Perthamide C inhibits eNOS and iNOS expression and has immunomodulating activity invivo.

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Here we have characterized perthamide C, a cyclopeptide from a Solomon Lithistid sponge *Theonella swinhoei*, which displays an anti-inflammatory/immunomodulatory activity. The study has been performed using the carragenan-induced mouse paw edema that displays an early (0-6h) and a late phase (24-96h).
Perthamide C significantly inhibits neutrophils infiltration in tissue both in the early and late phases. This effect was coupled to a reduced expression of the endothelial nitric oxide synthase (eNOS) in the early phase while cyclooxygenase-1 and 2 (COX-1, COX-2), and inducible NOS (iNOS) expression were unaffected. In the late phase perthamide C reduced expression of both NOS isoforms without affecting COXs expression. This peculiar selectivity toward the two enzymes deputed to produce NO lead us to investigate on a possible action of perthamide C on lymphocytes infiltration and activation. We found that perthamide C inhibited the proliferation of peripheral lymphocytes, and that this effect was secondary to its metabolic activation *in vivo*. Indeed, in vitro perthamide C did not inhibit proliferation as opposite to its metabolite perthamide H.
In conclusion, perthamide C selectively interferes with NO generation triggered by either eNOS or iNOS without affecting either COX-1 or COX-2. This in turn leads to modulation of the inflammatory response through a reduction of vascular permeability, neutrophil infiltration as well as lymphocyte proliferation.