DNA GYRASE ACTIVITY INHIBITION BY PEPTIDES FROM CcdB PROTEIN

Saulo Santesso Garrido; Camila Ap.Cotrim; Eliane Trovatti; Reinaldo Marchetto

UNESP – Instituto de Química – Depto. Bioquímica e Tecnologia Química, Araraquara – SP - Brasil

DNA gyrase is a bacterial DNA topoisomerase responsible for disentangling DNA during DNA replication and transcription. It is the target of several antibacterial agents, including the toxin CcdB. The mechanism of the blocking of the gyrase activity by CcdB is still an object of many debates, but is consensus that the Arg462 residue of GyrA subunit of gyrase and Trp99-Ile101 fragment of CcdB, are involved. As an approach to the problem and to the development of new inhibitors of gyrase, we have synthesized peptide analogues of the CcdB protein and studied its activity by supercoiling assays and bacterial growth. Four analogues were designed and synthesized by SPPS, all containing the C-terminal a-helices (Ser84-Ile101) of the natural CcdB, and important sequences for interaction with the gyrase. All peptides showed inhibition of the supercoiling activity, but the dimer $(CcdB3B)_2$ was the better (MIC = 100 µM). Peptides free not showed antimicrobial activity, but when encapsulated in Liposome (SUV), specially the dimer, were able to inhibit the bacterial growth in liquid culture medium. The growth inhibition *in vitro* was about 80% for Gram negative bacteria. The conclusion that emerges from these data is that the dimeric structure confers an important structural characteristic for the peptide analogues that facilitates the molecular adjustment to the binding site of the enzyme.

Support: FAPESP and CNPq