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882-1 BIOCHEMICAL AND FUNCTIONAL CHARACTERIZATION OF DIGUANYLATE CYCLASE LIC_11128 FROM Leptospira interrogans SEROVAR COPENHAGENI FIOCRUZ STRAIN L1-130.

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Resumo:

Leptospirosis is a worldwide spread zoonosis caused by pathogenic bacteria of the genus *Leptospira*. The pathogenic leptospires species survive a variety of adverse conditions in the external environment and inside the host, producing several mechanisms for their survival. One of these mechanisms is the production of bis-(3′-5′) cyclic dimeric guanosine monophosphate (c-di-GMP), a cellular second messenger that controls several behaviors in bacteria, including the regulation of production of virulence factors. Understanding the production of proteins involved in c-di-GMP synthesis, degradation, and signaling by leptospires is critical to understanding how the bacterium survives. Unfortunately, there are few studies on c-di-GMP production and its influence on bacterial virulence. The LIC_11128 protein is a diguanylate cyclase, responsible for the synthesis of c-di-GMP in *L. interrogans* serovar Copenhageni Fiocruz strain L1-130. Previous studies from our group have shown, *in vitro*, that rLIC_11128 is a dimeric protein, in which one of its monomers binds to 2,5-diketopiperazine Brevianamide F, a secondary metabolite produced by a few fungi and bacteria. To evaluate if *L. interrogans* was affected by the presence of Brevianamide F, we added 100 µM and 300 µM of Brevianamide F to the culture and observed that there was a decrease in the population of leptospires treated compared to the control group ($p<0.05$). We evaluated if *L. biflexa* serovar Patoc 1 strain Paris (non-pathogenic bacterium) was affected by Brevianamide F and the results were similar to those observed with *L. interrogans*. To evaluate whether Brevianamide F affected the growth of other bacteria, we performed the same experiment with *Chromobacterium violaceum*, *Escherichia coli*, *Pseudomonas aeruginosa*, and *Staphylococcus aureus*. Unlike Leptospira, these bacteria showed an increase in their growth when compared to the control group ($p<0.05$). Finally, to evaluate the diguanylate cyclase activity of the enzyme in the presence of Brevianamide F by ion exchange chromatography, we incubated 600nM of the rLIC_11128 with 1mM guanosine-5'-triphosphate (GTP) and 50µM Brevianamide F. The results showed that the enzyme has diguanylate cyclase activity independent of the presence of Brevianamide F. Our results show that Brevianamide F affects the growth of bacteria of the genus *Leptospira*, unlike other genera of bacteria. Furthermore, the diguanylate cyclase activity of rLIC_11128 is independent of the presence of Brevianamide F.

Palavras-chave:

2,5-diketopiperazine, Brevianamide F, c-di-GMP signaling, leptospirosis, LIC_11128

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