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Polyunsaturated fatty acid biosynthesis in myxobacteria: different PUFA synthases and their product diversity†

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Polyunsaturated fatty acids (PUFAs), particularly the omega-3 long-chain PUFAs (LC-PUFAs) eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are well known for their beneficial health effects. The obvious limitation of the present EPA/DHA key source, fish oil, demands for alternative and sustainable PUFA resources and several biotechnological approaches addressing this problem are currently under development. Different marine microorganisms are known to produce PUFAs *de novo* under strictly anaerobic conditions employing polyketide synthase (PKS)-like enzymes known as PUFA synthases. Here, we report for the first time the characterization of such PUFA synthases from terrestrial origin. Two distinct types of PUFA biosynthetic gene clusters were discovered, originating from linoleic acid producing myxobacteria of the genus *Sorangium* as well as from species of the recently discovered myxobacterial genus *Aetherobacter*, that turned out to be prolific producers of EPA and DHA. The identified biosynthetic pathways differ significantly from the marine systems in terms of gene organization, catalytic domain arrangement and sequence identity of the encoded PUFA synthases. Notably, a unique domain, which most likely acts as 1-acylglycerol-3-phosphate *O*-acyltransferase was identified in these myxobacterial PUFA synthases. As the native producer strains grow slowly, are difficult to handle and genetic modification has proven difficult, synthetic biotechnology approaches were applied to establish a heterologous production platform in the myxobacterial model strain *Myxococcus xanthus*.

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Introduction

Long-chain polyunsaturated fatty acids (LC-PUFAs), including *n*-3 and *n*-6 long-chain fatty acids, are inherent constituents of nutritional research and have gained increasing scientific interest over the past decade. Numerous studies address beneficial effects of LC-PUFAs on human health. In particular, the *n*-3 LC-PUFAs eicosapentaenoic acid (EPA, 20 : 5, *n*-3) and docosahexaenoic acid (DHA, 22 : 6, *n*-3) are associated with prevention and treatment of cardiovascular diseases, obesity, and diabetes due to their blood pressure-lowering and anti-inflammatory properties.[1] They have been shown to inhibit the formation of pro-inflammatory eicosanoids derived from *n*-6 long-chain fatty acids, such as arachidonic acid (AA, 20 : 4, *n*-6), and to promote the formation of endogenous anti-inflammatory and pro-resolving lipid mediators.[2,3]

As awareness towards beneficial properties of *n*-3 LC-PUFAs increases, the demand for dietary PUFA supplements has risen intensely over the past few years and will most likely continue to grow significantly. Fish oil is the most abundant and widely used natural source for EPA and DHA these days. However, since the supply of high quality fish oil is significantly declining, it is necessary to establish alternative and sustainable biological sources.[4] Of great interest are the prokaryotic and eukaryotic microorganisms capable of producing LC-PUFAs in high amounts.[5] To make use of their biosynthetic capacity and to develop suitable biotechnological production processes, the characterization of the involved biosynthetic pathways is of crucial importance. The most prominent and predominant pathways in eukaryotic PUFA producers represent the aerobic pathways, that combine several oxygen-dependent desaturases and elongases for the conversion of saturated fatty acids into PUFAs.[6] An alternative pathway was discovered in marine microbes that employs iterative type I fatty acid synthase (FAS)/polyketide synthase (PKS)-like enzymes (PUFA synthases) for *de novo* biosynthesis of LC-PUFAs from acyl-CoA precursors under strictly anaerobic conditions (Fig. 2A).[7–9] The biosynthetic machineries are encoded by PUFA (*pfa*) biosynthetic gene

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