



Plant Unsaturated Fatty Acids: Biosynthesis and Regulation

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In most plants, major unsaturated fatty acids (UFAs) are three C18 species, namely, oleic (18:1), linoleic (18:2), and α -linolenic (18:3) acids. These simple compounds play multiple crucial roles *in planta* and are also important economic traits of oil crops. The enzymatic steps of C18 UFA biosynthesis have been well established. However, the associated FA/lipid trafficking between the plastid and the endoplasmic reticulum remains largely unclear, as does the regulation of the expression and activities of the involved enzymes. In this review, we will revisit the biosynthesis of C18 UFAs with an emphasis on the trafficking, and present an overview of the key enzymes and their regulation. Of particular interest is the emerging regulatory network composed of transcriptional factors and upstream signaling pathways. The review thereby provides the promise of using physical, biochemical and/or genetic means to manipulate FA composition and increase oil yield in crop improvement.

Keywords: unsaturated fatty acids, biosynthesis, regulation, transcriptional factors, signaling pathways

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Specialty section:

This article was submitted to
Plant Metabolism
and Chemodiversity,
a section of the journal
Frontiers in Plant Science

Received: 13 November 2019

Accepted: 18 March 2020

Published: 23 April 2020

Citation:

He M, Qin C-X, Wang X and
Ding N-Z (2020) Plant Unsaturated
Fatty Acids: Biosynthesis
and Regulation.
Front. Plant Sci. 11:390.
doi: 10.3389/fpls.2020.00390

INTRODUCTION

Unsaturated fatty acids (UFAs), aliphatic carboxylic acids with one or more double bonds mostly in *cis* configuration, are fundamental to higher organisms. In most plants, the predominant UFAs are three 18-carbon (C18) species, i.e., 18:1 (oleate), 18:2 (linoleate), and 18:3 (α -linolenate) (Harwood, 1988), where m:n stands for an FA with m carbon atoms and n double bonds. These simple compounds play multiple crucial roles and are deeply associated with both abiotic and biotic stresses. Besides membrane ingredients and modulators in glycerolipids, as well as carbon and energy reserve in triacylglycerols (TAGs), C18 UFAs serve as intrinsic antioxidants, precursors of various bioactive molecules [typically the stress hormone jasmonic acid (JA)], and stocks of extracellular barrier constituents such as cutin and suberin (Ohlrogge and Browse, 1995; Harwood, 1996; He et al., 2018). Moreover, C18 UFAs *per se* also play regulatory roles in plant defense (Lim et al., 2017). 18:1, for example, is involved in the crosstalk between salicylic acid (SA) and JA signaling pathways against pathogen invasion (Kachroo et al., 2001).

C18 UFAs are also important economic traits of oil crops. For one thing, 18:2 and 18:3, the two polyunsaturated FAs (PUFAs), are dietary essential FAs, because we human beings are incapable of their biosynthesis; however, high 18:1 or 18:3 and low 18:2 are beneficial for our health. For another, these organic substances are raw materials of manifold commodities such as biofuels, cosmetics, detergents, and pharmaceuticals (Harwood, 1996). Of note, their anti-stress roles, wholesome properties and industrial applications all highlight the significance of manipulating FA composition and increasing oil yield in crop improvement. In this review, therefore, we will revisit the biosynthesis of C18 UFAs and present an overview of the key enzymes and the regulation of their expression and activities. An emphasis is put on the associated FA/lipid trafficking between

the plastid and the endoplasmic reticulum (ER). Of particular interest is the regulatory network composed of transcriptional factors (TFs) and upstream signaling pathways, which is beginning to be deciphered.

BIOSYNTHESIS OF C18 UNSATURATED FATTY ACIDS

The enzymatic cascade for C18 UFA generation has been well established and documented (e.g., reviews Ohlrogge and Browse, 1995; Harwood, 1996), as illustrated in **Figure 1**. Here, the biosynthetic procedure in *Arabidopsis* is taken as an example. Briefly, in plastids, FAs are synthesized *de novo* from acetyl-coenzyme A (CoA), owing to the concerted action of acetyl-CoA carboxylase (ACC) and FA synthase (FAS). Once produced, 18:0 conjugated to acyl carrier protein (ACP) primarily enters the unsaturation program administered by a series of FA desaturases (FADs). 18:1-ACP is rapidly created by stearoyl-ACP desaturase (SAD). However, the biosynthesis of C18 PUFAs is coupled to that of membrane glycerolipids, which is conducted in two parallel pathways — the ‘prokaryotic’ one in plastids and the ‘eukaryotic’ one in the ER.

To form a glycerolipid, two acyl chains are successively esterified to the *sn*-1 and *sn*-2 positions of glycerol-3-phosphate (G3P). In the prokaryotic pathway, 18:1 will only appear at *sn*-1 depending on the substrate preference of plastidial G3P acyltransferase (GPAT), as *sn*-2 is almost exclusively provided with 16:0. After vector glycerolipids such as phosphatidylglycerol (PG) and monogalactosyldiacylglycerol (MGDG) are generated, 18:1(Δ 9) is processed to 18:2(Δ 9, 12) by ω -6 FAD6 and then to 18:3(Δ 9, 12, 15) by ω -3 FAD7 or FAD8, where Δ and ω are counting from the carboxylic and methyl ends, respectively (Ohlrogge and Browse, 1995; Harwood, 1996).

In the eukaryotic pathway, acyl chains need to be firstly exported to the ER (for review, see Li et al., 2016; LaBrant et al., 2018). During the course, each is hydrolyzed by acyl-ACP thioesterase (FAT) into free FA and then re-activated by long-chain acyl-CoA synthetase (LACS). However, it is unknown yet which of the nine LACs are involved (Jessen et al., 2015). Although free FAs may transit the plastid inner envelope membrane (IEM) via simple diffusion, FATTY ACID EXPORT 1 (FAX1) — an integral protein embedded in the IEM via α -helical membrane-spanning domains — emerged as a likely transporter. Levels of ER-derived lipids decreased upon *FAX1* mutation but increased upon *FAX1* overexpression (Li et al., 2015). The novel FAX family consists of seven members. While FAX1 plays a prominent role in leaves and flowers (Li et al., 2015), FAX2 and FAX4 are important for seed oil accumulation (Tian et al., 2019; Li et al., 2020). Of note, FAX1 can rescue yeast (*Saccharomyces cerevisiae*) mutant defective in FA transport with a cargo preference for 16:0 over 18:1; however, 18:1 is the major FA exported out of plastids (Li et al., 2015). This might be due to the high availability of 18:1, an 18:1-favoring family member, and/or other export mechanisms.

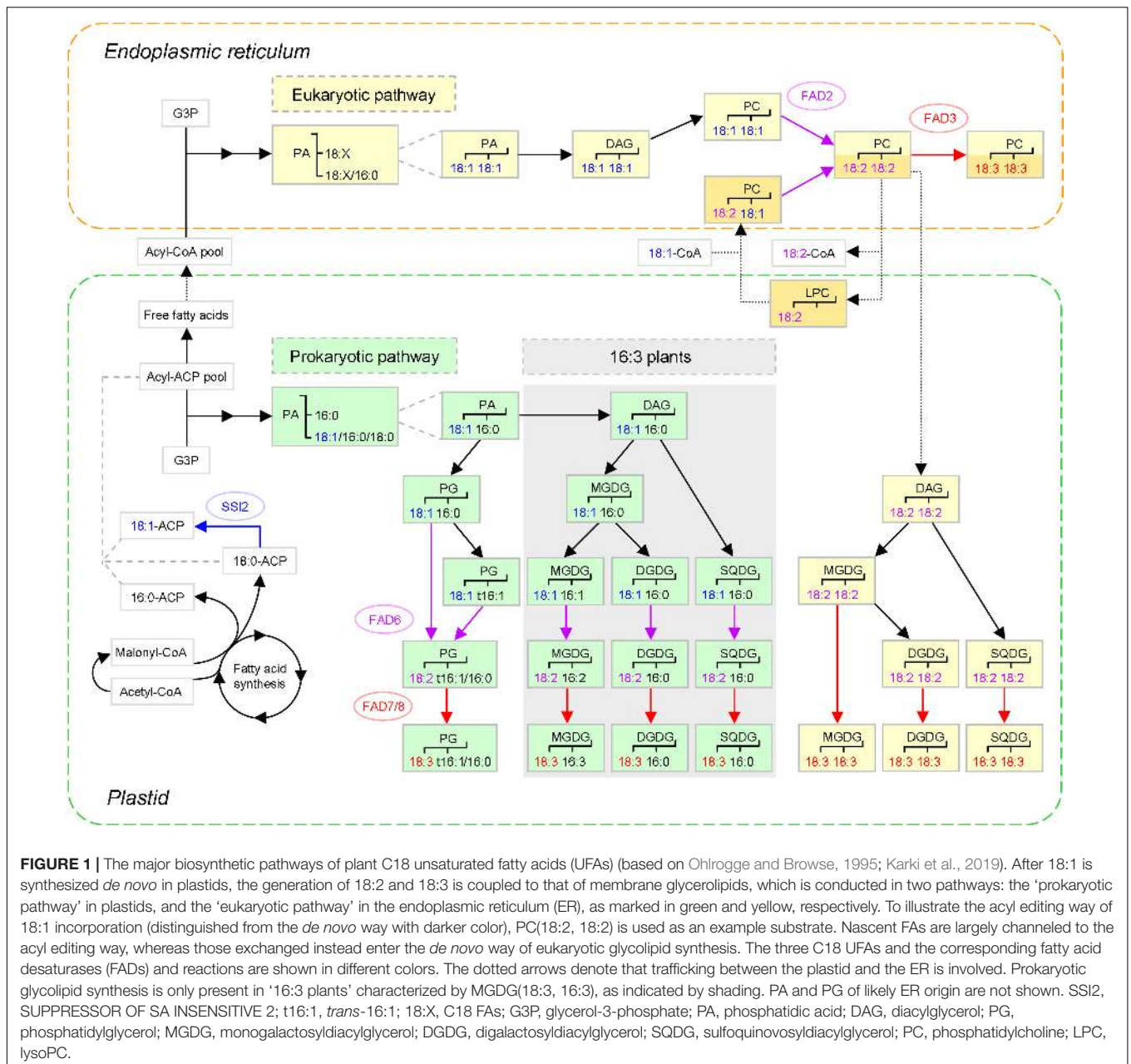
Currently, how free FAs cross the intermembrane space and then the outer envelope membrane (OEM) of plastids remain

questions to be answered. One candidate is the OEM-localized LACS9 that might drive FA export via vectorial acylation, a coupled process of transport and activation (Li et al., 2016). However, as with the ER-bound LACS4, its known role so far is to work for the reverse, i.e., ER-to-plastid lipid transfer. This is manifested by the *lacs4/9* double mutant showing impaired incorporation of radiolabeled FAs into plastidial galactolipids of ER origin, but not ER phospholipids. Moreover, LACS8 may play an overlapping role in the process, as suggested by the lethality of the triple mutant (Jessen et al., 2015).

In the cytoplasm, acyl-CoA binding proteins (ACBPs) (Li et al., 2016) offer an interorganelle delivery route for FAs to reach the cytosolic face of the ER where phosphatidylcholine (PC) synthesis occurs (Botella et al., 2017). ACBP4, -5, and -6 are cytosolic and may play overlapping yet distinct roles in seed acyl-lipid metabolism. Particularly, 18:1-CoA accumulates in both embryos and seedlings of the *acbp6* mutant, suggesting the involvement of ACBP6 (Hsiao et al., 2014). In addition, acylcarnitines were supposed to participate in shuffling FAs from plastids to the ER, based on the following facts: (1) acylcarnitine is a form of FA trafficking in animals and yeasts; (2) acylcarnitines are present in plants, with 18:1-carnitine being the relatively abundant one; (3) chloroplasts harbor carnitine transferase activities; (4) acylcarnitine pool enrichment is concomitant to membrane lipid biosynthesis (see review Jacques et al., 2018).

There are two ways for 18:1 to be incorporated into PC for desaturation (for review, see LaBrant et al., 2018). One is the *de novo* way of PC synthesis, in which 18:1 may take both positions of G3P, especially *sn*-2, which is biased toward it. Subsequently, phosphatidic acid (PA) is modified via diacylglycerol (DAG) into PC (Ohlrogge and Browse, 1995). The other is the acyl editing way of PC turnover, in which 18:1 can directly enter PC, mostly at *sn*-2 (Bates et al., 2009). This is based on the dynamic interconversion between PC and lysoPC. Notably, lysoPC acyltransferase (LPCAT) is capable of catalyzing both forward and reverse reactions and thus fulfilling the cycle on its own (Wang L. et al., 2012). It appears that nascent 18:1 exported out of plastids favors the shortcut in most tissues (LaBrant et al., 2018), which is enabled by the plastid-associated LPCAT1 and -2 (Wang L. et al., 2012; Karki et al., 2019). Next, the recycled PC is transported to the ER, possibly via ER-plastid membrane contact sites (MCSs). ACBPs might also be engaged, given their ability to bind PC (Li et al., 2016). Such renders an alternative plastid-to-ER delivery route for FAs, with PC serving as a carrier.

The unsaturation program is then carried on by ω -6 FAD2 and ω -3 FAD3. When 18:2-containing PC, e.g., PC(18:2, 18:2), is generated, lipid trafficking from the ER back to plastids occurs to supply its DAG backbone for glycolipid production (Ohlrogge and Browse, 1995). To date, the lipid species transferred and the underlying mechanisms are still unclear. Candidates for ER-to-OEM transport comprise PC and its metabolites — lysoPC, PA and DAG (LaBrant et al., 2018). In fact, the OEM outer leaflet contains a substantial amount of PC. ALA10, a phospholipid flippase of the P4-type ATPase family, was speculated to enrich PC in ER-plastid MCSs for translocation, given that its overexpression raised the level of 18:2-containing PC in chloroplasts (see review Botella et al., 2017).



Besides ACBPs or other lipid transfer proteins for direct shuttle, PC might turn to lysoPC that can rapidly move from the ER to chloroplasts (Bessoule et al., 1995). Based on the involvement of LACS4/9 in the process and a specific accumulation of free 18:2 in the double mutant, Jessen et al. (2015) proposed a model as follows. The transfer is initiated by an ER phospholipase A₂ (PLA₂) that prefers PC with *sn*-2 18:2. While the resultant lysoPC migrates to the plastid envelope, the liberated 18:2 is activated by LACS4/9 to establish a local 18:2-CoA pool, so that it can be specifically used by a plastidial LPCAT to regenerate PC. Of note, such coupled transport avoids the issue of losing *sn*-2 C18 FAs indicative of the ER origin, but is against the positional bias observed in leek (*Allium porrum*)

upon stereospecific labeling — *sn*-2 in PC vs. *sn*-1 in MGDG (Mongrand et al., 2000), unless a pool of *sn*-1 labeled PC is specialized as the MGDG precursor (like PC3 below).

Now, the lysoPC-mediated way is challenged by the new finding that LPCAT1 and -2 are required for acyl flux to, but not from, the ER (Karki et al., 2019). This was revealed by *in vivo* labeling analyses conducted on the *act1 lpcat1 lpcat2* triple mutant, taking advantage of the *act1* background that eliminates the prokaryotic pathway of the glycolipid assembly and elevates the eukaryotic pathway for compensation. It turned out that the direct incorporation of nascent FAs into PC was impaired. However, acyl flux was shifted toward *de novo* PC synthesis with a higher *sn*-1 label and there was little effect on MGDG production.

Accordingly, Karki et al. (2019) put forward spatial organization of metabolically distinct pools of PC, such as PC1 for acyl editing, PC2 as the bulk one from *de novo* synthesis, and PC3 (derived from PC2) for glycolipid formation. Possibly, PC1 and PC3 are allocated to different MCSs.

In their model, the neosynthesized FAs are largely channeled by LPCAT into PC for further desaturation, whereas the exchanged ones (cleaved by PLA₂ or LPCAT) instead enter the *de novo* eukaryotic pathway. Interestingly, a support is offered by an *in vivo* lipid 'tag and track' approach established via introducing an ER-resident $\Delta 6$ FAD that specifically acts on the *sn*-2 acyl chain of PC (Hurlock et al., 2018). A notable outcome was that ~10% of the unusual $\Delta 6$ FAs, e.g., 18:4($\Delta 6$, 9, 12, 15), in PC switched to *sn*-1, suggesting that they were released via acyl editing and then reused for *de novo* synthesis. Then, considering the reduced seed oil yield in *lacs4/9* (Jessen et al., 2015), it is possible that the two LACSs are involved in re-activating PLA₂-freed FAs, thereby affecting both TAG and eukaryotic galactolipid synthesis. This can be clarified by checking whether the *de novo* way is impaired in *lacs4/9*.

Notably, there is another way for lysoPC to regenerate PC, enabled by lysoPC transacylase (LPCT) and glycerophosphocholine acyltransferase (GPCAT) acting in concert. LPCT catalyzes acyl transfer from one lysoPC to another, resulting in PC and GPC. GPCAT then converts GPC back to lysoPC by using acyl-CoA (Lager et al., 2015). If this way operates in the OEM, then LACS4/9 can have an effect on lysoPC recycling. However, unless 16:0-containing PC is excluded from the transport and 16:0-CoA is unavailable for GPCAT, the C18 criterion will be challenged, as 16:0 may be transferred to *sn*-2, although 16:0-lysoPC is a preferred acyl acceptor (Lager et al., 2015). Moreover, a specific pool or compartmentalization might also be required, otherwise it would be incompatible with the observation that there is little change in the stereospecificity of the $\Delta 6$ FAs in chloroplastic PC (still ~90% at *sn*-2) (Hurlock et al., 2018).

With regard to plastid import, PA and DAG are candidates. Plastid envelope membranes harbor a lipid importing machinery called TGD for abnormal accumulation of trigalactosyldiacylglycerol (TGDG) in the mutants. It is composed of five proteins, with TGD4 forming a β -barrel in the OEM, TGD1-3 assembling a bacterial-type ABC transporter complex in the IEM, and TGD5 being a likely bridge in between (see reviews Li et al., 2016; Hölzl and Dörmann, 2019). PA is proposed to be a cargo of TGD, since both TGD4 and TGD2 can specifically bind it (Lu and Benning, 2009; Wang Z. et al., 2012). However, there is a possibility that PA is a functional component of TGD, acting as a membrane destabilizer to reduce the energy barrier for transport (LaBrant et al., 2018). Of note, the presence of ER-derived acyl chains in chloroplastic PG was tracked by using the $\Delta 6$ tag (Hurlock et al., 2018). This might result from PA import, because PA can be converted to not only DAG but PG in plastids (Figure 1), or PA generation from the imported DAG.

Surprisingly, a great discrepancy existed in the distribution of the $\Delta 6$ tag in the chloroplastic glycerolipid species examined — ~90% in PC, ~30% in PA, and ~50% in the

four thylakoid lipids occupied *sn*-2, rendering the precursor-product relationship elusive. This observation, together with the coexistence of eukaryotic 18:4 and prokaryotic 16:3 in the same MGDG molecule, led to the assumption that extensive acyl editing occurred in thylakoid lipids, which might be triggered by the presence of unusual acyl groups (Hurlock et al., 2018). However, if a proportion of the imported PA undergoes *sn*-2 deacylation and thus the characteristic 16:0 acylation, the phenomena can be accounted for. Interestingly, 16:3 might also have a eukaryotic origin, provided that the LPCT-GPCAT way is involved. Perhaps, tracking the $\Delta 6$ tag in the *lpcat1/2* background coupled with PLA₂ inhibition would give an answer. Finally, once DAG is modified to glycolipids, 18:2 can be further desaturated to 18:3 by FAD7/8.

KEY FATTY ACID SYNTHETIC ENZYMES AND THEIR REGULATION

FA biosynthesis is a basic yet dynamic process that is developmentally and physiologically regulated. Great strides have been made in characterizing the key enzymes for FA synthesis and understanding the regulation of their expression and activities. Particularly, ACC, which catalyzes the committed and rate-limiting step of *de novo* FA synthesis, has attracted much attention, leading to the discoveries of a large variety of genetic and biochemical mechanisms underlying its regulation, as described below. Given that most TFs identified (examples shown in Figure 2) target more than one FA synthetic gene, transcriptional regulation will be addressed in a separate section. Moreover, there is a large variation in the gene number of each enzyme in the plant kingdom; gene information of *Arabidopsis* will be introduced for reference.

Key Enzymes and Non-transcriptional Regulation

Acetyl-CoA Carboxylase

In nature, ACC exists in two physically distinct types: the prokaryotic one as a heteromeric multisubunit complex (htACC), and the eukaryotic one as a homomeric multidomain polypeptide (hmACC). In either form, ACC activity is based on four components — biotin carboxyl carrier protein (BCCP), biotin carboxylase (BC), and the α - and β -subunit of carboxyltransferase (CT). The majority of plants require both types, localizing htACC in plastids and hmACC in the cytoplasm (see reviews Sasaki and Nagano, 2004; Salie and Thelen, 2016).

In *Arabidopsis*, of the four individual proteins that assemble htACC in the stroma, BCCP is encoded by *CAC1A/BCCP1* and *CAC1B/BCCP2*, while BC, α -CT and β -CT are encoded by *CAC2*, *CAC3* and *accD*, respectively. Of note, *accD* is the only FA-related gene that resides mostly in the plastome. The exceptions comprise several seed-producing species, such as Poaceae (Konishi and Sasaki, 1994) due to gene loss or Gnepophyta (Sudianto and Chaw, 2019) due to nuclear transfer. Intriguingly, in some cases, an additional copy of the nucleus-encoded hmACC has somehow acquired a plastid-targeting transit peptide, thereby appearing in plastids as well. Therein, for

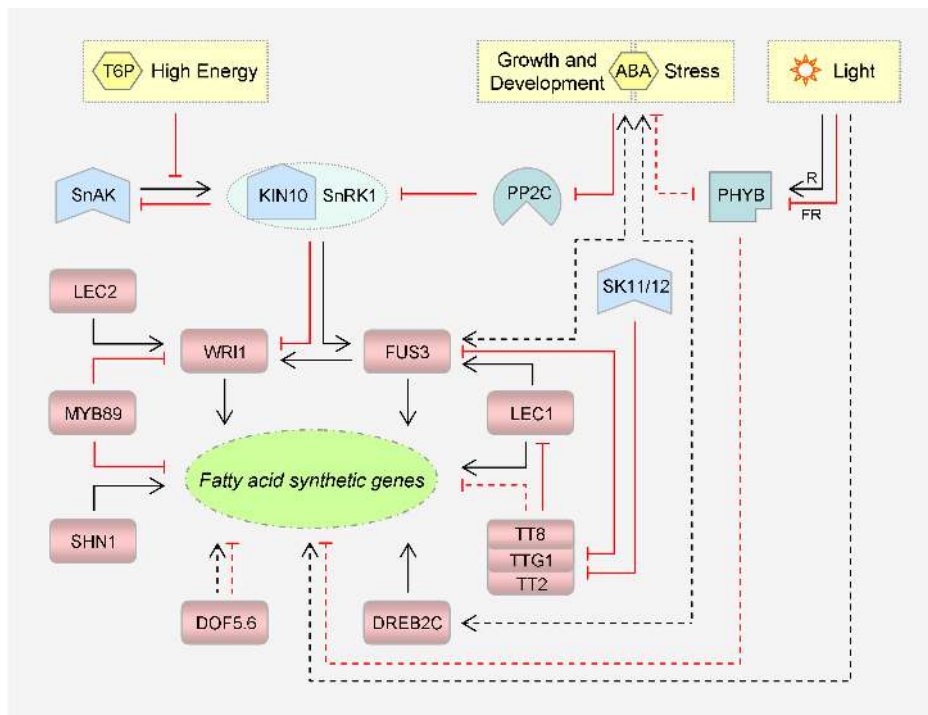


FIGURE 2 | Representative transcriptional factors and signaling pathways that regulate plant fatty acid synthesis. Please note that these transcriptional factors target different sets of fatty acid synthetic genes, directly or indirectly. TTG1, TT2 and TT8 can form a ternary complex to modulate gene expression. KIN10 is a catalytic subunit of SnRK1. Inhibitory effects are marked in red. Dashed lines denote indirect regulation. For simplicity, the intricate interactions among LEC1, LEC2 and FUS3 are not shown. T6P, trehalose 6-phosphate; SnRK1, sucrose non-fermenting 1-related protein kinase 1; SnAK: SnRK1-activating kinase; ABA, abscisic acid; PP2C, protein phosphatase 2C; R, red light; FR, far-red light; PHYB, phytochrome B; SK11/12, shaggy-like kinases 11/12; DOF, DNA binding with one finger; DREB, dehydration-responsive element-binding; WRI1, WRINKLED1; FUS3, FUSCA3; LEC1/2, LEAFY COTYLEDON 1/2; SHN1, SHINE1; TTG1, TRANSPARENT TESTA GLABRA 1; TT2/8, TRANSPARENT TESTA 2/8.

htACC, it acts as a replacement in Poaceae (Konishi et al., 1996) or a concomitant in some Brassicaceae members (Rousseau-Gueutin et al., 2013). Nevertheless, unlike *ACC1*, this *ACC2* gene seems to be dispensable in *Arabidopsis* (Babiychuk et al., 2011).

As the gatekeeper that governs carbon flux into FA synthesis, htACC has both its quantity and activity under tight control, which involves diverse mechanisms yet to be fully understood (Salie and Thelen, 2016). Particularly, given that the genome copy number of plastids is several hundred times higher than that of the nucleus in a cell, for efficient assembly the expression of the plastid-encoded β -CT ought to be coordinated with that of the other three nuclear-encoded subunits. This can be partly achieved at the levels post transcription, possibly via protein degradation of excess subunits (Sasaki and Nagano, 2004). β -CT appears to be a quantity control factor — overexpression of β -CT (Madoka et al., 2002), but not BCCP2 (Thelen and Ohlrogge, 2002) or BC (Shintani et al., 1997), could lead to a significant rise in protein levels of all other three subunits, though their mRNA levels were not affected.

Within the CT subcomplex, β -CT also serves as an activity control factor. In several angiosperms including pea (*Pisum sativum*) and *Arabidopsis*, RNA editing of the *accD* transcripts is required to generate a Ser-to-Leu conversion for the active form of CT (Sasaki et al., 2001). In pea leaves, β -CT is also a candidate

for Ser phosphorylation, which was suggested to have a positive effect on CT activity (Savage and Ohlrogge, 1999). Moreover, upon assembly, β -CT, together with α -CT, creates a target for redox regulation. An intermolecular disulfide bond (S-S) formed between their Cys residues appears to deactivate CT, rendering reductive thioredoxin an activator, as it can break S-S into thiols with the electrons generated in photosynthesis (Sasaki et al., 1997; Kozaki et al., 2001).

Within the BC-BCCP subcomplex, BCCP is an activity control factor. To date, two regulatory proteins that work via direct interaction with BCCP have been identified. One is a family of biotin attachment domain-containing (BADC) proteins that are non-biotinylated and thus inactive analogs of BCCP (Salie et al., 2016). Surprisingly, a discrepancy has arisen regarding the role of BADCs in regulating ACC activity, namely, inhibitors by displacing BCCP (Salie et al., 2016; Keereetawee et al., 2018) vs. activators by facilitating the assembly of BCCP-BADC-BC subcomplex (Shivaiah et al., 2020). The other is PII, a conserved sensor of the intracellular status of carbon, nitrogen and energy. It blocks BCCP via binding to the biotinylated region (Gerhardt et al., 2015), which can be reversed by 2-oxoglutarate, oxaloacetate and pyruvate (Feria Bourrellier et al., 2010). Notably, the latter two metabolites are major precursors of acetyl-CoA, indicating that feedforward activation happens to htACC, which

stands in opposition to feedback inhibition primarily from 18:1-ACP (Andre et al., 2012).

Moreover, in green tissues, light is a potent environmental stimulator of htACC, so that FA synthesis is coordinated with photosynthesis (Sasaki and Nagano, 2004). Upon illumination, multiple biochemical changes take place in the chloroplast stroma. Those favorable for FA synthesis include the increases in reduced thioredoxin, pH, and the concentrations of Mg^{2+} , ATP and NADPH (Sasaki et al., 1997; Hunter and Ohlrogge, 1998). For one thing, reduced thioredoxin, as already mentioned, relieves CT from S-S inhibition, while pH (from 7.0 to 8.0) and Mg^{2+} (from 1 to 3 mM) levels are elevated to the range optimum for the catalytic kinetics of htACC (Sasaki et al., 1997; Hunter and Ohlrogge, 1998; Kozaki et al., 2001); for another, ATP is a substrate for BC and NADPH is the reducing power for FA elongation and desaturation (Salie and Thelen, 2016).

3-Ketoacyl-ACP Synthases

FAS exists in two physically distinct types in nature as well: heteromeric type II and homomeric type I. Plants only have the type II system in plastids and mitochondria, where it is organized from multiple discrete enzymes and a non-catalytic cofactor, i.e., ACP (Yasuno et al., 2004). Of note, ACP is also an essential cofactor for SAD, FAT and plastidial GPAT (Tang et al., 2012). The key catalytic component of FAS is 3-ketoacyl-ACP synthase (KAS) that appends the C2 module via Claisen condensation, the first step in each elongation cycle (Yasuno et al., 2004).

In the biogenesis of 18:0 in plastids, however, three classes of KAS are engaged — KASIII for initial combination between acetyl-CoA and malonyl-ACP, KASI for sequential elongation till 16:0-ACP, and KASII (or FAB1) for additional extension to 18:0-ACP (Ohlrogge and Browse, 1995; Harwood, 1996). Accordingly, KASII activity is a major determinant of the ratio of C18 to C16 FAs in plant cells, as is evident in the *fatty acid biosynthesis 1-1 (fab1-1)* mutant of *Arabidopsis* that carries a partially defective KASII (Wu et al., 1994; Pidkowich et al., 2007). Moreover, it should be noted that 18:0 can also be synthesized by the mitochondrial FAS utilizing a singular KAS, although its physiological role and metabolic fate remain to be unveiled (Gueguen et al., 2000; Yasuno et al., 2004).

In *Arabidopsis*, each KAS is a single gene product. Apart from chain-length specificity, the three KAS members also differ in sensitivity to inhibitors such as cerulenin and thiolactomycin (Harwood, 1996; Jones et al., 2000). The two antibiotics are most effective against KASI and KASII, respectively. Insensitive to cerulenin as it is, KASIII is subjected to feedback inhibition like ACC, owing to its switch position in the acyl chain assembly. Nevertheless, medium-chain acyl-ACPs (e.g., 10:0-ACP) appear to be stronger effectors in different plant species (Brück et al., 1996; Abbadi et al., 2000), not least *Cuphea*, which deploys a specific KASIV for the manufacture of medium-chain FAs in seeds (Dehesh et al., 1998; Schütt et al., 2002).

Fatty Acid Desaturases

By inserting the first double bond into 18:0, SAD is crucial for C18 UFA biogenesis. Accordingly, SAD, as with FATs and acyltransferases, is a major determinant of the homeostasis

between unsaturated and saturated FAs. As an archetypal soluble FAD, SAD is normally kinetic in the stroma, keeping 18:0 at a quite low level (Harwood, 1996). In *Arabidopsis*, seven encoding genes have been identified. Now that the endogenous paralogs did not compensate for the *suppressor of SA insensitive 2 (ssi2)* or *fab2* mutation, SSI2/FAB2 is likely the predominant one engaged in the committed step of C18 unsaturation, which indeed exhibited the highest SAD activity (Kachroo et al., 2007). Impressively, based on the resolved crystal structure of SAD from castor (*Ricinus communis*) (Lindqvist et al., 1996), it is facile to manipulate the functional mode of acyl-ACP desaturases. For example, five amino-acid substitutions sufficiently turned a $\Delta 6$ 16:0-ACP desaturase into a $\Delta 9$ SAD (Cahoon et al., 1997).

The two sets of FADs that catalyze the subsequent unsaturation steps are all integral proteins acting on acyl-lipids. Apart from cellular location and lipid substrate, the two sets also differ in electron donor, with cytochrome b_5 for the ER FAD2-FAD3 and ferredoxin for the plastidial FAD6-FAD7/8 (Shanklin and Cahoon, 1998). In *Arabidopsis*, each of the five FADs is encoded by a single gene. Of note, in leaves, the ω -6 and ω -3 pair in each set may work as heterodimers to facilitate the metabolic channeling (Lou et al., 2014). Recently, the flippase ALA10 has been shown to interact specifically with FAD2 and may thereby affect the balance between FAD2 and FAD3, leading to the discharging and flipping of 18:2-containing PC (Botella et al., 2016).

C18 UFAs are closely intertwined with stresses as not only general defenders but primary victims; the toxic peroxidation product malondialdehyde (MDA) is widely used as an indicator of oxidative damage (Guo et al., 2012; He et al., 2018). In line with this, broadly speaking, these FADs can be labeled as stress-responsive, transcriptionally and/or post-transcriptionally, albeit the response varies with gene, tissue, species, and/or stress (examples listed in **Table 1**). Temperature is one of the main environmental factors that influence FAD expression. In most cases, the mRNA and/or protein levels of FADs, if responsive, will change inversely with ambient temperature (**Table 1**). It appears that protein degradation is a preferred level on which temperature imposes the effect. The amino acid segments accounting for the thermal instability of several FADs have been mapped, including the C-terminal region of FAD8 from *Arabidopsis* (Matsuda et al., 2005), the N-terminal and 241-334 regions of FAD2-1A from soybean (*Glycine max*) (Tang et al., 2005), and the N-terminal region of FAD3 from *Brassica napus* (Khuu et al., 2011). In addition, GmFAD2-1A and -1B have also been observed to undergo Ser185 phosphorylation that may impair their activities (Tang et al., 2005).

Glycerol-3-Phosphate Acyltransferases

The biosynthesis of C18 PUFAs being coupled to that of membrane lipids highlights the importance of GPAT. Composing a multigene family in *planta*, GPATs acylate the *sn*-1 or *sn*-2 position of G3P to form lysoPA, which is a common intermediate to membrane glycerolipids, storage TAGs, and extracellular polyesters (e.g., cutin) (Waschburger et al., 2018). In *Arabidopsis*, there are 10 GPAT genes designated *ATS1* (or *ACT1*) and *GPAT1-9*. Their products are distributed to three subcellular

TABLE 1 | Stress responses of plant fatty acid desaturases involved in C18 unsaturated fatty acid synthesis.

Gene	Species	Tissue	Stress response ^a	References
SAD	<i>Persea americana</i>	Fruit	Increased mRNA level under LT (4°C), wounding or fungal invasion	Madi et al., 2003
	<i>Solanum commersonii</i>	Leaf	Increased mRNA level after cold acclimation	Vega et al., 2004
	<i>Solanum tuberosum</i>	Leaf	No notable changes in mRNA level after cold acclimation	Vega et al., 2004
FAD2	<i>Arabidopsis thaliana</i>	Leaf	No notable changes in mRNA level at LT (6°C)	Okuley et al., 1994
	<i>Glycine max</i>	Seed	Decreased protein stability of FAD2-1A at HT (30°C)	Tang et al., 2005
	<i>Petroselinum crispum</i>	Leaf	Increased mRNA level under fungal elicitor	Kirsch et al., 1997a
FAD3	<i>Portulaca oleracea</i>	Leaf	Increased mRNA level of FAD2-2 under LT (5°C) or wounding	Teixeira et al., 2009
	<i>Arabidopsis thaliana</i>	Leaf	Increased mRNA level at LT (4°C)	Kreps et al., 2002
	<i>Triticum aestivum</i>	Root tip	Increased protein synthesis with slightly increased mRNA level at LT (10°C)	Horiguchi et al., 1996
FAD6	<i>Brassica napus</i>	/	Increased protein stability without notable changes in mRNA level at LT (10°C)	O'Quin et al., 2010
	<i>Vigna radiata</i>	Hypocotyl	Increased mRNA level under wounding	Yamamoto et al., 1992
	<i>Arabidopsis thaliana</i>	Seedling	Increased mRNA level under salt or osmotic stress (300 mM NaCl or mannitol)	Zhang et al., 2009
FAD7	<i>Glycine max</i>	Leaf	No notable changes in mRNA level with temperature	Heppard et al., 1996
	<i>Portulaca oleracea</i>	Leaf	Increased mRNA level under wounding but not LT (5°C)	Teixeira et al., 2009
	<i>Olea europaea</i>	Fruit	Decreased mRNA level at HT (35°C); no notable changes under wounding	Hernández et al., 2011
FAD8	<i>Arabidopsis thaliana</i>	Leaf	No notable changes in mRNA level at HT (30°C)	Gibson et al., 1994
		Leaf, root	Increased mRNA level under wounding	Nishiuchi and Iba, 1998
	<i>Zea mays</i>	Leaf	Decreased mRNA level at LT (5°C)	Berberich et al., 1998
FAD8		Root	Increased mRNA level under salt (400 mM NaCl)	Berberich et al., 1998
	<i>Petroselinum crispum</i>	Leaf	Increased mRNA level under fungal elicitor	Kirsch et al., 1997b
	<i>Arabidopsis thaliana</i>	Leaf	Decreased mRNA level at HT (30°C)	Gibson et al., 1994
FAD8		Leaf	Decreased protein stability at HT (27°C)	Matsuda et al., 2005
		Leaf, root	Increased mRNA level under wounding	Nishiuchi and Iba, 1998
	<i>Zea mays</i>	Leaf	Increased mRNA level at LT (5°C)	Berberich et al., 1998
	Root	Increased mRNA level under salt (400 mM NaCl)	Berberich et al., 1998	

^aLT: low temperature; HT: high temperature.

compartments (ATS1 to plastids, GPAT1-3 to mitochondria, and GPAT4-9 to the ER) to be involved in different metabolic pathways and biological functions (Chen et al., 2011; Sui et al., 2017; Jayawardhane et al., 2018).

With respect to C18 PUFA generation, ATS1 and GPAT9, the two *sn*-1 regiospecific members, control the entries of the prokaryotic and eukaryotic pathways, respectively (Jayawardhane et al., 2018; Waschburger et al., 2018). Localized in the stroma, ATS1 is the only soluble GPAT member. Interestingly, its orthologs in chilling-resistant plants like spinach (*Spinacia oleracea*) exhibit a pronounced preference for 18:1-ACP (Bertrams and Heinz, 1981). In contrast, those in chilling-sensitive plants like squash (*Cucurbita moschata*) barely discriminate between 18:1-ACP and 16:0-ACP (Frentzen et al., 1987). Bound to the ER membrane, GPAT9 is essential for the production of both membrane and storage lipids. The orthologs have been shown to favor certain substrate as well, for example, 18:1-CoA in *Arabidopsis* (Singer et al., 2016) vs. 16:0-CoA in sunflower (*Helianthus annuus*) (Payá-Milans et al., 2016).

Transcriptional Regulation and Signaling Pathways

Transcriptional Factors

Transcriptional regulation of FA synthetic genes (Figure 2) is more characterized in seeds, the TAG biofactories. Not surprisingly, a subset of enzymes is grouped into a regulon to be

coordinately regulated by the same TF, as exemplified by those cited hereafter. The first 'master regulator' to be identified is WRINKLED1 (WRI1), whose mutation caused an 80% reduction in seed oil content of *Arabidopsis* (Focks and Benning, 1998). Being a member of the APETALA2/ethylene response factor (AP2/ERF) superfamily of TFs, it functions via binding to the AW boxes harbored in the regulatory regions of the targets (see review Kong and Ma, 2018). To orchestrate carbon flux and energy reserve, WRI1 controls multiple genes involved in glycolysis and FA synthesis. Notably, it activates not only the anabolic genes including *BCCP2*, *ACP3*, *KASI*, and *FAD2* (Ruuska et al., 2002), but the regulatory genes including *BADC1*, -2, and -3 (Liu H. et al., 2019).

WRI1 is situated at a downstream node in an intricate regulatory network that governs seed development. The core regulators comprise ABSCISIC ACID INSENSITIVE 3 (ABI3) and three leafy cotyledon (LEC) group factors, i.e., LEC1, LEC2 and FUSCA3 (FUS3). Of them, LEC1 is a subunit of the heterotrimeric CCAAT-box binding factor (CBF, or NF-Y for nuclear factor Y), while the other three are B3 domain TFs recognizing RY motifs (see reviews Baud and Lepiniec, 2010; Kong and Ma, 2018). Nevertheless, WRI1 is not a direct target of ABI3 in *Arabidopsis* according to the chromatin immunoprecipitation (ChIP) assay (Mönke et al., 2012), and is only critical for specifying the activating role of LEC2 toward the TAG deposit (Baud et al., 2007). Upon overexpression, LEC1 is capable of inducing a larger set of FA synthetic genes, with

CAC2, *CAC3*, *ACP1*, *KASII*, *SSI2*, *FAD3*, etc. being appended to the list. This more global effect depends largely on *FUS3* and partially on *WRI1* and *ABI3* (Mu et al., 2008). In fact, *LEC1* can modulate FA synthesis in a direct manner by targeting *SSI2* (Junker et al., 2012), as can *FUS3* by targeting *KASI*, *ACP1*, and *FAD2* (Wang and Perry, 2013).

Accordingly, repressors of these master regulators impose a negative effect on FA biosynthesis. *TRANSPARENT TESTA 8* (*TT8*), for instance, can directly inhibit the transcription of *LEC1*, *LEC2*, and *FUS3* (Chen et al., 2014). This basic helix-loop-helix (bHLH) TF can form a ternary complex with an R2R3-MYB factor *TT2* and a WD40 repeat factor *TRANSPARENT TESTA GLABRA 1* (*TTG1*) to monitor carbon partitioning among metabolic pathways that share the same source, including seed oil, mucilage and flavonoid synthesis (Li et al., 2018). Interestingly, there is a *TT2-FUS3-TTG1* cascade linked via direct gene suppression (Wang et al., 2014; Chen et al., 2015). Further, *TTG1* can indirectly suppress *ABI3*, *LEC2*, *BCCP2*, *CAC2*, *FAD2*, *FAD3* and so on (Chen et al., 2015). Later, *MYB89* was identified as a repressor of *WRI1*. It can also inhibit *BCCP1*, *KASI*, *FAD2*, *FAD3*, etc., directly or indirectly (Li et al., 2017).

Members of the zinc finger DOF (DNA binding with one finger) family also participate in FA synthesis regulation (Wang et al., 2007; Deng et al., 2015). In *B. napus*, for example, knockdown of *DOF5.6* resulted in decreased expression of several *KASII* and *SAD* genes. Intriguingly, two *FAD3* genes exhibited different responses. *Bra018348* was down-regulated, whereas *Bra022767* was up-regulated, albeit the outcome was reduced 18:3 level (Deng et al., 2015). In addition, it is worth noting that *WAX INDUCER 1/SHINE1* (*WIN1/SHN1*), another AP2/ERF member known to be important for extracellular cuticle synthesis in epidermal cells, has its positive effect on intracellular oil yield in seed cells unveiled. In *B. napus*, *BCCP1* and *GPAT9* are among its direct targets (Liu N. et al., 2019).

The investigation of TFs acting in other plant tissues is also ongoing. Based on previous comparative transcriptome analysis, a fruit-specific complex network similar to the seed one has been established in the mesocarp of oil palm (*Elaeis guineensis*). *NF-YA3*, *NF-YC2* and *ABI5* directly activate *WRI1-1* and a subset of FA synthetic genes. *NF-YA3* can also physically interact with *NF-YC2*, *ABI5* and *WRI1-1*, thereby forming a TF complex to modulate gene expression. *WRKY40* then cooperates with *WRKY2* in repressing *ABI5* and thus oil synthesis (Yeap et al., 2017). Moreover, *DREB2C*, a third AP2/ERF member classified into subgroup 2 of the dehydration-responsive element-binding TF family, emerged to promote 18:3 production. When transformed into *Arabidopsis* from *Ammopiptanthus mongolicus*, a desert evergreen broadleaf shrub, *AmDREB2C* could up-regulate *AtFAD3* and *AtFAD8* in siliques and *AtFAD7* in leaves (Yin Y. et al., 2018).

Signaling Pathways

The upstream signaling pathways are also emerging (Figure 2). The *WRI1* regulon is naturally included in the energy-sensing signalosome centered on *SnRK1*, a conserved member of the sucrose non-fermenting 1-related protein kinase superfamily (see review Crepin and Rolland, 2019). It appears that *SnRK1* is more

subject to repression by high energy signals like sugars, leading to metabolic reprogramming from catabolism to anabolism. In the signaling triggered by trehalose 6-phosphate (T6P), an agent of cellular sucrose status, *WRI1* will be rescued from the suppression of *KIN10*, a catalytic α -subunit of *SnRK1* (Zhai et al., 2018). *KIN10* is enabled to phosphorylate and thus promote the proteolysis of *WRI1*, once its functional T-loop is phosphorylated by *SnRK1*-activating kinases (*SnAKs*, originally *GRIKs* for geminivirus rep-interacting kinases). However, T6P can directly bind to *KIN10*, thereby disturbing its affinity for and activation by *SnAKs*. It is delicate that the photosynthetically fixed carbon *per se* switches on FA synthesis so as to flow into storage. Notably, *FUS3* is a substrate of *SnRK1* as well; however, in contrast to *WRI1*, phosphorylation by *KIN10* is conducive to its protein stability and TF activity (Tsai and Gazzarrini, 2012; Chan et al., 2016).

The repressor *TTG1* is regulated by shaggy-like kinases 11/12 (*SK11/12*) that belongs to the glycogen synthase kinase-3 (*GSK3*) family (Li et al., 2018). Of note, *SK11* (or *ASK α*) can be induced by salt stress (Dal Santo et al., 2012). *TTG1*, together with *TT2* and *TT8*, coordinates carbon partitioning. However, they drive carbon flux into the synthetic pathways of seed coat mucilage and flavonoid pigments, which compete with oil for photosynthates (Li et al., 2018). One of their targets is *GLABRA2* (*GL2*). This homeobox TF is an activator of *MUCILAGE MODIFIED 4* (*MUM4*) that encodes the rhamnose synthase for mucilage biogenesis, and the mutation of either gene resulted in higher seed oil content (Shi et al., 2012). When *TTG1* is phosphorylated by *SK11/12* at Ser215, its interaction with *TT2* is abolished. This compromises recruitment of *TTG1* to the *GL2* locus, leading to down-regulation of *GL2* and an ultimate reduction of mucilage yield. FA synthesis is then enhanced at least partially due to increased carbon allocation (Li et al., 2018), as occurs upon deficiency of *TT4*, the chalcone synthase for flavonoid biogenesis. In the *tt4* mutant, *WRI1* and its downstream genes involved in glycolysis and FA synthesis are activated, thus driving the reorientated sugar source into the two pathways (Xuan et al., 2018).

Light is likely to regulate *FAD* expression in a species-specific manner at least at the transcriptional level. Those stimulated include *FAD7s* of *Arabidopsis* (Nishiuchi et al., 1995) and wheat (*Triticum aestivum*) (Horiguchi et al., 1996), *FAD3* and *FAD8* of soybean (Collados et al., 2006), *FAD2-3* and *-4* of cotton (*Gossypium hirsutum*) (Kargiotidou et al., 2008), and *FAD2-1*, *-2*, and *FAD6* of olive (*Olea europaea*) (Hernández et al., 2011). Potential light-responsive G-box motifs have been identified in common in the predicted promoters of *AtFAD2*, *GhFAD2-3*, and *-4* (Kargiotidou et al., 2008), suggesting a conserved regulatory mechanism. These sites might be recognized by phytochrome interacting factors (*PIFs*), a subfamily of bHLH TFs, or *ELONGATED HYPOCOTYL 5* (*HY5*), a basic leucine zipper (*bZIP*) TF. Either of them is regulated by phytochromes, which are photoreceptor proteins that perceive red and far-red light (Zhou et al., 2014; He et al., 2016; Legris et al., 2017). Nevertheless, phytochrome B (*PHYB*), which is also a thermosensor and can directly bind to G-boxes

(see review Delker et al., 2017), exhibited a negative effect on the transcription of *FAD7*, *FAD8*, and *ATS1* in rice (*Oryza sativa*), particularly under chilling stress (Yang et al., 2013). Notably, PHYA can antagonize PHYB in regulating the cold signaling of tomato (*Solanum lycopersicum*) (Wang F. et al., 2016), rendering it a candidate mediator of FAD photoactivation.

FA synthesis is subject to hormonal regulation by abscisic acid (ABA), auxin and JA, to name a few (Shahid et al., 2019). Remarkably, ABA, the central phytohormone that organizes plant development, growth and stress defense, appears to be implicated via multiple accesses: (1) ABI3 and ABI5 that are intrinsic components of ABA signaling. (2) DREB2C that is ABA-inducible and can exert a positive feedback on ABA biosynthesis in *Arabidopsis* (Je et al., 2014). It is worth noting that the *AtDREB2C* promoter was predicted to harbor diverse types of *cis*-acting elements (Sazegari et al., 2015), which are responsive to ABA, JA, SA, heat, cold, and defense, respectively, suggesting that the DREB2C regulon is part of the stress signalosome. (3) SnRK1 that is negatively regulated by type 2C protein phosphatases (PP2Cs) (Rodrigues et al., 2013). Such inhibition can be relieved by ABA upon binding to its receptors, as it does to activate SnRK2 in its own signaling. (4) FUS3 that can augment ABA biosynthesis and receive a protein-stabilizing effect in return (Gazzarrini et al., 2004; Lu et al., 2010). Notably, it offers one more nexus between ABA and SnRK1 pathways. (5) PHYB that appears to counteract ABA (and JA) in various stress responses (He et al., 2018). In tobacco (*Nicotiana tabacum*), for instance, the two can suppress each other's synthesis to affect salt tolerance (Yang et al., 2018). In addition, LEC1 is a potential integrator of ABA and light signaling pathways, which may act on *PP2CA*, *PIF5* and *HY5*, among others (Junker et al., 2012).

CONCLUSION AND PERSPECTIVES

The enzymatic steps involved in C18 UFA biosynthesis have been well established; however, the eukaryotic pathway has not yet been fully understood, which is complicated by acyl editing and FA/lipid trafficking between the plastid and the ER. Particularly, the consensus concerning how and which eukaryotic species return to the plastid envelope has not been reached. Now, the lysoPC-mediated way for PC translocation is being refuted, turning the involvement of LACS4/9 in ER-to-plastid transport into a puzzle. As one of the basic pathways of the metabolism to produce molecules with multiple biological roles, it is natural that

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FA synthesis is subject to elaborate regulation involving diverse genetic and biochemical mechanisms, which are far from being resolved. With respect to transcriptional regulation, a number of questions remain to be answered, such as which TFs are master regulators working in vegetative tissues, and how the FAD genes respond to environmental factors, including light and temperature. Noteworthy, comparative transcriptome or gene co-expression network analysis can provide valuable information for deciphering the regulatory networks (Yeap et al., 2017; Shahid et al., 2019; Yang et al., 2019). These high-throughput strategies also lead to the identification of potential microRNAs and long non-coding RNAs that fine-tune the expression of FA synthetic genes at the post-transcriptional level (Wang J. et al., 2016; Yin D.D. et al., 2018).

A better knowledge of the key enzymes and their regulation offers the promise of using physical, biochemical and/or genetic means to manipulate FA composition and increase oil yield, so as to meet the demand for improving the ability of crops to deal with multiple stresses, especially in the context of climatic change and soil salinization (Yuan et al., 2015; He et al., 2018), as well as producing edible oils with higher quality and more oleochemicals for industrial usage. A growing number of successes are being achieved via genetically engineering the key enzymes or TFs. For instance, transgenesis of *FAD3* or *DREB2C* resulted in elevated 18:3 content and ameliorated multistress resistance (Shi et al., 2018; Yin Y. et al., 2018). Interestingly, to achieve high 18:1 level that is good for oil stability and human health, *FAD2* has become a hotspot for targeted disruption by using CRISPR/Cas9, the powerful genome editing tool (Abe et al., 2018; Okuzaki et al., 2018; al Amin et al., 2019; Do et al., 2019). Nevertheless, crop improvement would be facilitated if the culture conditions involving light, temperature, fertilizers, and exogenous phytohormones are optimized for UFA synthesis.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

FUNDING

This work was supported by grants from Key R&D Project of Shandong Province (2019GSF107020).

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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