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Research review paper

Metabolic engineering for the microbial production of marine bioactive compounds

Xiangzhao Mao [a,b,*], Zhen Liu [b], Jianan Sun [b], Sang Yup Lee [a,**]

[a] Metabolic and Biomolecular Engineering National Research Laboratory, Department of Chemical and Biomolecular Engineering (BK21 Plus Program), BioProcess Engineering Research Center, Center for Systems and Synthetic Biotechnology, Institute for the BioCentury, KAIST, Daejeon, Republic of Korea
[b] College of Food Science and Engineering, Ocean University of China, Qingdao, People's Republic of China

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ABSTRACT

Many marine bioactive compounds have medicinal and nutritional values. These bioactive compounds have been prepared using solvent-based extraction from marine bio-resources or chemical synthesis, which are costly, inefficient with low yields, and environmentally unfriendly. Recent advances in metabolic engineering allowed to some extent more efficient production of these compounds, showing promises to meet the increasing demand of marine natural bioactive compounds. In this paper, we review the strategies and statuses of metabolic engineering applied to microbial production of marine natural bioactive compounds including terpenoids and their derivatives, omega-3 polyunsaturated fatty acids, and marine natural drugs, and provide perspectives.

Contents

* Corresponding author at: College of Food Science and Engineering, Ocean University of China, Qingdao, People's Republic of China.
** Corresponding author.
E-mail addresses: xzhmao@ouc.edu.cn (X. Mao), leesy@kaist.ac.kr (S.Y. Lee).

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1. Introduction

Marine bioactive compounds are playing increasingly important roles in the development of functional foods and drugs based on their antimicrobial, antitumor, antioxidant and other properties (Yamanaka et al., 2014; Lechner et al., 2011; Ambati et al., 2014). Marine bioactive compounds were discovered in many different marine organisms such as sharks (Xu et al., 2016b) and other fishes (Mühlroth et al., 2013), shrimps and crabs (Giuffrida et al., 2016), algae (Lemoine and Schoefs, 2010), sponges (Abdelmohsen et al., 2014), bacteria (Ukibe et al., 2009), cyanobacteria (Ongley et al., 2013), and others.

For some marine bioactive compounds traditionally isolated from the natural producers, attempts were made to produce them by metabolic engineered microorganisms. For example, attempts were made to produce squalene, which was traditionally obtained from the liver of deep-sea shark, by metabolically engineered microorganisms (Xu et al., 2016b). Rapid advances in systems biology and bioinformatics have allowed much more rapid discovery of novel biosynthetic pathways of marine bioactive compounds, facilitating the attempts to produce these bioactive compounds by metabolic engineering and synthetic biology (Lane and Moore, 2010).

Bio-based production of various chemicals, fuels and materials from renewable non-food biomass has become increasingly successful. A number of review papers on the strategies of metabolic engineering for the production of building block chemicals and polymers (Ahn et al., 2016; Lee et al., 2011a; Chung et al., 2015) and biofuels (Cho et al., 2015; Cheon et al., 2016; Choi et al., 2014) are available. Also, metabolic engineering of microorganisms for the production of secondary metabolites has been reviewed (Gustavsson and Lee, 2016; Kim et al., 2012b; Lee et al., 2011b; Hwang et al., 2014; Weber et al., 2015). Although there have been a few review papers on production of marine bioactive compounds by metabolic engineering, they are rather limited to several key products: astaxanthin (Ye et al., 2015), eicosapentaenoic acid (EPA; Hong et al., 2011), and omega-3 polyunsaturated fatty acids (omega-3 PUFAs; Gong et al., 2014). To the best of our knowledge, there is no comprehensive review covering production of diverse marine bioactive compounds by metabolic engineering and synthetic biology. In particular, there has been no review on metabolic engineering studies on the production of marine natural drugs. Although most of the discovered marine natural drugs still cannot be produced by metabolic engineering, there have been increasing cases reported on metabolic engineering of native organisms or heterologous hosts for the production of marine natural drugs such as enterocin (Bonet et al., 2014), lyngbyatoxin (Videau et al., 2016) and patellamides (Long et al., 2005). In this paper, we review the works on metabolic engineering and synthetic biology towards the production of marine bioactive compounds, which are for convenience classified as terpenoids and their derivatives, omega-3 PUFAs, and marine natural drugs (Fig. 1). We have to admit that most of the examples described below are product-specific case studies, yet without adopting systems-level metabolic engineering strategies or more recently available synthetic biology tools. Nonetheless, it is hoped that readers will be able to quickly update themselves through this review on what the state-of-the-art works are available for future studies.

2. Terpenoids and their derivatives

Terpenoids are natural compounds built up from isoprene subunits (Ajikumar et al., 2008). Squalene ($C_{30}H_{50}$) naturally accumulating in the liver of deep-sea shark is a marine terpenoid (Donald et al., 1997).

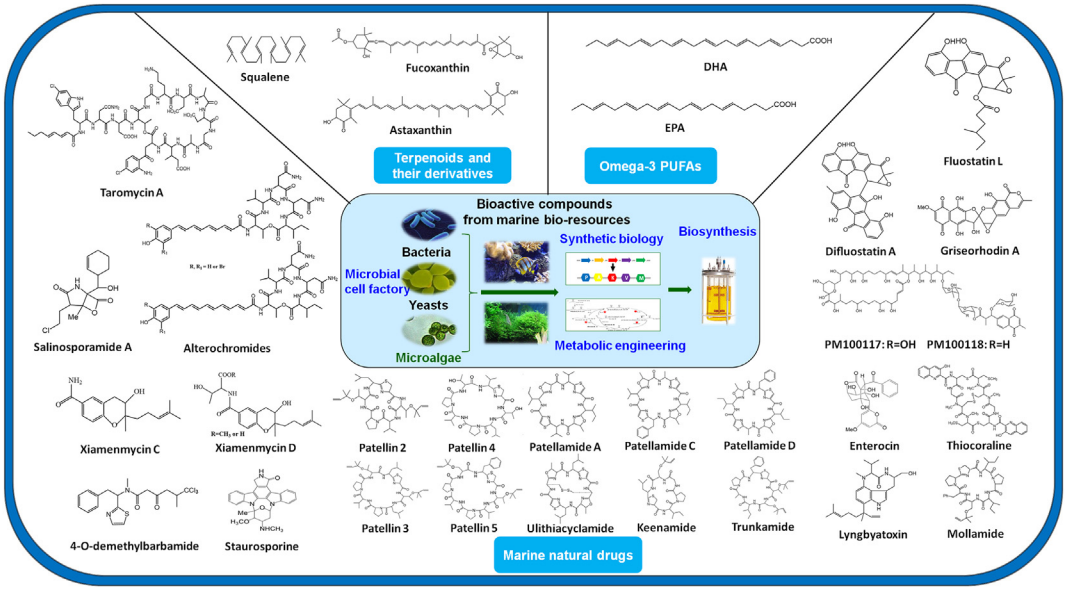

Fig. 1. Marine bioactive compounds produced by bacteria, yeasts and microalgae developed by metabolic engineering and synthetic biology. The bioactive compounds can be grouped into terpenoids and their derivatives, omega-3 PUFAs and marine natural drugs.

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