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Review article

From nature to creation: Going around in circles, the art of peptide cyclization

Rui-Yang Zhang [a], Parashar Thapa [a,b], Michael J. Espiritu [a], Vinay Menon [a,c], Jon-Paul Bingham [a,*]

[a] Department of Molecular Biosciences and Bioengineering, College of Tropical Agriculture and Human Resources, University of Hawai'i, Honolulu, HI 96822, USA
[b] Department of Physiology and Membrane Biology, School of Medicine, University of California, Davis, CA 95616, USA
[c] Department of Genetics, Texas Biomedical Research Institute, San Antonio, TX 78245, USA

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ABSTRACT

Cyclic peptides and cyclotides are becoming common identities within the present efforts seen in peptide engineering – as we seek approaches to achieve potent biological activity, pharmacological selectivity, structurally stability and oral bioavailability. Yet this unique family of peptides has faced uncommon hurdles in their discovery, synthesis and bioengineering, retaining to characteristics that truly deviate these from their linear counterparts. In this mini-review we take a board spectrum approach to introduce this novel family of biomolecules and the troubles that they face in their sequence and disulfide connectivity assignment, together highlighting the present combined strategies involved in cyclic peptide/cyclotide synthesis and modification. These efforts have circumvented otherwise impossible hurdles in their manipulation and production that are only now advancing cyclic peptides/cyclotides as research probes and future pharmaceutical templates.

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* Corresponding author.
E-mail address: jbingham@hawaii.edu (J.-P. Bingham).

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1. Introduction

Peptide research has been a major and diverse field of study within biochemistry for many decades. The majority of peptides found in nature are folded in their three-dimensional conformations. The specific three-dimensional structures offer peptides unique activity and selectivity. Generally, peptides contain free *N*- and *C*-termini and these peptides have undergone extensive characterization and have seen wide applications in research and medicine. However a growing class of distinct peptides in which the free *N*- and *C*-termini have been connected with a conventional peptide bond forming the circular backbone, have been discovered and are now being commonly referred to as 'cyclic' peptides. This term has been used in many contexts that may create confusion as to the nature of the peptide in question. For example, this term has been used to refer to peptides with disulfides, with terminus and side chain linkages, and those with the aforementioned property of an *N*- to *C*-terminal linkage. Recently the term "cyclotide" has also been coined. This term refers to naturally occurring *N*- to *C*-terminal linked peptides found in plants that have a characteristic intercysteine knot motif (ICK).[1] Here we have attempted to provide further distinction and clarity in the use of these often-confusing terminologies, as illustrated in Table 1.

Peptides containing a cyclic backbone have been observed in all kingdoms of life, such as in: bacteria,[2–4] fungi,[5,6] plants[7–9] and animals[10,11] (Table 2). To date, 948 suspected cyclic backbone sequences have been documented in Cybase (http://www.cybase.org.au), a database that catalogues cyclic peptides and proteins.[12,13]

Naturally occurring cyclic peptides belong to a diverse array of polypeptide families, most of which appear to be associated with a number of biological activities such as cytotoxic,[14–16] antimicrobial,[17] hemolytic,[17–19] anti-HIV,[19–23] antihelmintic[24] and insecticidal activity.[25,26] The presence of a cyclic peptide backbone in these molecules offers an advantage over traditional peptides by increasing their resistance to exoprotease degradation and thus enhancing their molecular stability and half-life.[27] In particular, head-to-tail cyclization stabilizes both the *N*- and *C*-termini of the peptide and precludes digestion by exoproteases. These particular features have shown to increase their circulatory half-life, which is of major interest in the development of orally available peptide based pharmaceuticals.[28] Furthermore, the combination of backbone cyclization together with the abundance of disulfide bonds typically observed within cyclic peptides from plants, known as "cyclotides" (Table 1), has been suggested as possible novel 'pinned' scaffolds for drug design and development.[29–31] These same structural characteristics observed in cyclotides are now being applied via peptide bioengineering to other peptides, such as neurotoxic peptides from cone snails, as will be illustrated later.

Table 1
Distinction and clarification of the term 'cyclic peptide'

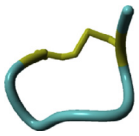
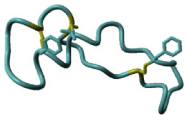
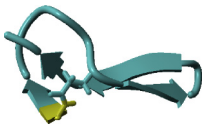
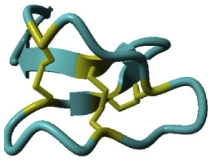
Previously Used Terminology	Cyclization Architecture	Revised Terminology	Representative Peptide	Representative Structure	Ref.
"Cyclic Peptide"	**Side chain to side chain cyclization**: Disulfide bonds, Thioether bonds, etc.	Cyclic Peptide type I	Contryphan-R		40
"Circular Peptide"/ "Cyclic Peptide"	**Backbone cyclization:** (*N*- to *C*-terminal) with or without the presence of separate covalent interaction(s) between side chains	Cyclic Peptide type II	Subtilosin A		41
"Cyclic Peptide"	**Terminus to side chain cyclization**: *N*-terminal to side chain, *C*-terminal to side chain	Cyclic Peptide type III	Microcin J25		42
"Cyclotide"	**Backbone cyclization (*N*- to *C*-terminal) containing an inhibitory-cysteine knot (ICK) domain**: plant derived	Cyclotide	Kalata B1		43

Table 2
Diversity of naturally occurring cyclic peptides.

Kingdoms	Family	Peptide	Organism	αα	Sequence	S-S bond	Ref.
Bacteria	Bacteriocins	Subtilosin A	*Bacillus subtilis*	35	NKG**C**AT**C**SIGAA**C**LVDGPIPDFEIAGATGLFGLWG	–	3
		Ent AS-48	*Enterococcus faecalis*	70	MAKEFGIPAAVAGTVLNVVEAGGWVTTIVSILTAV GSGGLSLLAAAGRESIKAYLKKEIKKKGKRAVIAW	–	2,4
Fungi	Amatoxins	α-Amanitin	*Amanita phalloides*	8	IWGIG**C**NP	–	6
	Phallotoxins	Phallacidin	*Amanita phalloides*	7	AWLVD**C**P	–	5
Animals	θ-Defensins	RTD-1	*Macaca mulatta*	18	R**C**I**C**TRGF**C**R**C**L**C**RRGV**C**	+	10
		Retrocyclin-1	*Homo sapien*	18	GI**C**R**C**I**C**GR**C**I**C**R**C**I**C**GR	+	11
Plants	Cyclotides	Kalata B1	*Oldenlandia affinis*	29	GLPV**C**GET**C**VGGT**C**NTPG**C**T**C**SWPV**C**TRN	+	7,9
		MCoTI-II	*Momordica cochinchinensis*	34	GGV**C**PKILKK**C**RRDSD**C**PGA**C**I**C**RGNGY**C**GSGSD	+	8