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Review

Peptides as a strategy against biofilm-forming microorganisms: Structure-activity relationship perspectives

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ABSTRACT

Biofilm forming microorganisms substantially enhance their virulence and drug resistance causing and alternatives are need to combat this health problem. In this context, peptides are an exceptional strategy in drug design and pharmaceutical innovation due to their diverse chemical features, biological activity and biotechnological relevance. Therefore, this study proposes a comprehensive assessment of a wide range of peptides, targeting biofilms. It provides chemical and molecular information and a Structural Activity Relationship perspective in order to delineate minimal requirements for antibiofilm activity and contributing to the development of new antibiofilm agents. In light of this, it was possible to propose a peptide design model (X_1-X_2-X_3-X_4-X_5-X_6-X_7-X_8-X_9-X_{10}-X_{11}-X_{12}-X_{13}-X_{14}-X_{15}-X_{16}-X_{17}-X_{18}-X_{19}-X_{20}) to be tested in the war against resistant microorganisms.

1. Introduction

Besides the recognized and increasing problematic issue of bacterial resistance, biofilm formation represents a rising clinical threat. In a hospital scenario, biofilm formation may cause or worsen infections, since the microorganisms are resilient to most of the treatments available (Bjarnsholt et al., 2013). Biofilm is defined as a microbial lifestyle in which microbial adhere to a surface and produce a matrix that enables them to overcome a series of environmental stresses due to their interaction abilities. Several mechanisms have been proposed to explain the drug resistance within biofilms, including the delayed/suppressed penetration of the antimicrobial agent into the extracellular matrix, the presence of metabolically inactive 'persister' cells, and the increased ability to exchange mobile genetic elements encoding resistance (Hoiby et al., 2010; Mah, 2012a; Mah, 2012b).

It is increasingly evident that alternatives are need to combat drug-resistant organisms and biofilms. In this context, peptides are an outstanding strategy because they able to establish diverse biomolecules (Yoshikawa, 2015) due to chemical features like malleability and multifunctionality. Peptides are the source of many bioactive compounds with distinct activities, such as immunomodulation (Faruqi, 2013; Sanchez-Margalet et al., 2003; Pennington et al., 2015; Pasikowski et al., 2011), antitumor (Bajou et al., 2014; Chernysh et al., 2002; Martinez-Hoyer et al., 2015), anticancer (Leuschner and Hansel, 2004; Berge et al., 2010; Ciocca et al., 2012), antimicrobial (Hancock and Sahl, 2006; Dinh et al., 2015; Ganz, 2003), and, currently, antibiofilm (Lum et al., 2015; Wu et al., 2015; de la Fuente-Nunez et al., 2015). Also, several physico-chemical parameters including charge, hydrophobicity, and secondary structure are possible targets to modify and to influence the peptide activity and differential selectivity.

In addition, it is well established that peptides can play an interesting role in development of new biomaterials having anti-infective activity. They act in the earliest step in the pathogenesis of foreign-body-related infections in bacterial adhesion; the colonization will hardly occur if bacteria can not adhere to a surface (Campoccia et al., 2013; Glinel et al., 2012).

A few publications have addressed Antimicrobial Peptides (AMPs) as peptide models against biofilm-forming microorganisms (Jorge et al., 2012; Strempel et al., 2015; Di Luca et al., 2014; Schillaci et al., 2013) then, it will not be the focus of this work.

Even more, applicability of AMPs as antibiofilm agents is hindered by some problems, like the absence of a defined mechanism of action, cytotoxicity, stability, bioavailability and adaptive bacterial resistance (Jorge et al., 2012; Di Luca et al., 2014; Schillaci et al., 2013; Wang et al., 2014).

Despite these peptide advantages, the structure-activity relation-

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Table 1
Peptide information in alphabetical order: peptides with both Gram positive (G +) and negative (G −) antibiofilm relative activity tested.

ID	Peptide	General information/range of concentration tested	N° AA	Sequence	*Theoretical	
					Molecular weight	Total net charge
1	AS10	It is a shortened variant of the known cathelicidin-related antimicrobial peptide (CRAMP) discovered in the	26	KIGEKLKKIAQKIKNFFQKL-VPQPEQ	3.069.717	5
2	P318	islets of Langerhans of the murine pancreas, in which each amino acid of the native sequence was individually (10th aa) replaced by an alanine residue; 6.25–12.25 μM	26	KIGEKLKKIAQKIKNFFAKL-VAQPEQ	2.992.627	5
3	Battacin analogue	A cyclic lipopeptide produced by the soil isolate *Paenibacillus tianmunesis* that belongs to the octapeptin group of peptide antibiotics characterized by a high percentage of the nonprotein amino acid α,γ-diaminobutyric acid (Dab) and a branched β-hydroxy fatty acid tail linked to a cyclic heptapeptide moiety; 1–100 μM	17	$_{D}$.Dab-Dab-Dab-L-$_{D}$-F-Dab-Dab-L	x	x
4	BL-DZ1	Identified (14 kDa) as BL00275, accession number gi52082584, from *B. licheniformis* ATCC 14580. The purified protein was stable at 75 °C for 30 min and in the pH range between 3.0 and 11.0; however, it was sensitive to the enzymes trypsin and proteinase K; 1.60 mg/mL	ns	Ns	x	x
5	BMAP27-Melittin	Both are antimicrobial peptides (AMPs), the bovine derived BMAP-27 and the bee venom derived melittin. This hybrid peptide consists of an N-terminal fragment obtained from residues 9–20 of BMAP-27 and a C-terminal fragment from residues 2–9 of melittin. It displays a total helicity of 76.2%, net charge of + 6, hydrophobicity of 0.531, and hydrophobic moment of 0.64	21	KFKKLFKKLSPVIGAVLKVLT	2.352.019	6
6	Coprisin	It is a defensin-like peptide (AMP) from the dung beetle *Copris tripartitus*. Combinations of coprisin and other conventional antibiotics (ampicillin, vancomycin, and chloramphenicol) also showed antibiofilm properties against preformed biofilms; 8–16 μg/mL	43	VTCDVLSFEAKGIAVNHSA-CALHCIALRKKGGSCQNGV-CVCRN	4.477.251	3
7	DispersinB™ and KSL combination	DispersinB™ is a naturally occurring enzyme (40 kDa, glycoside hydrolase) produced by an oral bacterium *Aggregatibacter actinomycetemcomitans*, an antibiofilm	10	KKVVFKVKFK	1.250.618	5
8	DispersinB™ and KSL-W combination	enzyme based wound gel in combination with a synthetic broad-spectrum cationic antimicrobial decapeptide, 1.31 kDa; 0.9–8 μg/mL	10	KKVVFWVKFK	1.308.661	4
9	Gramicidin A	They are linear pentadecapeptides with a molecular mass of approximately 1900 Da and consist of alternating L- and D-amino acids. The natural mixture of gramicidins contains predominantly (85%) gramicidin A, which is hydrophobic, forming a β-bonded helix; 20 mg/L	15	XGALAVVVWLWLWLW	1.712.116	0
10	Holothuroidin 1	Natural peptide fraction (AMP) from the coelomocyte cytosol from *Holothuria tubulosa* (sea-cucumber).	12	HLGHHALDHLLK	1.389.5	0
11	Holothuroidin 2	1389.5 Da, 7.56 of pl, and 1547.6 Da, + 0.9 total net charge, 42.86% total hydrophobic ratio, 7.56 of pl, both with an α-helical secondary structure; 3.1–6.2 mg/mL	14	ASHLGHHALDHLLK	1.547.6	0
12	IDR-HH2	Synthetic analogs of host defense peptide (HDP) termed	12	VQLRIRVAVIRA	1.393.747	3
13	IDR-1002	innate defense regulator (IDR) peptides; 5–80 μg/mL	12	VQRWLIVWRIRK	1.6530.52	4
14	IDR-2009		12	KWRLLIRWRIQK	1.696.116	5
15	K4K20S4	They are dermaseptins, linear polycationic peptides arranged in amphipathic α-helices in nonpolar solvents.	28	ALWKTLLKKVLKAAAKAAL-KAVLVGANA	2.861.579	6
16	K4S4	They all have a conserved Trp residue at position 3, an AG(A)KAAL(V/G)G(N/K)AV(A) consensus motif in the middle region and a positive charge attributable to the presence of Lys residues that punctuate an alternating hydrophobic-hydrophilic sequence. These derivatives combine two substitutions: methionine with lysine at position 4 and asparagine with lysine at position 20; 0.4–25 μg/mL	28	ALWKTLLKKVLKAAAKAAL-NAVLVGANA	2.847.513	5
17	NapFFKK	They are ultrashort aromatic peptides that self-assemble	4	NapFFKK	568.699	x
18	NapFFFKK	into inherently antimicrobial hydrogel nanostructures. They consist of two phenylalanine building blocks conjugated to a molecule of high aromaticity, such as naphthalene (Nap) or 9-fluorenylmethoxycarbonyl (Fmoc); 0.5–2 (*w/v* %)	5	NapFFFKK	715.875	x
19	Paracentrin 1	Based on a peptide fraction from the coelomocyte cytosol (5-kDa), it is composed of fragments of a β-thymosin from *Paracentrotus lividus*, mainly enriched by residues such as lysine, with a pI of 10.72 and a net charge of + 1	11	EVASFDKSKLK	12.514.417	1

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