The magainins: antimicrobial peptides with potential for topical application


Recently a number of endogenous host defence molecules with antimicrobial activity have been identified in mammals, invertebrates and amphibians (for reviews see Ganz, Selsted & Lehrer, 1990; Boman, 1991; Lehrer, Ganz & Selsted, 1991). Within this group of antimicrobial agents there are several small peptides (2–4K) that include the defensins (found predominantly in mammalian phagocytes), cecropins, diptericins, attacins, apidaecins, abaecin, royalisin (all from insect sources) and the magainins (amphibian source). A number of semi-synthetic magainins are currently under development as topical antimicrobial agents with potential dermatological, ophthalmic and periodontal applications (Anonymous, 1992). This article briefly reviews the current status of the magainins, and considers the structure, mode of action and antimicrobial spectrum of these peptides.

Amongst the defensins, the magainins (or magainin analogues) are the most advanced in terms of commercial development (Rennie, 1993). It is for this reason that this article focuses on the magainins since they have a greater chance of reaching the clinic than do other host defence peptides.

Magainins were identified in the skin secretions of the African clawed frog, *Xenopus laevis*, by Zasloff and co-workers (Zasloff, 1987; Zasloff, Martin & Chen, 1988). These host defense peptides are secreted by granular glands in the skin of the frog in response to tissue injury (MacDonald, Berkowitz & Jacob, 1990). Magainins 1 and 2 (mgn1 and 2) (also known as PGS-peptides beginning with glycine and ending with serine) are 23 residue peptides with the following sequences (Zasloff et al., 1988; Williams et al., 1990): mgn1, Gly-Ile-Gly-Lys-Phe-Leu-His-Ser-Ala-Gly-Lys-Phe-Gly - Lys - Ala - Phe - Val - Gly - Glu - Ile - Met - Lys - Ser; mgn2, Gly - Ile - Gly - Lys - Phe - Leu - His - Ser - Ala - Lys - Lys - Phe - Gly - Lys - Ala - Phe - Val - Gly - Glu - Ile - Met - Asn - Ser. PGLa (peptide beginning with glycine and ending with leucine amide), is another antimicrobial peptide (21 residues) isolated from frog skin (Williams et al., 1990) and has the following sequence: Gly - Met - Ala - Ser - Lys - Ala - Gly - Ala - Ile - Ala - Gly - Lys - Ile - Ala - Lys - Val - Ala - Leu - Lys-Ala-Leu-NH₂. Although PGLa displays little sequence homology with mgn1 or mgn2 these peptides are all positively charged and can form amphiphilic helices about 30 Å in length (Williams et al., 1990). Because these features are common to polypeptides that bind to lipid bilayers it has been suggested that magainins and PGLa act as transmembrane helical channel former that dissipate the membrane potential (Zasloff, 1987).

Subsequent membrane depolarization studies in *Escherichia coli* using tetraphenyl phosphonium ion (TPP⁺) to measure the membrane potential have indeed confirmed that mgn2 and PGLa dissipate the membrane potential (Westerhoff et al., 1989; Juretic, 1990). Although mgn1 was not specifically examined in these studies (Westerhoff et al., 1989; Juretic, 1990) its structural similarity to mgn2 implies a similar mode of action. Antimicrobial agents that dissipate the membrane potential invariably have secondary effects on bacterial metabolism leading to stimulation of autolytic enzyme activity, bacterial lysis and cell death (Oliva et al., 1992). Although it is not known whether exposure of bacteria to magainins and PGLa leads to bacterial lysis, the bactericidal activity of these peptides (Levison et al., 1990; Silva, Tang & Maloy, 1990) is consistent with a chain of events initiated by dissipation of the membrane potential and involving bacterial lysis before cell death.

Since mgn2 and PGLa also depolarize mitochondria (Westerhoff et al., 1989) and liposomes (Juretic, 1990), it has been suggested that the membrane depolarizing peptides secreted by *X. laevis* would likely attack all cell membranes in their vicinity (Juretic, 1990). This relatively non-specific activity would only be useful to the host if it can protect itself from the activity of its own products. This is likely to be achieved post-translationally by the
generation of active peptides through proteolysis of longer peptide precursors that are presumably secreted on to the skin surface before cleavage occurs to produce the biologically active fragment (Zasloff, 1987; Zasloff et al., 1988; Juretic, 1990). Indeed, cDNA analysis suggests that mgn1 and mgn2 are both present in a single precursor peptide of approximately 160 amino acids which contains one copy of mgn1 and two copies of mgn2 (Zasloff, 1987; Zasloff et al., 1988; Juretic, 1990). Both mgn1 and mgn2 are flanked in the precursors by sequences that are putative proteolytic cleavage sites (Zasloff, 1987; Zasloff et al., 1988; Juretic, 1990).

Early magainins and PGLa had relatively poor antibacterial potencies and a limited spectrum of activity (Zasloff et al., 1988; MacDonald & Maloy, 1990). To improve peptide activity and spectrum, synthetic analogues have been designed involving selected amino acid substitutions and deletions, repeats of small peptides and protection of sites likely to be susceptible to enzymatic attack (MacDonald & Maloy, 1990). In particular, optimization of anti-staphylococcal and anti-pseudomonal activity has been sought in order to satisfy the requirements for application of these agents as topical antimicrobials. Compared to mgn1 and mgn2, the more recently synthesized peptides MSI-91, -94, -95 and -103 are all more active against Staphylococcus aureus and Pseudomonas aeruginosa (Table). Further studies have led to the identification and selection of peptides MSI-78, -136, 238, -239 and -404 that are currently under development (Magainin Pharmaceuticals Inc., 5110 Campus Drive, Plymouth Meeting, PA, USA) as topical antiinfective agents with potential dermatological ophthalmic and periodontal applications (Anonymous, 1992). The pathogens encompassed comprise staphylococci, Pseudomonas spp., Porphyromonas gingivalis and Acanthamoeba spp. (Anonymous, 1992). The latter can cause a painful, sight threatening disease of the human cornea.

The magainins possess several attractive features as antimicrobial agents: e.g. (a) their ease of chemical manipulation to produce analogues with improvements over the parent molecules in potency and spectrum of action and (b) their activity against bacteria (e.g. methicillin-resistant S. aureus) resistant to conventional agents (Jacob et al., 1990; Anonymous 1992). Nevertheless, the problem of producing peptides at a reasonable cost still remains a challenge to their introduction as topical antimicrobial agents for widespread use (Anonymous, 1992).

Table. Antimicrobial activity of naturally occurring and synthetic magainin peptides against S. aureus and P. aeruginosa

<table>
<thead>
<tr>
<th>Organism</th>
<th>mgn1</th>
<th>mgn2</th>
<th>MIC mg/L</th>
<th>MSI 91</th>
<th>MSI 94</th>
<th>MSI 95</th>
<th>MSI 103</th>
</tr>
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<tbody>
<tr>
<td>S. aureus</td>
<td>&gt; 100</td>
<td>35-70</td>
<td>16</td>
<td>8</td>
<td>16</td>
<td>8</td>
<td>16</td>
</tr>
<tr>
<td>P. aeruginosa</td>
<td>&gt; 100</td>
<td>35-70</td>
<td>4</td>
<td>4</td>
<td>8</td>
<td>16</td>
<td></td>
</tr>
</tbody>
</table>

Based on Zasloff et al. 1988; Jacob, MacDonald & Maloy, 1990.

References


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**References**

3. Hell, K. et al., Chemotherapy, 1989, 35 (3), 228-235
4. Estimated current cash annual sales worldwide – Data on file: Roche Products Ltd.

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