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REVIEW

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ABSTRACT

Mollusks are excellent dietary sources for LC-PUFA. However, the main challenge limiting mollusk production is the high mortality rate of molluskan larvae in early life cycle stages. This paper reviews scientific evidences on molecular and biochemical studies of LC-PUFA biosynthesis in commercially important molluskan species. It carefully summarizes the pertinent data published on specific research questions to improve the understanding of the diverse evidences. It is helpful to clarify the current state of research and determine topics for future studies on LC-PUFA biosynthesis in mollusks. From the analysis of published data, mollusks have the ability to biosynthesis LC-PUFA to a certain extent. LC-PUFA biosynthesis information of commercially important molluskan species can be useful to determine the fatty acids essential for their diet. Therefore, specific management strategies or feeds can be developed to strengthen the industry by improving the health and survival rate of molluskan larvae.

Introduction

Long chain-polyunsaturated fatty acids (LC-PUFA) are fatty acids with more than two double bonds and more than 19 carbon numbers, including the well-known n-6 series of arachidonic acid (20:4n-6, ARA), and n-3 series of eicosapentaenoic acid (20:5n-3, EPA) and docosahexaenoic acid (22:6n-3, DHA). The primary producers of LC-PUFA include microalgae, some non-autotrophic protozoa, bacteria, fungi, etc. (Martins et al. 2013; Vrinten et al. 2013). In animals, LC-PUFA biosynthesis is usually carried out through aerobic pathways, in which desaturases are one of the key enzymes involved (Figure 1) (Castro, Tocher, and Monroig 2016). Vertebrates lack of ωx desaturase, thus they are unable to biosynthesis of linoleic acid (18:2n-6, LA) and α-linolenic acid (18:3n-3, ALA), but they possess some ability to convert LA and ALA from food into n-6 LC-PUFA and n-3 LC-PUFA, respectively (Cook and McMaster 1996; Sprecher 2000; Hastings et al. 2001; Monroig and Kabeya 2018). Unlike vertebrates, ωx desaturases are widely present in invertebrates, including cnidarians, rotifers, nematodes, mollusks, arthropods and annelids (Kabeya et al. 2018). Up to now, at least two mollusks (limpet *Patella vulgate* (Kabeya et al. 2018) and common octopus *Octopus vulgaris* (Garrido et al. 2019)) have been reported to process two methyl-end (or ωx) desaturases, one of which exhibits Δ12 activity and converts oleic acid (18:1n-9, OA) to LA. The second ωx desaturase exhibits Δ15 activity and can biosynthesis ALA from LA. In addition to Δ15 desaturation, the

second ωx desaturase also shows Δ17 and Δ19 desaturase activities, which enable the conversion of C18 to C22 n-6 LC-PUFA substrates to corresponding n-3 LC-PUFA (Kabeya et al. 2018). The animal biosynthesis pathways of EPA and ARA from ALA and LA involve two different desaturases, namely Δ6 and Δ5 desaturases, or Δ8 and Δ5 desaturases in the biosynthesis pathway of Δ6 and Δ8, respectively. The production of DHA from EPA requires several additional steps, including two elongation steps by Elovl5/2/4 and Elovl2/4, one desaturation step by Δ6 Fad, and a peroxisome chain shortening step. In organisms containing Δ4 Fad, DHA can be directly produced from 22:5n-3.

LC-PUFAs are very important for human health and play a crucial role in membrane structure, neurodevelopment, immune response and disease treatment (Fritsche 2006; Russo 2009; Moylan et al. 2013). In general, LC-PUFA cannot be sufficiently biosynthesized in the human body, therefore LC-PUFAs or LC-PUFA precursors must be acquired from the diet (Bell et al. 2007; Bell and Tocher 2009). Traditionally, marine fish has been the primary dietary source of EPA and DHA for humans, but due to overfishing, marine fish numbers are in perilous decline (William and Burdge 2006), while aquaculture has became an alternative source of LC-PUFA and increasingly fills this demand (FAO 2018; Tan et al. 2020a). Unfortunately, due to the lack of omega-3 LC-PUFA in vegetable oils (the main feed ingredient), lipid quality of farmed fish is much lower than that of wild-caught fish (Blanchet et al. 2005; Sprague, Dick, and
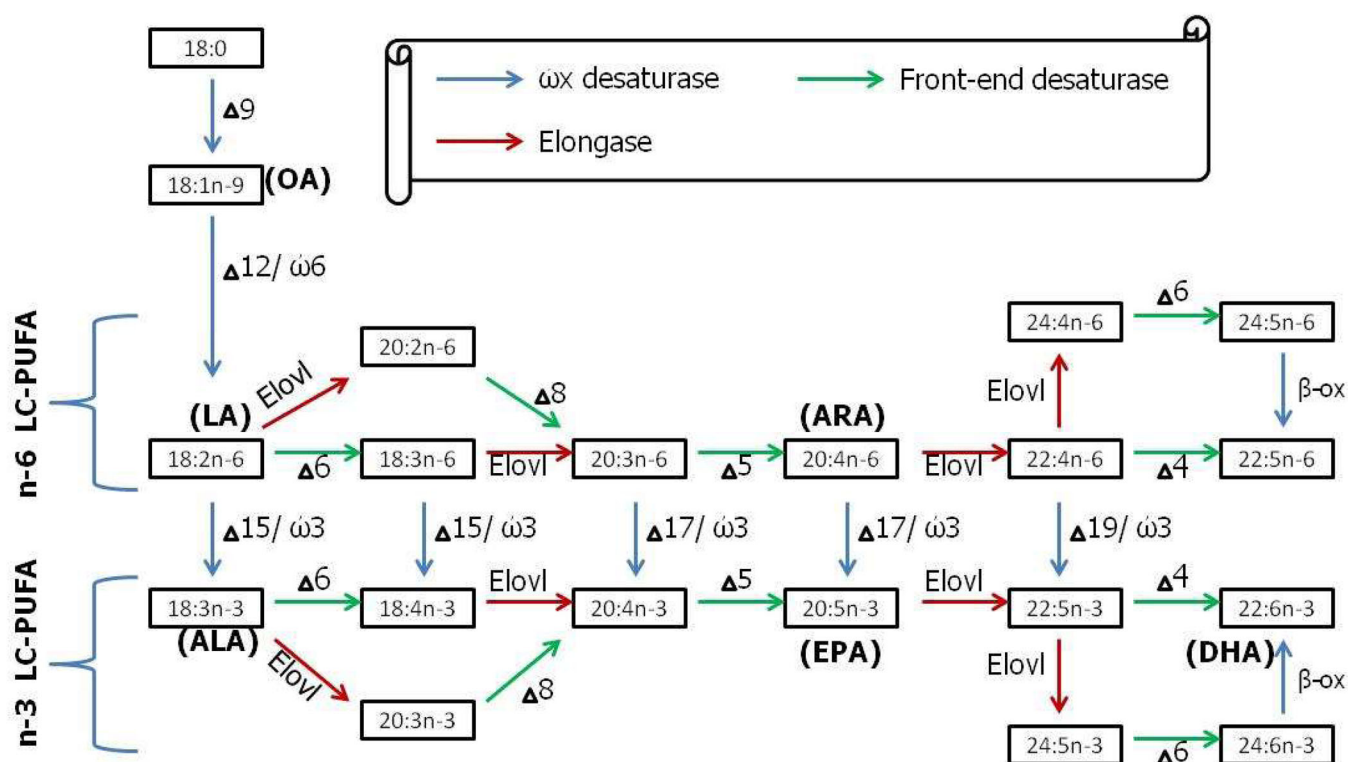
Figure 1. Biosynthesis pathways of long-chain polyunsaturated fatty acid (LC-PUFA) in animals (Elovl = Elongation reactions; ß-ox= ß- oxidation). Adapted from Monroig and Kabeya (2018).

Tocher 2016; De Roos et al. 2017). The shortage of high quality lipid resources has stimulated the exploration of alternative sources of natural LC-PUFA. It is well known that molluskan fatty acids are highly unsaturated, mainly due to they graze on marine phytoplankton rich in LC-PUFA (Joseph 1982; Pirini et al. 2007). Therefore, mollusks are gradually becoming an excellent dietary source for LC-PUFA (Surm et al. 2015; Castro, Tocher, and Monroig 2016; Tan et al. 2020a).

Unfortunately, intense fishing pressures and unsustainable exploitation methods deplete the natural molluskan population (Tan and Ransangan 2016a). Regular visits to landing centers and wet markets over the years have shown that the proportion of large mollusks in catch has declined, the sex ratio has been skewed, the catch per unit effort has declined, and immature virgins are under heavy fishing pressure (Dolorosa and Dangan-Galon 2014). All these observations indicate that the mollusk fishing industry is unsustainable and that the level of current fishing pressure is indeed far beyond the reproductive and recruitment capacity of most mollusks (Oon 1980; Rueda and Urban 1998; Tan and Ransangan 2016a).

At an unprecedented increase in demand, the supply of mollusks captured in the wild has declined, which has driven people's interest in molluskan aquaculture. To date, molluskan aquaculture accounts for 21.4% (17.14 million tonnes) of total aquaculture production, with Asia being the largest contributor (92.3%) (FAO 2018). Mollusk aquaculture, especially bivalve aquaculture, has brought significant social and economic benefits to coastal communities in Asia (Tan et al. 2019). It is well known that bivalves feed mainly on phytoplankton, which is the major source of LA, ALA, C20 and C22 fatty acids (FAs) (Viso and Marty 1993; Zhukova, Imbs, and Yi 1998; Tan and Ransangan 2016b). Therefore, marine bivalves are rich in LC-PUFA and can be produced in large quantities (Naylor et al. 2000; Deutsch et al. 2007; Tan et al. 2020b; Tan et al. 2020c; Tan et al. 2020d), providing an ideal alternative protein and LC-PUFA source for marine fish and wild-caught mollusks (Tan et al. 2020a). Aquaculture of these unfed species (especially bivalves, filter feeders) not only requires minimal maintenance cost and effort (Tan and Ransangan 2016c), but is also environmentally friendly and produces high quality aquaculture products rich in LC-PUFA.

In mollusk hatcheries, a major but unresolved challenge is the high mortality rate of molluskan larvae in early life stages, especially in the stage of metamorphosis to benthic life (Monroig, Guinot, et al. 2012; Tan and Ransangan 2016a; Tan and Zheng 2019; Tan and Zheng 2020). LC-PUFA is a key nutrient that is crucial to the survival, growth and reproduction of mollusks (Navarro and Villanueva 2003; Pernet, Bricelj, and Parrish 2005; Monroig, Guinot, et al. 2012; Tan et al. 2020c). As a result, research of LC-PUFA biosynthesis in mollusks has become a priority topic. Many feeding experiments have shown that mollusks may have LC-PUFA biosynthesis capability (De Moreno, Moreno, and Brenner 1976; Waldock and Holland 1984; Zhukova and Svetashev 1986; Zhukova 1991; Durazo-Beltrán et al. 2003; Caers et al. 2003; Xu et al. 2004; Bautista-Teruel, Koshio, and Ishikawa 2011; Da Costa et al. 2012). Moreover, some genes/enzymes involved in LC-PUFA biosynthesis have been functionally characterized in several mollusks, which provides molecular evidence that mollusks also

possess Fads and Elvols involve in LC-PUFA biosynthesis (Li et al. 2013; Liu, Guo, et al. 2014; Liu, Zhang, et al. 2014; Liu et al. 2013; Monroig, Guinot, et al. 2012; Monroig, Navarro, et al. 2012; Monroig et al. 2016; Ran et al. 2018, 2019).

In this paper, the molecular cloning and functional characterization of cDNA encoding fatty acyl desaturases (Fads) and elongases (Elvols) involve in LC-PUFA biosynthesis in commercially important mollusks were reviewed. This paper summarizes the available data on LC-PUFA biosynthesis in commercially important mollusks. The contents of this review are very useful in determining essential FAs for commercially important molluskan species. Therefore, specific management strategies or feeds can be formulated to improve the health and survival rate of molluskan larvae.

Biochemical studies on the LC-PUFA biosynthesis in aquaculture important mollusk species

The study of fatty acids in mollusks (mainly bivalves and gastropods) began in the 1870s (Ackman, Epstein, and Kelleher 1974). Lipid composition and metabolism of many marine mollusks have been well documented, with cephalopods, bivalves, and gastropods as excellent sources of omega-3 (Giri and Ohshima 2012; Surm, Prentis, and Pavasovic 2015; Tan et al. 2020c). Earlier studies have reported that mollusks have very limited or no ability to synthesize $n-3$ and $n-6$ LC-PUFAs through elongation and desaturation of LA and ALA (Waldock and Holland 1984; Chu and Greaves 1991) because they seem to lack the Δ6 FAD that completes the first step of LC-PUFA biosynthesis (Pirini et al. 2007). Nevertheless, feeding experiments and gene expression studies have shown that they may have some ability to biosynthesis LC-PUFA.

The results of feeding experiments with radioactive fatty acids have shown that clam *Mesodesma mactroides* have the ability to elongate LA and ALA (De Moreno, Moreno, and Brenner 1976). Moreover, Pacific oyster *Crassostrea gigas* has been demonstrated to desaturate and elongate 14 C-labeled LC-PUFA precursors, which are provided through diet (microalgae), to LC-PUFAs including EPA and DHA (Waldock and Holland 1984). In addition, other studies have shown that bivalves have the ability to synthesize some peculiar fatty acids called non-methylene interrupted fatty acids (NMIs) (Zhukova and Svetashev 1986; Zhukova 1991). Other indirect studies have also implied that some bivalves, such as Chilean scallop *Argopecten purpuratus* (Caers et al. 2003) and *Solen marginatus* (Da Costa et al. 2012) have some degree of C18 to C20 bioconversion. Other feeding experiments have also shown that abalone may have the ability to convert LA into ARA and EPA (Durazo-Beltrán et al. 2003; Xu et al. 2004; Bautista-Teruel, Koshio, and Ishikawa 2011). However, it is undeniable that these activities may also be caused by symbiotic bacteria inhabit in mollusks.

On the other hand, a gene expression study based solely on the primers based on the Δ6 Fad sequences of rainbow trout suggests that the Jade Tiger hybrid abalone has a Δ6

desaturase (Mateos, Lewandowski, and Su 2011, 2012a, 2012b). Moreover, through blasts against the genome of Pacific oyster *Cr. gigas* (Zhang et al. 2012), some putative fatty acyl desaturases, such as Δ5-like (EKC23483) and Δ6-like (EKC33620) desaturases, as well as some Elovl-like proteins (EKC25061, EKC38587, EKC32059) are identified, which may provide some clues that Pacific oyster may have the ability of sequential desaturation and elongation of essential LC-PUFA precursors (LA and ALA). Recently, a meta-analysis of known facts about PUFA biosynthesis in aquatic invertebrates has also revealed that genes for de novo LC-PUFA biosynthesis are widespread in invertebrates (Kabeya et al. 2018). However, the existence of Fads and Elovls needs to be confirmed by cloning and functional characterization.

Molecular studies on the LC-PUFA biosynthesis pathways in aquaculture important molluscs

In mollusks, desaturase and elongase involved in LC-PUFA biosynthesis have been cloned and characterized from two cephalopods (common octopus *Octopus vulgaris* (Monroig, Guinot, et al. 2012; Monroig, Navarro, et al. 2012; Monroig et al. 2017; Garrido et al. 2019) and common cuttlefish *Sepia officinalis* (Monroig et al. 2016)), three marine bivalves (noble scallop *Chlamys nobilis* (Liu et al. 2013; Liu, Guo, et al. 2014; Liu, Zhang, et al. 2014), razor clam *S. constricta* (Ran et al. 2018, 2019) and Portuguese oyster *Crassostrea angulate* (Zhang et al. 2018)) and one gastropod (abalone *Haliotis discus hannai* (Li et al. 2013)) as summarized in Tables 1 and 2.

Cephalopods

Cephalopods are supplied almost exclusively from wild-caught populations (Vidal, Villanueva, and Andrade 2014). It seems doubtful whether marine fisheries can continue to meet the increasing demand for cephalopods. Since 1950, annual global cephalopod landings have increased steadily, from 0.5 million tons to about 4 million tons in 2016 (FAO 2018). Cephalopods have emerged as the main candidate species for diversifying aquaculture because of their attractive features for aquaculture. Among those deserving attention are short life cycle (4 to 18 months), high food conversion rate (30 to 50%) and they promptly lay eggs when keep in captivity (Lee 1995; Vidal, Villanueva, and Andrade 2014). However, the production of cephalopod aquaculture has been limited by the massive mortality of paralarvae, early pelagic life stages. High mortality and low growth in early pelagic life stages are due to a lack of essential dietary LC-PUFA (Navarro and Villanueva 2003). Since then, many studies have focused on the determination of essential fatty acid requirements in early life stages of common octopus and their ability to biosynthesis LC-PUFA through bioconversion of dietary essential LC-PUFA precursors (Monroig, Guinot, et al. 2012; Monroig, Navarro, et al. 2012; Monroig et al. 2017; Garrido et al. 2019).

Table 1. Substrate conversion rates of yeasts transformed with Elovl2 and Elovl4 isolated from Cephalopods (O. vulgaris and S. Officinalis) (Source: Monroig, Guinot, et al. 2012; Monroig et al. 2016) and bivalves (C. nobilis, S. constricta and Cr. angulata) (Source: Liu et al. 2013; Liu, Zhang, et al. 2013; Liu, Zhang, et al. 2014; Zhang et al. 2018; Ran et al. 2019).

Substrate	Product	Cephalopod				Bivalve					Activity
		O. vulgaris Elovl2/5	O. vulgaris Elovl4	S. Officinalis Elovl2/5	C. nobilis Elovl2/5	C. nobilis Elovl4	S. constricta Elovl4a	S. constricta Elovl4b	S. constricta Elovl4c	Cr. angulata Elovl2/5	
18:2n-6	20:2n-6	40.8	1.1	50.0	37.4	–	0.7	0.4	0.6	25.1	C18 to C20
	22:2n-6	–	26.2	–	–	–	–	–	–	–	C20 to C22
	24:2n-6	–	–	–	–	–	–	–	–	–	C22 to C24
18:3n-3	20:3n-3	13.4	2.8	32.0	19.1	–	4.2	1.6	3.7	6.5	C18 to C20
	22:3n-3	–	3	–	–	–	–	–	–	–	C20 to C22
	24:3n-3	–	–	–	–	–	–	–	–	–	C22 to C24
18:3n-6	20:3n-6	52.3	0.8	51.0	23.5	–	0.57	0.47	4.37	6.8	C18 to C20
	22:3n-6	–	–	–	–	–	–	–	3.0	–	C20 to C22
	24:3n-6	–	–	–	–	–	–	–	–	–	C22 to C24
18:4n-3	20:4n-3	36.9	1	51.0	–	–	0.9	0.5	5.3	–	C18 to C20
20:4n-6	22:4n-6	–	1.0	37.0	28.5	32.0	1.3	1.2	1.91	1.5	C20 to C22
	24:4n-6	–	6.2	–	–	9.0	–	–	61.8	–	C22 to C24
20:5n-3	22:5n-3	2.4	1.9	8.0	7.1	18.0	1.7	100.0	6.2	0.8	C20 to C22
	24:5n-3	–	8.1	21.8	–	5.0	0.4	78.5	–	–	C22 to C24
22:4n-6	24:4n-6	15.9	3.6	3.1	–	–	1.2	2.2	–	–	C22 to C24
	26:4n-6	–	44.5	37.1	–	–	–	32.3	–	–	C24 to C26
	28:4n-6	–	94.1	100.0	–	–	–	–	–	–	C26 to C28
	30:4n-6	–	91.5	42.2	–	–	–	–	–	–	C28 to C30
22:5n-3	24:5n-3	–	4.8	10.1	–	–	2.1	14.9	–	–	C22 to C24
	26:5n-3	–	37.9	59.9	–	–	–	68.0	–	–	C24 to C26
	28:5n-3	–	95.0	100.0	–	–	–	18.4	–	–	C26 to C28
	30:5n-3	–	93.5	68.5	–	–	–	–	–	–	C28 to C30
	32:5n-3	–	51.9	68.5	–	–	–	–	–	–	C30 to C32
22:6n-3	24:6n-3	–	0.7	–	–	–	–	–	–	–	C22 to C24
24:5n-3	26:5n-3	–	1.4	–	–	–	–	–	–	–	C24 to C26
	28:5n-3	–	88.8	–	–	–	–	–	–	–	C26 to C28
	30:5n-3	–	88.6	–	–	–	–	–	–	–	C28 to C30
	32:5n-3	–	63.2	–	–	–	–	–	–	–	C30 to C32
	34:5n-3	–	17.3	–	–	–	–	–	–	–	C32 to C34

Table 2. Substrate conversion rates of yeasts transformed with Fads from Cephalopods (*O. vulgaris* and *S. Officinalis*) (Source: Monroig, Navarro, et al. 2012; Monroig et al. 2016), bivalves (*C. nobilis*, *S. constricta* and *Cr. angulata*) (Source: Liu et al. 2013; Liu, Zhang, et al. 2014; Ran et al. 2018, 2019) and gastropod (*H. discus*) (Source: Li et al. 2013).

		Conversion rate (%)									
		Cephalopod		Bivalve					Gastropod		
Substrate	Product	*O. vulgaris* Fad	*S. Officinalis* Fad	*C. nobilis* Fad5	*C. nobilis* Fad8	*S. constricta* Fad5a	*S. constricta* Fad5b	*S. constricta* Fad6	*H. discus* Fad1	*H. discus* Fad2	Activity
18:2n-6	18:3n-6	1.0	–	–	–	–	–	1.6	–	–	Δ6
18:3n-3	18:4n-3	1.0	–	–	–	–	–	3.6	–	–	Δ6
20:2n-6	20:3n-6	19.0	–	48.0	29.0	–	–	–	–	–	Δ8
20:3n-3	20:4n-3	33.0	–	26.0	13.0	–	–	–	–	–	Δ8
20:4n-6	20:4n-6	39.0	39.0	17.0	–	13.4	11.0	–	15.3	14.9	Δ5
20:4n-3	20:5n-3	39.0	48.0	16.0	–	11.7	8.6	–	31.4	16.0	Δ5
18:00	18:1n-13	20.0	–	39.0	–	16.2	21.4	–	–	–	Δ9
16:00	16:1n-11	54.0	–	–	–	–	–	–	–	–	Δ9

In 2011, Monroig, Navarro, et al. (2012) reported for the first time that the existence of fatty acid desaturase (Fad) in mollusks, common octopus *Octopus vulgaris*. Subsequently, the *O. vulgaris* Elovl5/2 gene (Monroig, Guinot, et al. 2012) and *O. vulgaris* Elovl4 gene (Monroig et al. 2017) have been cloned and functionally characterized. *O. vulgaris* Fad shows Δ5 desaturation activity, *O. vulgaris* Elovl5/2 shows substrate specificity similar to that of vertebrate Elovl5, while *O. vulgaris* Elovl4 shows the ability to elongate 22:5n-3 to 24:5n-3 (Monroig et al. 2017). Although Δ5 Fad enables common octopus to produce EPA and ARA from the dietary substrates of 20:4n-3 and 20:3n-6, respectively, and Elovl4 can compensate for the ability of Elovl5/2 to elongate 22:5n-3 through the Sprecher pathway, but the biosynthesis of EPA, ARA and DHA is still impossible due to the lack of Δ6 or Δ4 desaturation activities (Monroig, Guinot, et al. 2012; Monroig Navarro, et al. 2012; Monroig et al. 2017). Molecular evidence provided by the Octopus bimaculoides genome project (Albertin et al. 2015) shows that the genome of cephalopods contains a single Fad-like desaturase, which is likely to be a Δ5 desaturase. Therefore, EPA, ARA and DHA are essential fatty acids for common octopus. Recently, Garrido et al. (2019) have successfully cloned and functionally characterized two methyl-end (or ωx) desaturases from common octopus *O. vulgaris*. The results have shown that the two ωx desaturases exhibit the regioselectivities of Δ12 and ω3, in which the *O. vulgaris* Δ12 desaturase allow the biosynthesis of dietary essential OA into LA, and then the *O. vulgaris* ω3 with Δ15 activity converts LA into ALA. In addition to Δ15 desaturation, *O. vulgaris* ω3 also process Δ17 activity, allowing conversion of various C-18 and C-20 n-6 LC-PUFA substrates into corresponding n-3 LC-PUFA (enable the production of EPA from ARA). Therefore, ARA and DHA appear to be more limited than EPA and should be considered as the key essential fatty acids for common octopus (Garrido et al. 2019).

On the other hand, two genes (*S. officinalis* Elovl and *S. officinalis* Fad) have been cloned and characterized from common cuttlefish *Sepia officinalis* (Monroig et al. 2016). The results have shown that the *S. officinalis* Elovl could elongate C18 and C20 PUFA substrates, but has no activity on C22 PUFAs, while *S. officinalis* Fad exhibits Δ5-desaturase activity. Since *S. officinalis* Fad does not exhibits Δ4, Δ6

or Δ8 desaturation activities, it is impossible for common cuttlefish to biosynthesis EPA, ARA and DHA from dietary essential C18 PUFA precursors. As a result, like common octopus, EPA, ARA and DHA are essential for common cuttlefish (Monroig et al. 2016). It should be noted that the cDNA encoding enzymes involved in LC-PUFA biosynthesis isolated from common octopus and common cuttlefish are more efficient toward n − 6 PUFA substrates than their homologous n − 3 substrates (Tables 1 and 2).

Bivalves

Bivalve aquaculture is one of the fastest growing food industries in the world. Bivalves, especially cockles, oysters, mussels, and clams, are important sources of animal protein (Tan and Ransangan 2016a, 2016b), with high LC-PUFA content (ARA, EPA and DHA of 19 to 23%, 13 to 16% and 10 to 14%, respectively) (Ruano et al. 2012; Tan et al. 2020c). Bivalve aquaculture accounts for 14 to 16% of the average per capita animal protein for 1.5 billion people, supporting the livelihoods of over 200,000 people mainly in developing countries (FAO 2018). Most bivalves (89%) produced around the world come from aquaculture (FAO 2016). To date, mollusk aquaculture accounts for 21.42% (17.14 million tonnes) of total aquaculture production, of which Asia is the largest contributor (92.27%) (FAO 2018).

To date, genes involved in LC-PUFA biosynthesis have been cloned and characterized from three marine bivalves, including noble scallop *C. nobilis* (Liu et al. 2013; Liu, Guo, et al. 2014; Liu, Zhang, et al. 2014), razor clam *S. constricta* (Ran et al. 2018, 2019) and Portuguese oyster *Cr. angulate* (Zhang et al. 2018). Four genes (Elovl2-like, Elovl4, Fad5 and Fad8) involved in LC-PUFA biosynthesis have been cloned and characterized from noble scallop *C. nobilis* (Liu et al. 2013; Liu, Guo, et al. 2014; Liu, Zhang, et al. 2014). *C. nobilis* Elovl2-like possess the ability to elongate C18 and C20 to C22 (Liu et al. 2013), *C. nobilis* Elovl4 exhibits elongation activity of C24 (Liu, Zhang, et al. 2014), while *C. nobilis* Fad5 and *C. nobilis* Fad8 show desaturation activities of Δ5 and Δ8, respectively (Liu, Guo, et al. 2014) (Table 4). These studies provide the first molecular evidence that mollusks, especially marine bivalves, can biosynthesize ARA and EPA at least though the "Δ8 pathway", with initial

elongations of LA and ALA to 20:2n-6 and 20:3n-3, respectively, then Δ8 desaturation to 20:3n-6 and 20:4n-3, and a final Δ5 desaturation to ARA and EPA. Since no desaturase with Δ4 and Δ6 activities has been found, DHA may not be synthesized in *C. nobilis* (Liu, Zhang, et al. 2014). Therefore, DHA appears to be an essential fatty acid for *C. nobilis*.

In recent years, Fad5a, Fad5b Fad 6, Elovl 2/5, Elovl 4a, Elovl 4 b and Elovl c genes have been cloned and characterized from Razor clam, *S. constricta*. Razor clam Fad5a, and Fad5b exhibit Δ5 desaturasion activity, while Fad6 is a Δ6 Fad with very low conversion efficiency (less than 5%) (Ran et al. 2018). *S. constricta* Elovl 2/5 possess the ability to elongate C18 and C20 to C22, while Elovl4a, Elovl4b and Elovlc have elongation activity of C20 and C22 LC-PUFA substrates (Ran et al. 2019). The overall findings suggest that *S. constricta* possess the ability of biosynthesis of ARA and EPA though "Δ6 pathway", which consists of initial Δ6 desaturations of LA and ALA to 18:3n-6 and 18:4n-3, respectively, followed by elongations to 20:3n-6 and 20:4n-3, and a final Δ5 desaturation to ARA and EPA. However, DHA biosynthesis appears to be limited due to the low desaturation activity of Fad 6 (Ran et al. 2018, 2019). Therefore, like *C. nobilis*, DHA is essential fatty acid for *S. constricta*.

On the other hand, Portuguese oyster *Cr. angulata* Elovl has been cloned and functionally characterized (Zhang et al. 2018). *Cr. angulata* Elovl possess the ability to elongate n-3 and n-6 LC-PUFA substrates with chain lengths of C18 and C20, and its efficiency is much lower than that of Elvol2/5 in *C. nobilis* (Liu, Zhang, et al. 2014). Although gene responsible for elongation step has been identified in *Cr. angulata*, Fad cDNA with Δ5 and Δ8-desaturation activities has not been identified. Therefore, it is not clear whether *Cr. angulata* can biosynthesis ARA and EPA from dietary essential LA and ALA.

Similar to cephalopods, marine bivalves LC-PUFA biosynthesis genes have higher biosynthesis efficiency in biosynthesis $n-6$ PUFA than that of its homologous $n-3$ PUFA (Liu, Guo, et al. 2014; Liu, Zhang, et al. 2014; Zhang et al. 2018; Ran et al. 2018, 2019). Moreover, the ability of *C. nobilis* and *S. constricta* to produce DHA is limited, which means that they would rely heavily on dietary DHA from DHA rich marine plankton. These results indicate that marine bivalves, especially noble scallops and razor clams, have strong adaptability to the marine environment.

Gastropods

The gastropod (mainly abalone) fisheries landings have gradually decreased from nearly 20,000 metric tons (mt) in the 1970s to about 6,500 mt in 2015 (Cook 2016). Over exploitation, illegal fishing, disease, increased predation and habitat degradation are all responsible for this decline. Following such declines, several fisheries have suffered severe quota restrictions or have been completely de-commercialized. The rapid development of abalone aquaculture is the result of the decline in the abalone supply in wild capture fishery at a time when there is an unprecedented increase in demand. To date, farmed abalone production has reached 130,000 mt/year, and China is the largest contributor (about 90%) (Cook 2016).

Two putative Δ5 desaturases were cloned from abalone *Haliotis discus hannai*, where functional assays in yeast confirmed that both Δ5 desaturases process the Δ5 activity toward 20:3n-6 and 20:4n-3 (Li et al. 2013). Unlike cephalopods and bivalves, both Δ5 desaturases in abalone appear to prefer 20:4n-3 than 20:3n-6. Although the gene responsible for Δ5 desaturation has been identified in abalone, no Fad cDNA with Δ6 or Δ8- activity has been found. Moreover, genes responsible for elongation step have also not been identified. Therefore, it is not clear whether abalone can biosynthesis ARA and EPA from dietary essential PUFA precursors.

Interestingly, like razor clams, abalone also exhibits multiple Δ5 desaturase transcripts. The existence of multiple transcripts of Δ5 Fads in the two species might be related to their special physiological needs. At the molecular level, they may be caused by alternative splicing from one gene, variations in chromosomal numbers or that they are basically different genes (Brenna, Kothapalli, and Park 2010). The exact reason can only be understood when their complete genome information is available.

Concluding remarks

Evidences from analytical, biochemical and molecular studies have shown that some mollusks possess the ability to biosynthesis LC-PUFA from dietary LA and ALA. At the molecular level, Fads and Elvols have been isolated from some commercially important mollusks and, in many cases, functionally characterized. In noble scallops and razor clams, the coexistence of Δ8/Δ5 and Δ6/Δ5 desaturase activities enable the EPA and ARA biosynthesis via the Δ8 and Δ6 pathway, respectively. However, such a metabolic ability appears to be absent in other molluskan species with single Fad of Δ5 desaturase, including common octopus, common cuttlefish and abalone. Therefore, EPA, ARA and DHA are probably essential for cephalopods and gastropods. On the other hand, C18 and C20 appear to be the preferred elongation substrates for molluskan Elovl5/2. Present of Elovl4 in common octopus and noble scallops enable them to elongate 22:5n-3 to 24:5n-3, and thus compensates for the lack of C22 elongase activity in Elvol5/2. This highlights the functional characterization of desaturase and elongase genes an essential tool for confirming the specific reactions of candidate enzymes in the PUFA biosynthetic pathways. Since LC-PUFA in diet has a great influence on the survival rate of molluskan larvae, it is of great significance to provide diets that can meet the essential lipid nutritional requirements of molluskan larvae at an effective cost. The information provided in this review can be used as a reference for feed formulation of molluskan larvae in hatchery, so as to improve the health and survival rate of molluskan larvae.

For future studies, there are some questions to be addressed. For biosynthesis of LC-PUFA, there are still many commercially important mollusks to be studied. In addition, Fads and Elvols enzymes of terrestrial and freshwater mollusks are still uncharacterized. Information on LC-

PUFA biosynthetic pathway in terrestrial and freshwater mollusks is essential for understanding the evolution and ecological adaptation of mollusks in different environments. Finally, the ωx desaturases and Elovl4 orthologues remain largely uncharacterized as well their exact role in different molluskan species.

Disclosure statement

No potential conflict of interest was reported by the authors.

Funding

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