Elucidation of synthetic and natural multifunctional peptides for development of biotechnological tools

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Peptide rational design was here used to guide the creation of novel compounds that could help on resistant bacteria control. Firstly, two novel short β-lactamase inhibitors with five amino acid residues length were generated. Molecular modeling associated to peptide synthesis improved bactericidal efficacy in addition to amoxicillin, ampicillin and cefotaxime. Docked structures were consistent with calorimetric analyses against bacterial □-lactamases. These two compounds were further tested in mice. Whereas commercial antibiotics alone failed to cure mice infected with *Staphylococcus aureus* and *Escherichia coli* expressing β-lactamases, infection was cleared when treated with antibiotics in combination with peptides, clearly suggesting that peptides were able to neutralize bacterial resistance. Moreover, host-defense peptides derived from mastoparan and clavanin families were redesigned in order to improve antimicrobial activities and decrease mammalian cell toxicity. Both peptides were evaluated in sepsis and wound model infections showing the ability to control the infection caused by Gram-positive and -negative pathogenic bacteria. Moreover in all cases, immune response was also evaluated. In summary, the unusual peptides here described provide leads to overcome β-lactamase-based resistance, a remarkable clinical challenge.