Structure function and evolution of the enzymes involved in the biosynthesis of 5-thiohistidines: from life in the ocean to implications for human health

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Proteins evolution is determined by different factors: mutations of the encoding genes, selection on protein structure and function, regulation of gene expression patterns, position in biological networks. As protein sequence evolves, enzymes can change their reaction profile and accommodate different substrates, thus many enzymes perform multiple reactions and are called promiscuous. Many studies have revealed a possible role of promiscuous enzymes as intermediates in the evolution of novel functions. Ocean offers a unique opportunity to study protein evolution as life began in the ocean and tells the story of how the most complex organisms evolved from primordial bacteria. The ability of organisms to adapt to the changing conditions of the habitat is crucial to guarantee their survival and reproduction. Adaptation to the living environment drives the innovation, exchange, and demise of enzyme function. At the metabolic level, this process of adaptation is related to the ability of enzymes to evolve beneficial functions and improve the fitness in a changing environment. On the other hand, mankind can get ideas from nature and exploit the unique properties displayed by specialized enzymes and molecules for biotechnological and pharmaceutical applications.

This PhD project aims to integrate comparative genomics and transcriptomics, with protein biochemistry, in order to shed light on the evolution of the enzymes involved in the biosynthesis of 5-thiohistidines with great potential as pharmaceuticals. 5-thiohistidines are sulphur-redox molecules, named also ovothiols, because isolated in large amounts in sea urchin eggs. These molecules display unique antioxidant properties and have been recently proposed as anti-proliferative compounds. The discovery of the enzyme responsible for the first step of the 5-thiohistidines biosynthesis, 5-histidylcysteine sulfoxide synthase (OvoA) in bacteria and the upcoming availability of new sequenced genomes open new perspectives for structural, biochemical and pioneering functional studies of the pathway that in marine organisms produces ovothiol. At present, there is a gap of knowledge about the mechanism of action of OvoA, the biological significance of ovothiol biosynthesis in the ocean and its potential pharmacological applications. To cover this gap, this project implies the following tasks and objectives: 1. *in silico* analysis of marine genomes and transcriptomes to reconstruct the evolutionary history of OvoA; 2. cloning of OvoA and/or novel protein domains from marine model organisms to study the structure and function relationship of the enzyme and the implications for its evolution; 3. biochemical approaches to disclose the molecular interactions of 5-thiohistidines with a just identified enzymatic target of human cancer cells for pharmaceutical exploitations.