Potent Elastase Inhibitors from Cyanobacteria: Structural Basis and Mechanisms Mediating Cytoprotective and Anti-Inflammatory Effects in Bronchial Epithelial Cells

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Introduction

Marine cyanobacteria are prolific and potent producers of serine protease inhibitors. Here we comprehensively characterized new elastase inhibitors from marine cyanobacteria, defined their selectivity, molecular basis of potent activity and cellular effects in bronchial epithelial cells.

Experimental

^{1}H and 2D NMR spectra were recorded on a Bruker Avance II 600 MHz spectrometer equipped with a 5 mm TXI cryogenic probe using residual solvent signals as internal standards.

Results and Discussion

Using ^{1}H NMR-guided purification, six new members of the 3-amino-6-hydoxy piperidone (Ahp)- and 2-amino-2-butenoic acid (Abu)-containing cyanobacterial cyclodepsipeptides were purified and given the trivial names symplostatins 5–10. Structure-activity relationship studies and X-ray cocrystal structure analysis allowed a detailed assessment of critical and tunable structural elements for potent elastase inhibition. Comprehensive protease profiling indicated preferential selectivity of these compounds for elastase. To realize the therapeutic potential of these cyclodepsipeptides, we probed the cellular effects of a novel and representative family member, symplostatin 5, which attenuated the downstream cellular effects of elastase in an epithelial lung model system, alleviating clinical hallmarks of chronic pulmonary diseases such as cell death, cell detachment and inflammation. This compound attenuated the effects of elastase on receptor activation, proteolytic processing of the adhesion protein ICAM-1, NF-κB activation and transcriptomic changes, including the expression of pro-inflammatory cytokines *IL1A*, *IL1B* and *IL8*.

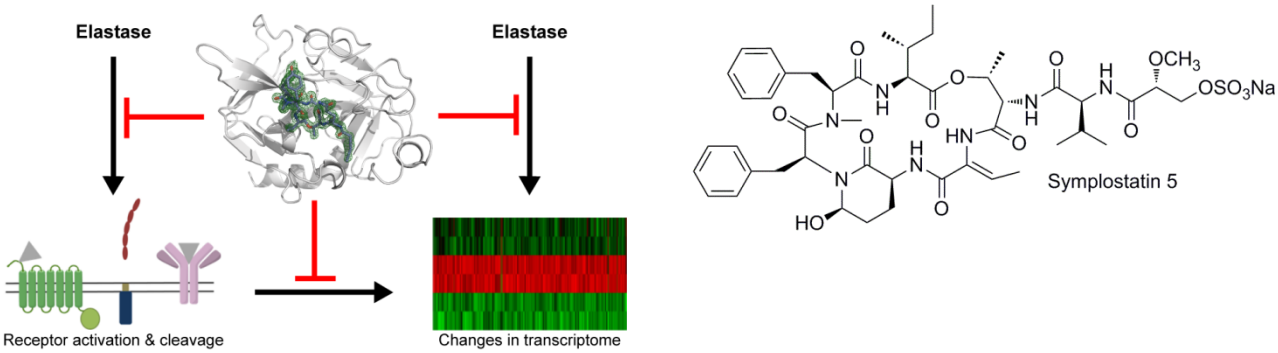

Figure 1. Mechanism of action of cyclodepsipeptide elastase inhibitors from marine cyanobacteria and the model compound symplostatin 5.

Conclusions

Cyanobacterial cyclodepsipeptide elastase inhibitors demonstrated potent and selective inhibitory activity, with superior in vitro activity in modulating the cellular effects of elastase.

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References

[1] Salvador, L.A., *et al*., Journal of Medicinal Chemistry, **56**, 1276-1290 (2013).