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Abstract

From Hymenoptera Venom to Bioactive Peptides †

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Abstract: Animal venoms contain hundreds of molecules, the majority of these molecules have pharmacological activity. The medicinal uses of scorpion and snake venoms are well documented in folk remedies and in traditional Western and Chinese medicine (Harvey et al., 1998, Koh et al., 2006). The first AMP from animal venoms was discovered in 1967. Melittin is the main active component of Apis mellifera bee venom with anti-Gram + and Gram- activity but also anti-fungal, anti-parasitic, anti-HIV and anti-cancer activity but is highly toxic to mammalian cells (Fennel et al., 1967). Since then, nearly 2900 AMPs have been identified to date, of which more than 2400 (83%) have antibacterial activity and more than 1300 are derived from animal venoms (Wang et al., 2004; 2009; 2016). We have identified, isolated, and characterised a peptide from hymenopteran venom with gram-acting antibacterial and antitumour activity. In a structure-activity study using several synthetic analogues, the activity and stability of this peptide were improved. Indeed, these analogs inhibit the growth of Pseudomonas (P.) aeruginosa with a MIC ranging from 0.78 to 3.125 micromolar. The novel L- and D- peptides : i) don't exhibit any hemotoxicity up to 10 mM; ii) they have a strong therapeutic index not only for Gram-bacteria P.aeruginosa (Therapeutic Index of 3200) and E. coli (T .I of 1600), (iii) they showed no cytotoxicity against normal human cells (HUVEC, IMR 90 and BEAS cells) at high concentration; iiv) stability assay showed that only D- aa analogs were not affected by proteases and human serum, demonstrating that they can be used without inactivation by digestive intestinal digestive enzymes; v) the use of HeLa TLR4/IL-8 Renilla Luciferase cell line showed that they inhibit the binding of Gram negative lipopolysaccharide (LPS) to TLR4 and the related inflammation in a dose-dependent way with IC50 ranging from 7.2 μM to 16.8 μM; vi) they do not induce bacterial resistance after 30 days, no variation in MIC being observed unlike in the case of imipenem and Gemifloxacin against P. aeruginosa which increased after exposure to the antibiotic for 10 days. The preliminary results showed that the antibacterial effect of the peptides is related to their ability to rapidly (within few minutes) permeabilize the bacterial membranes (European patent2020 EP19218273.1).