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On ovothiol biosynthesis and biological roles: from life in the ocean to therapeutic potential

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Ovothiols are sulfur-containing natural products biosynthesized by marine invertebrates, microalgae, and bacteria. These compounds are characterized by unique chemical properties suggestive of numerous cellular functions. For example, ovothiols may be cytoprotectants against oxidative stress, serve as building blocks of more complex structures and may act as molecular messengers for inter- and intracellular signaling. Detailed understanding of ovothiol physiological role in marine organisms may unearth novel concepts in cellular redox biochemistry and highlight the therapeutic potential of this antioxidant. The recent discovery of ovothiol biosynthetic genes has paved the way for a systematic investigation of ovothiol-modulated cellular processes. In this highlight we review the early research on ovothiol and we discuss key questions that may now be addressed using genome-based approaches. This highlight article provides an overview of recent progress towards elucidating the biosynthesis, function and potential application of ovothiols.

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1 Background and open challenges

The extraordinary beauty of marine landscapes has always inspired scientists and artists for the huge richness in biodiversity, reflecting billions of years of evolution. Marine diversity also extends to molecular scales making the oceans one of the largest repositories for natural products with amazing structures and potentially life-saving therapeutic activities.[1] One particularly interesting group of natural compounds are sulphur-containing molecules because of their ability to participate in cellular redox chemistry. Low-molecular-weight thiols, thiones, thioethers and disulfides play a key role in maintaining cellular redox homeostasis and enable organisms to survive taxing and changing environmental conditions.[2,3] Probably one of the most abundant, yet least investigated marine sulfur compound is ovothiol A (**1**, Fig. 1). This 5-thiohistidine has been isolated for the first time from sea urchin eggs, which resulted in its naming ovothiol.[4–6] The unique antioxidant properties[7–9] and the broad distribution among marine invertebrates, microalgae and Proteobacteria provide reason to believe that ovothiol A and its derivatives ovothiol B and C (**2** & **3**, Fig. 1) play important roles in cellular biochemistry.[10,11]

In the past, systematic investigations on the physiological function of thiohistidines were difficult, because the origin and distribution of these compounds was obscure. The recent identification of ovothiol biosynthetic genes[10] and the growing availability of sequenced genomes from bacteria, fungi and higher eukaryotes, have opened new avenues to examine several key questions, including those about (i) the evolutionary origin of ovothiols (ii) the distribution of ovothiol biosynthetic genes among extant marine organisms (iii) the catalytic mechanisms of ovothiol biosynthetic enzymes and most importantly, (iv) the physiological role of ovothiol. Answers to these questions are likely to uncover novel concepts in redox biochemistry and may also inspire the development of novel therapeutic approaches and biotechnological applications based on thio-histidines.

The objective of this article is to summarize current answers to these questions. We will also identify future challenges and discuss how bioinformatics, comparative and functional genomics, structural biology and enzymology should be combined to develop a comprehensive perspective on ovothiols in marine organisms, and to unravel the potential of ovothiol biosynthesis in the emerging research field of blue biotechnology.

2 Occurrence of ovothiol and related marine thiohistidines

Almost forty years ago ovothiols were recognized as common metabolites in marine invertebrates. Ovothiol A, 5(*N*π)-methyl thiohistidine (**1**, Fig. 1) was isolated from the eggs of the sea urchins *Paracentrotus lividus*,[4] and *Arbacia lixula*, in the holothuroid, *Holothuria tubulosa*, the asteroids, *Astropecten aurantiacus* and *Marthasterias glacialis*,[5] the mottled sea star, *Evasterias troschelii*,[7] in the eggs and biological fluids of

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