 through the p53 binding site and, induce cell-cycle arrest and apoptosis in a p53-dependent manner. They are highly potent and selective compounds. Their rigid scaffold enables efficient mimicking of p53 binding (Fig. 2d). Nutlins are also known to inhibit tumor growth in human xenograft models (Vassilev et al. 2004; Grasberger et al. 2005).

BCL-2 Family Proteins

BCL-2 family proteins play a key role in apoptosis regulation. Members of the BCL-2 family participate in a complex network of PPI in either pro-apoptotic manner (e.g. BAK, BAX, BID, BIM, NOXA, HRK, PUMA, BAD) or anti-apoptotic manner (e.g. BCL-xL, BCL-2, BCL-w, MCL-1, A1) (Youle and Strasser 2008; Moldoveanu et al. 2014). The interactions between members of the two classes of proteins are directed in the sensing of cellular stress thereby modulating induced cell death by apoptosis. Pro-apoptotic proteins are classified into three, namely; effectors, direct activators and de-repressors/sensitizers. Anti-apoptotic proteins, just like the effectors (e.g. BAK, BAX), have four BCL-2 homology domains (BH1–BH4) that harbors a shared folding motif which creates a hydrophobic groove called the BC groove. The BC groove mediates the binding to an α-helical stretch of BH3-only proteins, including direct activators (BID, BIM, and PUMA) and de-repressors/sensitizers (BAD, NOXA and HRK). This binding interaction involves highly conserved hydrophobic and polar residues that closely interact with the BC groove (Fig. 3a). The specificity required for the interactions within the BCL-2 family members is precisely orchestrated through the variations in the remaining BH3 sequence (Youle and Strasser 2008; Moldoveanu et al. 2014).

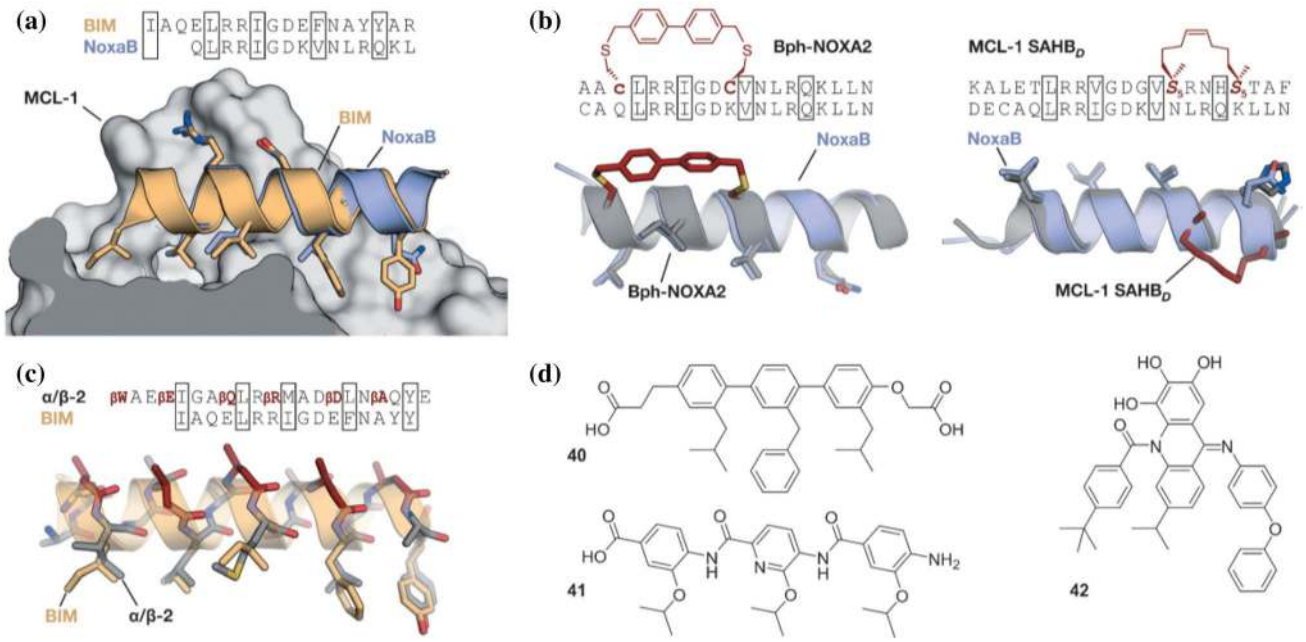

Fig. 3 PPI involving proteins of the BCL-2 family: **a** Superimposed crystal structures of BIM (orange, PDB 2L9) and NoxaB (blue, PDB2NLA) bound to MCL-1 (Czabotar et al. 2007). **b** Superimposed crystal structures of NoxaB (blue, PDB 2NLA) with (left) bisaryl cross-linked peptide Bph-Noxa2 (gray, PDB 4G35, c = d-cysteine) (Muppidi et al. 2012) and (right) stapled peptide MCL-1 SAHBD (gray, PDB 3MK8) (Stewart et al. 2010). Cross-links are highlighted in red (side chains of amino acids in boxes are shown explicitly). **c** Superimposed crystal structures of BIM (orange, PDB 2L9) and α/β-peptide a/b-2 (gray/red, PDB 4BPI) (Smith et al. 2013). β-Amino acids are highlighted in red (βE, βQ, βR, βD, and βA are β3-amino acids that correspond to E, Q, R, D, and A, respectively). **d** Structural mimetics of helical MCL-1 binding peptides (Li et al. 2014). (Color figure online)

Proteins of the BCL-2 family are considered high-interest targets in the field of drug development and their modulation has been widely addressed using different strategies (Moldoveanu et al. 2014). The relevant PPI between BCL-2 family members have been targeted for inhibition using class A peptidomimetics. For example peptides stabilized by thiol-based cross-links, hydrocarbon-stapling approaches and hydrogen-bond surrogates. Class B mimetics such as α/β-peptides and class C mimetics such as sterically constrained and hydrogen-bond-guided structural mimetics have been used as inhibitors of these interactions (Grossmann et al. 2015).

The cross-linking of D-Cys(c) and L-Cys using a bisaryl moiety at positions i and i + 7 stabilized the NOXA derived peptide and provided a selective binder of MCL-1. The NOXA derived peptide-MCL-1 complex (Fig. 3b) observed the presence of edge-to-face π-π interactions between the MCL-1 and the aryl cross-link (Muppidi et al. 2012). Utilising this structure as a foundation for further modifications and to improve the cellular activity, the hydrophobicity was increased by the introduction of backbone N-methylation and replacing non-interacting charged amino acids with Ala. A number of "stabilized a-helices of BCL-2 domains" (SAHBs) have been produced by using the peptide-stapling technique. The incorporation of the hydrocarbon cross-link increased the resistance to proteolysis, cellular uptake and helicity of these BH3-derived peptides. However, not all of these peptides were efficient enough to inhibit the PPI between BCL-2 family members. In leukemia cells, the SAHB from the BH3 domain of the BID protein proved to induce apoptosis in vitro and in vivo (Walensky et al. 2004). The MCL-1-derived SAHB inhibits the BAK-MCL-1 complex formation and subsequently induce cell death by caspase-dependent apoptosis. The direct participation of the staple in target binding is proved in the complex of the crystal structure of this stapled peptide with MCL-1 (Fig. 3b). However synthesis, testing and screening of several stapled peptides was required to select efficient PPI inhibitors (Stewart et al. 2010). SAHB peptides also provide valuable insights into the molecular regulation of proteins of the BCL-2 family (Gavathiotis et al. 2008).

Class B peptidomimetics which include heterogeneous (e.g. α/β peptides) and chimeric foldamers (e.g. α/β + α) provided the desired inhibitors to disrupt PPI between proteins of the BCL-2 family. Pure β-peptides did not inhibit these PPI. The αααβ pattern was used to mimic the BIM BH3 helix and provide binders of BCL-xL and MCL-1 proteins (Boersma et al. 2012). The ααβαααβ backbone was used to a PUMA BH3 derived peptide to obtain foldamers with high binding affinity for the same proteins (Horne and Gellman 2008). Surprisingly the selectivity for the targets in both cases is highly dependent on the number and position of α-to-β3 replacements.

According to Sadowsky et al. (2007), a chimeric peptide (α/β + α) with a 9-mer α/β-peptide at the N-terminus and a 6-mer α-peptide at the C-terminus proved more potent than the natural BAK 16-mer. The chimeric peptide efficiently inhibited formation of the BAK-BCL-xL complex by binding at the same position targeted by the natural peptide (Sadowsky et al. 2007). The N-terminal fragment features an equivalent ratio of α- and β amino acids and projects a new helical disposition called the 14/15 helix (Hayen et al. 2004). The proteolytic stability and selectivity within the BCL-2 family members increased and a subsequent release of cytochrome c was observed in cell lysates. The optimization provided foldamers with increased proteolytic stability but insignificant cellular uptake (Sadowsky et al. 2007).

Using terphenyls as sample models of class C peptidomimetics to mimic the location of hot-spot residues of helical BH3 peptides (Yin et al. 2005), a number of terphenyls inhibited the interaction of BCL-2, BCL-xL and MCL-1 with either BAX or BAK, or with BAD or BIM in cultured cells. This inhibition triggers cell induced death by apoptosis in a caspase-dependent manner (Kazi et al. 2011). A number of heterocyclic scaffolds containing pyridazine also inhibited the the BAK–BCL-xL complex formation in vitro (Biros et al. 2007). Biphenyls, benzoylureas, and trispyridylamides, derived from hydrogen-bond-guided scaffolds were also reported to inhibit the formation of BAK–BCL-xL complex in vitro (Rodriguez et al. 2009). The oligoamide scaffolds made from different combinatorial ratios of pyridine and phenyl rings observed that the molecules containing a higher percentage of phenyl rings inhibits the BAK–BCL-xL complex more efficiently because of their increased hydrophobicity and flexibility.

However, this trend was not observed in cell-based assays probably because of potential off-target effects and differences in cell permeability (Yap et al. 2012). The scaffold with one pyridine ring and two phenyl rings inhibits the formation of BAK–BCL-xL and BAK–MCL-1 complexes thereby mediating cell induced death by apoptosis in cancer cell lines. Noteworthy, the compound also exhibits inhibitory effects on tumor growth in mouse models (Cao et al. 2013). In human cell culture, terephthalamides also disrupted the BAK–BCL-xL complex formation (Rodriguez et al. 2009). Computational studies and NMR spectroscopy observed binding to the same cleft as the BAK BH3 peptide. Finally, BIM–BCL-2 and BIM–MCL-1 PPI were addressed using cross-acridine scaffolds (Li et al. 2014).

Class D mimetics of small molecule have also been used to inhibit the same interactions. ABT-236 and ABT-737 are examples of small molecule Class D peptidomimetic which inhibit the Bcl-xL/Bak PPI in the apoptosis pathway (Lee et al. 2007, Tse et al. 2008). ABT-263 binds with high affinity to anti-apoptotic proteins BCL-2 and BCL-XL and with lower affinity to BCL-w (Tse et al. 2008). ABT-263

has demonstrated impressive single agent activity against lymphoid malignancies and small cell lung cancer (SCLC). Phase I/II trials report that ABT-263 was either effective as a single agent (Roberts et al. 2012) or in combination with other drugs in refractory chronic lymphocytic leukaemia (CLL) (Kipps et al. 2017). ABT-737 binds to Bcl-2/Bcl-xL (but not Mcl-1) with high affinity and disrupts their interaction with pro-apoptotic Bax/Bak, thus enhancing apoptosis (Parrondo et al. 2013).

Inactivating the anti-apoptotic BCL-2 family proteins with small molecule BH3 mimetic drugs is one potential 'push' as displacing the active but sequestered pro-apoptotic proteins results in mitochondrial outer membrane permeabilization (Leber et al. 2010; Del Gaizo Moore and Letai 2013; Shamas-Din et al. 2013). Small molecule BH3 mimetics, like ABT-263 (Navitoclax) and ABT-199 (Venetoclax), mimic the binding of BH3 peptides to the hydrophobic BH3 domain-binding groove of anti-apoptotic proteins and thus displace BH3-only proteins and active BAX/BAK from anti-apoptotic proteins (Tse et al. 2008; Souers et al. 2013). By binding to the BH3 domain-binding grooves of anti-apoptotic proteins, ABT-263 inhibits BCL-2, BCL-XL and BCL-W, whereas ABT-199 only inhibits BCL-2. ABT-199 is approved for use in chronic lymphocytic leukemia and both drugs are being used in dozens of clinical trials as single agents and in combination with other therapies (Delbridge et al. 2016). Other BH3 mimetics are emerging (Ashkenazi et al. 2017). They include another BCL-2-specific inhibitor (Servier's S55746); the BCL-X_L-specific WEHI-539 (Lessene et al. 2013) and its more potent derivatives A-1155463 and A-1331852 (Leverson et al. 2015).

Some cancers depend primarily on MCL-1 for survival (Grabow et al. 2014; Zhang et al. 2011; Xiang et al. 2010) and others acquire resistance to drugs that target BCL-2/BCL-XL/BCL-W by upregulating MCL-1 (Adams and Cory 2018). The small molecule MCL-1 inhibitor, S63845 shows promise as a therapeutic (Kotschy et al. 2016). S63845 was efficacious in killing multiple cancer-derived cell lines in vitro and had potent anti-tumor activity in pre-clinical mouse models of hematological malignancies in vivo while sparing normal tissues. Another cancer treatment strategy would be small molecule activation of BAX and/or BAK. The BAK BH3 helix was stabilized using the hydrogen-bond surrogates thereby increasing the helicity and proteolysis resistance. However, it resulted in the loss of binding affinity as compared to the wild-type peptide. A subsequent sequence optimization provided a peptide with improved affinity (Adams and Cory 2018).

Transmembrane Receptors

Transmembrane receptors are vital in signaling processes that connect extracellular events with intracellular responses. Their impaired functioning is implicated with numerous pathogenic states that include cancer (Yarden and Pines 2012). Receptors are activated by the binding of effectors (protein ligands, peptide hormones and small molecules) and may at times require additional cofactors, highlighting the complexity of the signaling networks. Over the years several PPI inhibitors that are recognized by receptors have been designed from peptide sequences. Examples of such PPI inhibitors include α/β-peptides that target the receptor binding site of vascular endothelial growth factor (Haase et al. 2012) and helical β peptides that inhibit the interaction between the high-density lipoprotein and scavenger receptor B (Werder et al. 1999).

A hyperactivity of epidermal growth factor receptor (EGFR) tyrosine kinase is implicated in the tumorigenesis and tumor development different types of cancer (Yarden and Pines 2012). PPI inhibitors of EGFR target the interaction between EGFR and cofactor Grb2 (growth factor receptor bound protein 2) (Furet et al. 1998), the intracellular adenosine triphosphate binding site (Yarden and Pines 2012) or the extracellular receptor binding site (Li et al. 2005). The dimerization mediated by a coiled coil structure is implicated as a vital step for the receptor activity (Jura et al. 2009). And to inhibit this dimerization, peptides which proved active in cell-based assays were developed. These include all-hydrocarbon-stapled peptides and corresponding peptides with an open cross-link bearing the two olefin side chains (Walensky and Bird 2014; Grossmann et al. 2015). Hanold and coworkers also introduced a non-helical, triazolyl-bridged peptide targeting EGFR dimerization (Hanold et al. 2015).

G-protein coupled receptors (GPCR) are a large family of transmembrane receptors that are activated by a number of different ligands which include but not limited to peptide hormones. Several inhibitors of peptide ligand/receptor interactions have been developed and have been extensively reviewed (Ruiz-Gomez et al. 2010). The similarity observed in the interactions between receptors and peptides or proteins suggests that the application of PPI inhibitor concept to interfere with peptide–receptor interactions may also be a potential drug target. The incorporation of benzodiazepines into Angiotensin II and the use of a glucose scaffold presenting Somatostatin side chains in a β-turn conformation are good examples. The final peptidomimetics observed affinity for AT1 and AT2 receptors (Gallo-Payet et al. 2011) and a potent agonist of the Somatostatin receptor (Hirschmann et al. 1993), respectively. The trans-pyrollidine-3,4-dicarboxamide scaffold led to high-affinity ligands for human opioid receptors.

The glucose and the trans-pyrollidine-3,4-dicarboxamide highlighted above are both class C structural-turn mimetics (Whitby et al. 2011). GPCR protein effectors are also known to interact with agouti (ASP) and agouti-related protein

(AGRP) probably because of the C-terminal binding site that reveals a cysteine knot presenting three crucial residues in a turn structure as observed by the NMR (McNulty et al. 2001). The isolated binding motif can be chemically stabilized by addition of a lactam bridge on the position initially occupied by a disulfide bridge (Thirumoorthy et al. 2001). Other GPCRs recognize binding partners through their helical interaction domains. Helical α/β-peptides inhibit the interaction between parathyroid hormone and the parathyroid hormone-related peptide receptor (Cheloha et al. 2014), whereas hydro carbon stapled peptides with enhanced agonist potency are agonists of vaso-active intestinal peptide receptor 2 (VPAC2) (Giordanetto et al. 2013).

Integrins play a vital role in the interaction of extracellular matrix protein with the cell surface and in cell– cell adhesion in vertebrates. Misregulation of certain integrin receptors is linked to several diseases including cancer (Desgrosellier and Cheresh 2010). Integrins are composed of an α- and a β-subunit; many of which recognize binding partners through an Arg-Gly-Asp (RGD) sequence (Fig. 4a) (Pierschbacher and Ruoslahti 1984). Haubner and co-workers integrated the RGD sequence into cyclic pentapeptides and increased their activity and bioavailability (Haubner et al. 1997). Optimization efforts resulted in the identification of the macrocyclic inhibitor cyclo (RGDfV) called Cilengitide (Dechantsreiter et al. 1999) and the cyclic pentapeptide cyclo (RGDf-N(Me)V). The latter combines high receptor affinity and selectivity with improved biostability and oral availability (Fig. 4b) (Conibear et al. 2014).

Small GTPases

Small GTPases are switch-like proteins that exist in two distinct conformational states and are defined by their binding

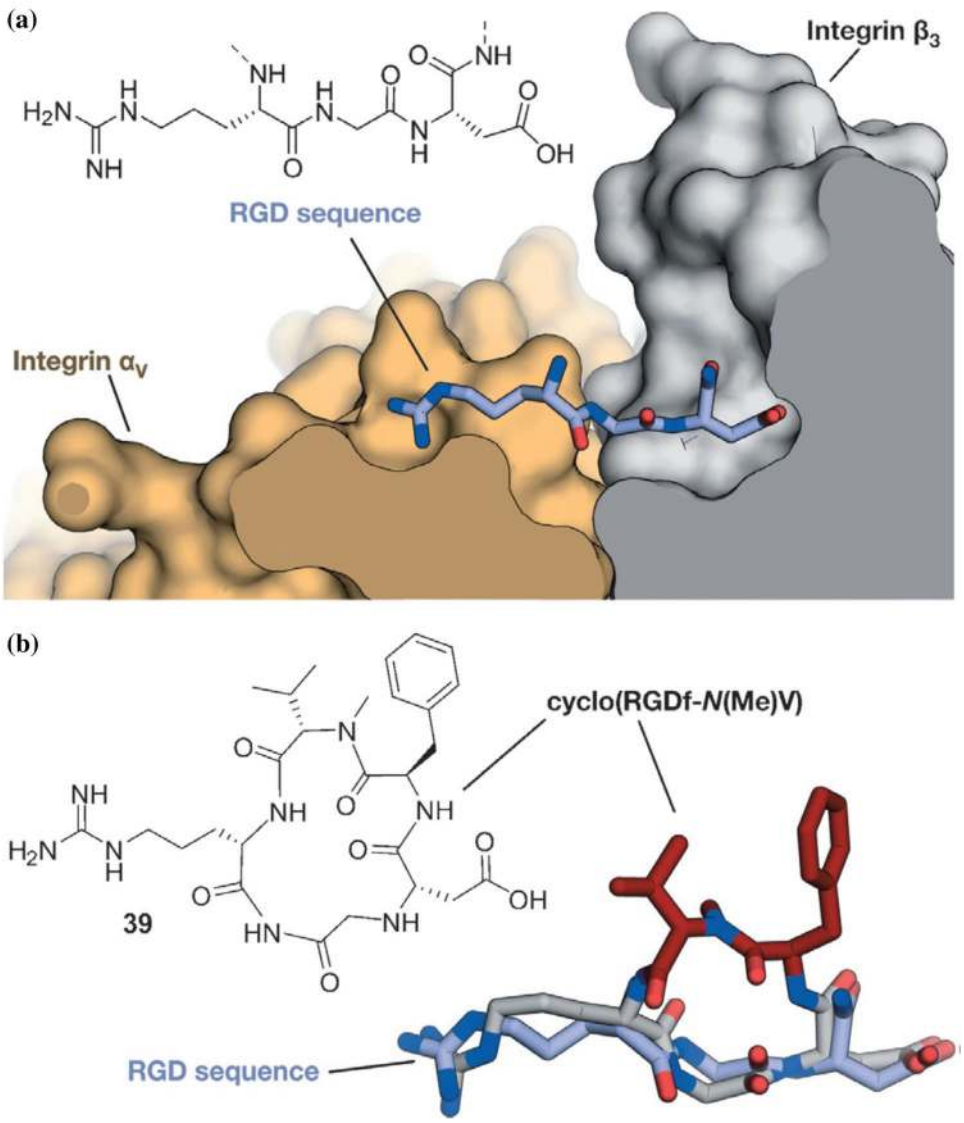

Fig. 4 RGD–integrin interaction: **a** Crystal structure of the RGD sequence from fibronectin bound to the αV (orange) and β3-subunit (gray) of the integrin receptor (PDB 4MMX). **b** Chemical structure of the cyclic pentapeptide cyclo (RGDf-N(Me)V) and crystal structures (gray/red, PDB 1L5G) (Marelli et al. 2014) superimposed with fibronectin RGD (gray; red = constraining amino acids; f = D-phenylalanine). (Color figure online)

to triphosphate (GTP) or guanosine diphosphate (GDP) (Bourne et al. 1990). When bound to GTP, they adopt an active conformation that facilitates binding to effector proteins thereby triggering downstream signaling events. The nucleotide binding state is regulated by PPI. Guanine nucleotide exchange factors (GEF) mediate a GDP to GTP exchange while GTPase-activating proteins (GAP) promote hydrolysis of bound GTP to GDP. Malfunctioning of GTPase regulation has implications in cancer formation and propagation. One good example is the proto-oncogene Ras which gives its name to a subfamily of related proteins such as Rab (Ras related in brain) and Rho (Ras homology) proteins (Spiegel et al. 2014a). Their targeting has proved extremely challenging because of the involvement of numerous PPI in small GTPase regulation and signal propagation (Spiegel et al. 2014b). The use of an HBS-stabilized a-helix derived from a GEF protein of Ras (Sos) is one successful example. The modified peptide HBS3 binds the GDP bound form of Ras with micro molar affinity and is capable of inhibiting the nucleotide exchange by Sos in vitro and in cell culture (Patgiri et al. 2011).

Hydrocarbon peptide stapling was used to stabilize an α-helix of the Rab6-interacting protein, an effector of Rab GTPases. Most strikingly class A mimetics i, i + 4 stapled peptide StRIP3 showed micro molar affinity for the active form of Rab8a and was able to compete with effector binding in vitro (Spiegel et al. 2014a). Hamilton and co-workers reported a class C mimetic based on a 5-6-5 imidazole-phenyltriazole scaffold to target Cdc42, a member of the Rho GTPase family. By mimicking three residues (Leu, Lys, Gln) of the GEF protein Dbs, the compound was able to inhibit the Dbs-promoted nucleotide exchange in vitro (IC50 = 67 mm) (Cummings et al. 2009). However, despite extensive efforts, clinically relevant compounds that directly target small GTPases remain elusive.

Transcriptional Regulation

Protein–protein interactions are key in transcriptional regulation pathways that include the NOTCH, Wnt, and Hedgehog signaling cascades. Impaired modulation of such pathways has strong implications in the genesis and progression of various types of cancer (Katoh 2007). Verdine and Bradner research groups designed peptidomimetics aimed at targeting transcription factor complexes (Moellering et al. 2009). They reported the development of hydrocarbon-stapled peptides for the inhibition of NOTCH signaling. The binding of protein ligands to NOTCH transmembrane receptors facilitates the activation of NOTCH target genes which triggers proteolytic cleavage of the intracellular domain of NOTCH (ICN) (Bray 2006). The ICN activates transcription by forming a trimeric complex with the coactivator proteins of the mastermind-like (MAML) family and DNA bound transcription factor CSL in the nucleus. On the basis of the α-helical binding domain of MAML, the i, i + 4 stapled peptide SAHM1 was developed. The peptide observed robust cellular uptake and potent inhibition of the trimer formation in vitro (Moellering et al. 2009). Cell-based assays confirmed the inhibition of NOTCH dependent gene expression. SAHM1 treatment observed specific antiproliferative effects in a mouse model of NOTCH driven T-cell acute lymphoblastic leukemia (Moellering et al. 2009).

Based on the a-helical b-catenin binding epitopes of Axin and BCL9 hydrocarbon-stapled peptides were used to target the Wnt signaling cascade (Hahne and Grossmann 2013). The Wnt signaling is activated by the binding of extracellular Wnt protein ligands to a receptor complex, which subsequently leads to intracellular inhibition of a multiprotein destruction complex consisting of scaffolding proteins such as protein kinases and Axin. In the absence of the Wnt ligand the complex facilitates the degradation of the protein β-catenin. The inhibition of the destruction complex in the presence of Wnt ligand triggers accumulation of β-catenin and its translocation into the nucleus. In the nucleus it binds to transcription factors of the LEF/TCF family and co-activators such as B-cell lymphoma 9 protein (BCL9) enabling the activation of transcription of the Wnt target genes (Katoh 2007).

The direct targeting of β-catenin has been a long standing goal (Hahne and Grossmann 2013). The i, i + 4 stapled peptides StAx-35R (Grossmann et al. 2012) and SAH-BCL9B (Takada et al. 2012) were developed. In cell-based assays the StAx-35R prevents the formation of a complex between LEF/TCF transcription factors and β catenin thereby inhibiting target genes under the control of Wnt signaling (Grossmann et al. 2012). The correct subcellular localization is essential for efficient inhibition of the signaling cascade (Cui et al. 2013). The SAH-BCL9B prevents the interaction between co-activator BCL9 and β catenin thereby inhibiting a subset of Wnt target genes that control stem-cell-like behavior in some forms of cancer. SAH-BCL9B reduces tumor growth, metathesis and invasion in mouse xenograft models (Takada et al. 2012).

Hydrocarbon- stapled peptides were also used to modulate other facets of gene expression. In histone methylation processes the complex between EED (embryonic ectoderm development and suppressor of zeste 12 homologue) and EZH2 (enhancer of zeste homologue 2) is vital. The complex formation was inhibited using EZH2-derived stapled peptides (Kim et al. 2013). Stapled peptides have also been used to target protein–protein complexes involved in the regulation of mRNA transcription (Lama et al. 2013) and DNA protection mechanisms (Frank et al. 2014). Estrogen receptors are activated by steroid hormones and regulated by co-activator proteins. The hyperactivation of these transcription factors has been implicated in the development

of cancer (Darnell 2002). Co-activator proteins bind the receptor through a nuclear receptor box (NR-box) consisting of a LXXLL motif. Upon binding the motif adopts an α-helical secondary structure (Fig. 5a). Attempts to stabilize the binding motif in its active conformation were done using disulfide (PERM-1, Fig. 5b), lactam, or thioether side chain to side chain cross-links (Galande et al. 2004). A lactam cross-linked peptide was further modified by incorporating unnatural amino acids, increasing the selectivity between receptor subtypes (Geistlinger and Guy 2003). Stapled peptides (i, i + 4) were designed using the crystal structure of nuclear receptor co-activator (NRCA) peptide 2 bound to ERα (Fig. 5a).

Structural studies revealed significant variations in the binding mode, affinity and selectivity. Notably, one of the crucial Leu amino acids was replaced by a building block in the formation of the marcocycle (Sp2; Fig. 5b). In this case, the hydrophobic cross-link is involved in the binding, thereby leaving the remaining residues of the stabilized peptide in good alignment with the wild-type peptide (Phillips et al. 2011). A structural mimetic was designed based on pyridylpyridone derivatives with substitutions in the 2-pyridyl and 1,5-pyridone positions (e.g. 44) to provide compounds that compete with the natural binding sequence in vitro (Hamilton and coworkers designed). The crystal structure aligns well with the Leu side chains of the helical LXXLL motif (Fig. 5c) (Becerril and Hamilton 2007). Another PPI with implications in the occurrence of cancer is the interaction between hypoxia-inducible transcription factors (HIFs) and p300/CBP coactivator proteins. HIFs are expressed under the cellular state of reduced oxygen levels.

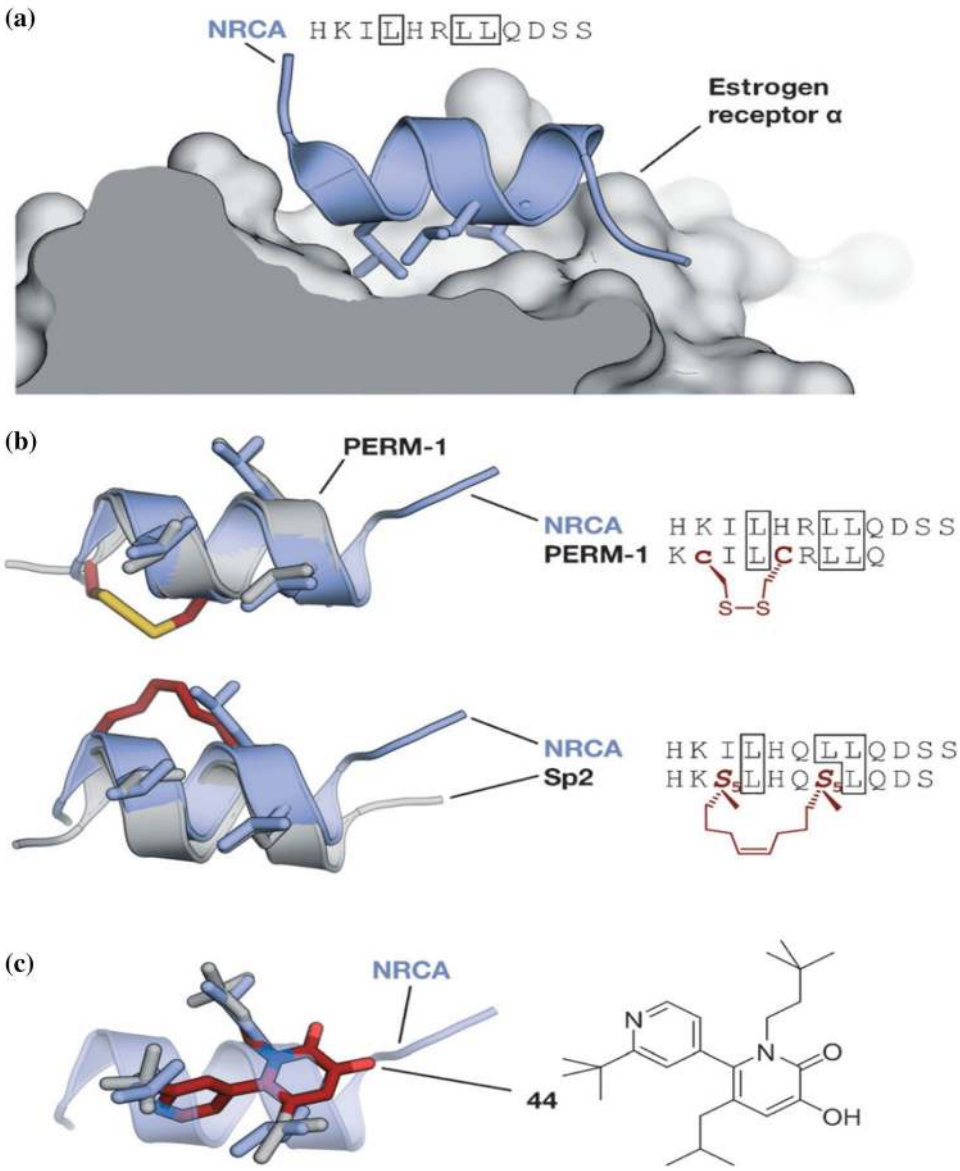

Fig. 5 Estrogen receptor (ER) coactivator interaction: **a** Coactivator peptide NRCA bound to ERa (gray; PDB 2QGT); **b** top: superimposed crystal structures of NRCA (blue, PDB 2QGT) and disulfide cross-linked PERM-1 (gray, PDB 1PCG; left). Cys and d-Cys **c** are highlighted in red, the disulfide bridge in yellow; sequences of cross linked peptide (right). Bottom: Superimposed crystal structures of NRCA (blue, PDB 2QGT) and stapled peptide Sp2 (gray, PDB 2YJA; left). The cross-link is highlighted in red. Sequences of stapled peptide (right). Selected side chains are shown explicitly and highlighted in sequence. **c** Superimposed crystal structures of NRCA (blue, PDB 2QGT) and 6-(2-tert-butyl-4-pyridyl)-3-hydroxy-5-isobutyl-1-(3,3-dimethylbutyl) 1H-pyridin-2-one (44, gray/red, CCDC: 636896) (Grossmann et al. 2015). (Color figure online)

In cancer cells, the interaction between HIFs and its co-activators can trigger the expression of genes that promote invasion, angiogenesis, and a modified metabolism (Hirota and Semenza 2006). The interaction between HIF-1α and p300/CBP is mediated by two short α helices in HIF-1α. Arora and co-workers designed a number of different peptidomimetics based on these peptide sequences. Initial efforts focused on hydrogen-bond surrogates to yield modified peptides inhibit complex formation (Henchey et al. 2010a, b; Kushal et al. 2013). Stabilized peptides showed inhibitory effects both in murine tumor xenografts and cancer-cell-based assays. Class C peptidomimetics observed potency in inhibiting the HIF-1ap300/CBP interaction (Lao et al. 2014a, b; Burslem et al. 2014). Aromatic oligoamides showed inhibitory effects in vitro (Burslem et al. 2014). Class C oligooxopiperazine helix mimetics (OHM, 37) compete with HIF-1α binding in vitro, reduces the expression of hypoxia-inducible genes in cell-based assays and is active in murine tumor xenografts. These results highlight the remarkable potential of α-helix mimetic based on oligooxopiperazine scaffolds (Lao et al. 2014a, b).

Conclusions and Future Perspectives

The discovery of PPI as potential drug targets for therapeutics has been an impressive journey to fame over the years. The continuously improving technology expertise in PPI-focused drug approach has brought the once intractable and undruggable approach on the spotlight as significant drug development strategy. The PPI-focused drug technology presents an emerging field for drug discovery and researchers have siphoned new technologies that have the potential to move this field further up the technology development curve and enable the regular discovery of PPI modulators. Peptidomimetics tend to mimic peptide side chains to take advantage of the binding affinity of a number of hot spot residues. The use of peptidomimetics has recently come of age with new drugs going into clinical trials. We envision that research in peptidomimetics will continue to be an indispensable tool to target PPI in drug discovery for the foreseeable future.

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Compliance with Ethical standards

Conflict of Interest The authors declare no conflict of interest.

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