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Invited review

Disulfide-rich macrocyclic peptides as templates in drug design

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ABSTRACT

Recently disulfide-rich head-to-tail cyclic peptides have attracted the interest of medicinal chemists owing to their exceptional thermal, chemical and enzymatic stability brought about by their constrained structures. Here we review current trends in the field of peptide-based pharmaceuticals and describe naturally occurring cyclic disulfide-rich peptide scaffolds, discussing their pharmaceutically attractive properties and benefits. We describe how we can utilise these stable frameworks to graft and/or engineer pharmaceutically interesting epitopes to increase their selectivity and bioactivity, opening up new possibilities for addressing 'difficult' pharmaceutical targets.

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1. Introduction

Therapeutic molecules currently on the market can be broadly divided into two categories according to their molecular weights – small molecules of <500 Da and biologics of >5000 Da. Biologics typically have higher target potencies and specificities than small molecules due to an increased number of interactions with their targets. These favourable features mean that they potentially have fewer off-target side-effects than small molecule drugs. However, disadvantages associated with biologics include their generally poor membrane permeability, low bioavailability and metabolic instability. Thus, biologics typically require delivery via injection, which is not a preferred route of administration due to poorer patient compliance, higher cost of goods and more stringent storage requirements than small molecule drugs. These disadvantages are generally not observed with small molecule drugs, which mostly obey Lipinski's 'rule-of-five' [1]. In addition to having the favourable drug-like pharmacokinetic properties associated with this rule, small molecule drugs are also relatively inexpensive to manufacture. However, small molecules often suffer from low target specificities that can lead to side-effects.

Peptide-based drugs offer an alternative class of molecules for drug development that can tackle molecular spaces that have been considered undruggable by small molecules or biologics [2]. In this article we focus on a particular class of peptides, namely disulfide-rich peptide macrocycles, as we believe that these are an especially promising group of molecules for drug development.

In general, the field of peptide-based therapeutics has received growing attention from the pharmaceutical industry in recent years, in large part due to some of the attractive properties of peptides compared to small molecule or protein-based drugs, including their unique size range, synthetic accessibility and combinatorial diversity [2–4]. Peptide-based therapeutics include peptides comprised solely of proteinogenic amino acids, as well as peptides incorporating a variety of modifications, including cyclisation, incorporation of unnatural amino acids (e.g. β-amino acids), alternatives to amide linkers (e.g. esters) and linker groups (e.g. disulfide bonds, PEG linkers). A few examples of peptide-based drugs currently on the market that include some of these modifications are shown in Fig. 1.

The wide range of disease states that can be targeted by peptide therapeutics highlights the broad potential of this therapeutic drug class [4,5]. Nevertheless, peptides still account for only a small fraction of new drugs reaching the market: during 2011–2013, there were 96 new molecular entities (NMEs) approved by the US FDA, of which, nine were peptide therapeutics (Table 1) [6–8]. This

Abbreviations: BBI, Bowman Birk inhibitor; BTD-2, baboon θ-defensin 2; CCK, cyclic cystine knot; CsA, Cyclosporin A; GC-C, guanylyl cyclase C; GPCR, G-protein coupled receptor; HIV, human immunodeficiency virus; kB1, kalata B1; KLK4, kallikrein-related peptidase 4; LAM, laminin α1 chain; MOG, myelin oligodendrocyte glycoprotein; NME, new molecular entity; nAChR, nicotinic acetylcholine receptor; OPN, osteopontin; PPI, protein–protein interaction; QK, a VEGF peptide mimic; RTD-1, rhesus θ-defensin 1; SFTI-1, sunflower trypsin inhibitor-1; US FDA, United States Food and Drug Administration.

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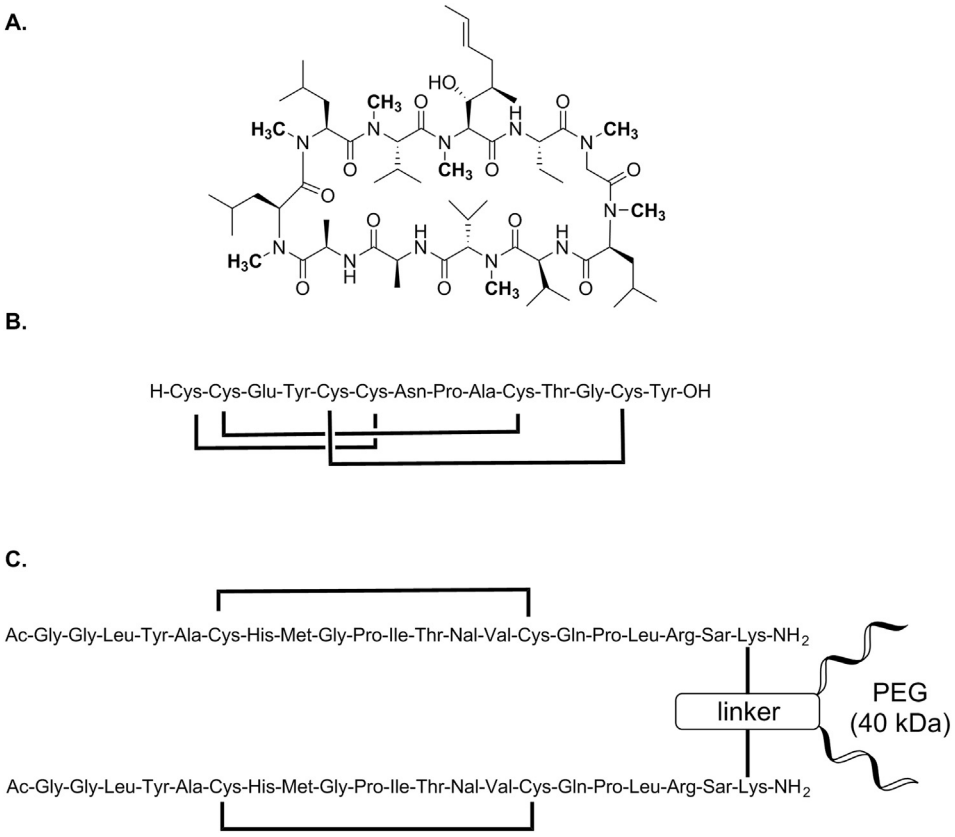

Fig. 1. Structures of selected examples of peptide-based therapeutics approved by the US FDA. Disulfide bond connectivity is indicated by bold lines linking cysteine residues in panels B and C. A. Cyclosporin A; B. Linaclotide; C. Peginesatide (Nal = 3-(1-napthyl)alanine and Sar = N-methylglycine).

review describes the current state of peptide-based therapeutics, and explores approaches to 'difficult' targets using disulfide-rich macrocyclic peptides. We conclude with a discussion of possible future trends and challenges in this field.

2. Peptides as drugs

Currently approved drugs target only about 2% of proteins encoded in the human genome and many of these targets are confined to specific classes of proteins such as GPCRs, enzymes, ion channels and transporters [9]. This low proportion of therapeutic targets could be greatly increased by targeting protein–protein interactions (PPIs), which are crucial in many biological processes. PPIs are difficult to target because the interaction interfaces are often composed of large and relatively flat surface regions [10,11]. Hence, they are generally considered especially difficult to target by small molecule therapeutics. As a result, recent years have seen an explosion in the development and approval of biologics targeting

Table 1
Peptide-based therapeutics approved by the US FDA during the period 2011–2013.[a]

Generic name (trade name)	Disease/target	Properties	Structural/therapeutic features
Boceprevir (Victrelis®)	Chronic hepatitis C infection	NS3/4A protease inhibitor	Short linear peptidomimetic; non-proteinogenic amino acids; short half-life
Telaprevir (Incivek®)	Chronic hepatitis C infection	NS3/4A protease inhibitor	6-mer linear peptide; non-proteinogenic amino acids
Icatibant (Firazyr®)	Hereditary angioedema	Bradykinin B_2 receptor antagonist	10-mer linear peptide; non-proteinogenic amino acids
Lucinactant (Surfaxin®)	Prevention of respiratory distress syndrome	Pulmonary surfactant	Mixture of active peptide (Sinapultide), lipids and fatty acid
Peginesatide (Omontys®)[b]	Anaemia due to chronic kidney disease	Synthetic, PEGylated erythropoiesis-stimulating agent	Disulfide-stabilised and PEGylated; long half-life (24–72 h)
Carfilzomib (Kypolis®)	Multiple myeloma	20S proteasome inhibitor	Linear tetrapeptide; extensive metabolism and short half-life
Linaclotide (Linzess®)	Irritable bowel syndrome with constipation; chronic idiopathic constipation	Guanylyl cyclase C agonist	Linear disulfide-stabilised 14-mer; orally administered
Pasireotide (Signifor®)	Cushing's disease	Somatostatin analogue	Cyclic hexapeptide; 12 h half-life; non-proteinogenic amino acids
Teduglutide (Gattex®)	Short bowel syndrome	Glucagon-like peptide 2 analogue	33-mer linear peptide; short half-life

[a] Listed in chronological order of approval dates. Data current as of December 2013.
[b] Drug voluntarily recalled in March 2013.

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