Mariarita Brancaccio (M.Sc)

Biological roles and pharmacological potentials of marine 5-thiohistidine compounds

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The Open University, UK

School of Life, Health and Chemical Sciences

Stazione Zoologica Anton Dohrn, IT

Department of Biology and Evolution of Marine Organisms

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Director of studies:

Dr. Immacolata Castellano
Department of Biology and Evolution of Marine Organisms,
Stazione Zoologica Anton Dohrn, Naples, Italy

Internal Supervisor:

Dr. Anna Palumbo
Department of Biology and Evolution of Marine Organisms,
Stazione Zoologica Anton Dohrn, Naples, Italy

External Supervisor:

Prof. Dr. Florian Seebeck
Department of chemistry
University Basel, Switzerland

Abstract

5-thiohistidines are histidine-derived thiols first isolated from marine invertebrates in complex with other larger molecules or in free methylated forms. The biosynthesis of these compounds has developed in bacteria, microalgae, and invertebrates, but it has been lost in vertebrates and consequently in humans. Among them, ovothiols are methyl-5-thiohistidines first discovered in sea urchins, where they play a key role in the protection of the eggs from the oxidative burst associated with fertilization and early embryos from environmental cues. The key enzymes responsible for ovothiol biosynthesis, the sulfoxide synthase OvoA and the β-lyase OvoB, have been characterised and comparative genomics has revealed that its biosynthesis is much more widespread than previously thought.

Recently, it has been demonstrated that ovothiol A (N-p-methyl-5-thiohistidine), purified from sea urchin *Paracentrotus lividus* eggs, exhibits anti-proliferative and anti-inflammatory activity in an *in vitro* model of human hepatocarcinoma cells and in an *in vitro* model of human endothelial cells, respectively.

In this *scenario*, the aim of my thesis was to investigate the biological roles and pharmacological potential of 5-thiohistidines.

To study the biological role of this metabolite and to deepen the distribution and diversification of the ovothiol pathway in the marine world, we conducted an in-depth analysis on bacterial genomes. We highlighted that most bacteria, especially those living in acquatic environment, including several symbionts and parasites, evolved the biosynthetic pathways of ovothiol, in particular both OvoA and OvoB.

Moreover, to shed new light on the use of these molecules as new anti-inflammatory agents, we used an *in vivo* model of hepatic fibrosis and *in vitro* system of human keratinocytes to mimic skin inflammation. We identified the molecular mechanisms underlying the action of these molecules in human disorders by emphasizing their anti-inflammatory capacity.