MOLECULAR MECHANISM OF SYNERGY BETWEEN THE ANTIMICROBIAL PEPTIDES PGLA AND MAGAININ 2

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The two antimicrobial peptides PGLa and magainin 2 (MAG2), both found in the skin of the African frog *Xenopus laevis*, are known to exhibit strong synergistic effects in bacterial killing, vesicle leakage and other membrane-related activities [1]. Here, we studied the synergy of the two peptides in an attempt to find the molecular mechanism behind the synergistic effect. A large number of mutants of the two peptides were investigated and the synergy tested using three complementary methods: (i) From a checkerboard assay, fractional inhibitory concentrations (FICs) were determined against two bacteria [2]. (ii) From a vesicle leakage assay, the increase in leakage of a 1:1 mixture of the two peptides compared to leakage of each peptide alone, showed the synergy effect in two different lipid systems [3]. (iii) From ^{15}N-NMR, the insertion of PGLa to a transmembrane orientation (suggesting the formation of a pore) in the presence of MAG2 was investigated; without MAG2 this transmembrane orientation is not obtained and thus this orientation indicates synergy [4]. It was possible to identify mutations reducing or inhibiting the synergy of the peptides, and a single amino acid mutation of PGLa was enough to completely abolish synergy. On the other hand, a previously non-synergistic peptide could by mutations of two amino acids be modified to show strong synergy with MAG2. From these results a model of the peptide-peptide complex in the membrane, likely responsible for synergy, could be developed and will be presented.

References: [1] E Strandberg, P Tremouilhac, P Wadhwani, AS Ulrich (2009). *Biochim Biophys Acta* **1788**, 1667. [2] S Ruden, K Hilpert, M Berditsch, P Wadhwani, AS Ulrich (2009). *Antimicrob Agents Chemother* **53**, 3538. [3] J Zerweck, E Strandberg, J Bürck, J Reichert, P Wadhwani, O Kukharenko, AS Ulrich (2016). *Eur Biophys J*, Doi: 10.1007/s00249-016-1120-7. [4] P Tremouilhac, E Strandberg, P Wadhwani, AS Ulrich (2006). *J Biol Chem* **281**, 32089.