The plant lipidome in human and environmental health

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Lipids and oils derived from plant and algal photosynthesis constitute much of human daily caloric intake and provide the basis for high-energy bioproducts, chemical feedstocks for countless applications, and even fossil fuels over geological time scales. Sustainable production of high-energy compounds from plants is essential to preserving fossil fuel sources and ensuring the well-being of future generations. As a result of progress in basic research on plant and algal lipid metabolism, in combination with advances in synthetic biology, we can now tailor plant lipids for desirable biological, physical, and chemical properties. We highlight recent advances in plant lipid translational biology and discuss untapped areas of research that might expand the application of plant lipids.

Glycerolipids consist of a glycerol backbone with various combinations of fatty acids and head groups, thus generating a vast array of molecular species (Fig. 1). Glycerolipids constitute the largest fraction of the plant lipidome, or the total collection of plant lipids, and their chemical diversity is associated with many cellular functions. Plants build photosynthetic and cell membranes from polar lipids (Fig. 1). During the evolution of land plants, developmental adaptations led to the sequestration of carbon fixed by photosynthesis into high-energy compounds in the form of neutral lipids (Fig. 1), such as triacylglycerols in seeds. Algae accumulate triacylglycerols to survive adverse conditions—for instance, in response to nutrient deprivation. Glycerolipids also serve as mobile signals in cellular regulation and communication, and they function as components in photosynthetic and other enzymatic complexes. Basic research in model plants such as Arabidopsis thaliana and algae such as Chlamydomonas reinhardtii has generated insights into the regulation, synthesis, assembly, storage, and turnover of the plant and algal lipidomes. This intellectual framework leads to a design toolbox that enables translational research, construction of novel biotechnological processes, and generation of bioproducts.

Although most plants share a common set of reactions in lipid metabolism, the unique, specialized metabolism of select plants draws interest as a starting point for novel bio-based industrial processes and for improving human nutrition. Rapid technological advances in synthetic biology aided by complementary “omics” approaches have enabled the translation of these basic design principles through genetic modification (GM) of crops to synthesize valuable lipids. Examples of successful translational plant lipid research abound. Plant oils can be produced with tailored compositions for downstream production of desirable varnishes, soaps, or specialized lubricants (I–6); vegetable oil in nonseed plant tissues, such as leaves, to increase the biomass energy content (7, 8); healthy fish oil–like vegetable oils in field-grown GM crops without depleting the oceans (9, 10); and a potentially leaner seed oil with lower caloric content that may aid in combating obesity (11). In more futuristic efforts, basic research on the formation of lipid droplets, which store neutral lipids in plants and algae, may lead to practical synthetic biology platforms for the safe sequestering and easy harvesting of bioactive and hydrophobic lipid-based molecules. Finally, uncoupling the intertwined nutritional state and regulation of cell division of algal cells governing oil accumulation looks promising as a model system for potentially addressing instances when this analogous relationship goes awry in human cells, which may lead to cancer.

Plants as chemical feedstock factories

A number of nondomesticated plant species (Table 1) produce less common fatty acids that are of interest for industrial or human health applications. These include fatty acids with short (<8 carbons), medium (8 to 14 carbons), or very long chain lengths (>20 carbons), with distinct patterns of unsaturation such as conjugated (separated by 1 carbon bond) ω3 or ω7 double bonds (positioned 3 or 7 carbons from the methyl end of the fatty acid, respectively), and with additional chemical modifications such as hydroxyl, epoxy, or cyclic groups (Fig. 1). Unusual fatty acids provide chemical feedstocks serving as precursors for lubricants, nutraceuticals, plastics, paints, natural insecticides, biodiesel, and jet fuels. In most cases, considerable constraint remains on cultivating nondomesticated plant species because of their poor agronomic performance or their adaptation to climates or ecological niches not permissive for widespread cultivation. Nevertheless, exploring the synthetic capacity of these nondomesticated plants has been essential for identifying specialized fatty acid synthesis and modification enzymes. These enzymes can be introduced into model plants for proof-of-concept demonstrations and ultimately into high-performing GM crops (Table 1).

The introduction of a diacylglycerol acyltransferase from the ornamental burning bush (Euonymus alatus) into the promising niche crop relative of canola, Camelina sativa, resulted in seeds with altered oil composition in which up to 85% of all triacylglycerols occur in the form of acetyl-triacylglycerols (11). Camelina is not a high-volume commodity crop, which should enable GM varieties to be more readily commercialized because of its easier identity preservation and stewardship. Acetyl-triacylglycerols contain a two-carbon acetyl chain at the sn-3 position of the glycerol backbone (Fig. 1). Development of this GM crop would address concerns about sustainable energy sources and the environment because acetyl-rich oils have reduced viscosity and freezing points and are therefore useful as replacements for fossil fuel–derived diesel #4 in heavy train and ship engines. More relevant to the average consumer, acetyl-triacylglycerols have a lower caloric value, providing a potentially leaner and healthier vegetable oil for human consumption.

Medium-chain fatty acids are also key ingredients for personal health care products such as lotions, shampoos, and soaps (1, 6) and are often sourced from plants with a limited global distribution, such as coconut. For the purpose of generating GM crops for the production of medium-chain fatty acids, cDNAs encoding specialized fatty acyl–acyl carrier protein thioesters with altered substrate specificities have been overexpressed in canola (6), tobacco (7), or Camelina (12); this prevents the conventional medium-chain fatty acid elongation to 16- or 18-carbon fatty acids in the plastid, resulting in altered acyl compositions of lipids. For example, after co-producing these thioestersases and medium-chain coenzyme A (CoA)–specific lysophosphatidate acyltransferases, which promote sn-2 incorporation into glycerolipids, from Cuphea sp. in Camelina, 14:0 (carbons:double bonds) accumulated up to 37% of total fatty acids in seeds (12). In vegetative tissues that are often even less accommodating to unusual fatty acids, medium-chain fatty acids were generated in tobacco leaves by transient co-production...
of selected thioesterases with the coconut lyso-
phosphatidate acyltransferase and the Arabi-
dopsis WRINKLED1 transcription factor, which
governs fatty acid biosynthetic gene expression
in all oil-accumulating tissues tested, such that
12:0, 14:0, and 16:0 accumulated up to 10%, 19%,
and 38%, respectively (1). Incorporation
of unusual fatty acids at the sn-2 glycerol
position is limited by endogenous fatty
acid-editing mechanisms (13) that still
need to be overcome to achieve higher
productivity.

Engineering of very-long-chain fatty
acids in two distinct but related species
showed that selection of the engineered
host plant is absolutely crucial. The expres-
sion of a cDNA encoding 3-ketoacyl-CoA
synthetase, which elongates long-chain
fatty acids from oilseeds enriched in ner-
vonic acid (24:1), produced only 13% 24:1
in Camelina versus up to 30% of total
fatty acids in the close relative Brassica
caritana (4, 14). Presumably, the higher
erucic (22:1) content in some Brassica
varieties presents a more readily avail-
able substrate for 24:1.

Crambe abyssinica, naturally high in erucic fatty acid, was
further engineered to enhance the pro-
duction of 22:1 and to reduce competing
lipid pathways, such that levels were in-
creased from 60% to 73% of all fatty acids
(3). These very-long-chain fatty acids find uses as
lubricants, synthetic rubber, and cosmetics addi-
tives; as precursors for nylon and plasticizers;
in the treatment of neurological diseases such as
multiple sclerosis; and in infant nutrient supple-
mentation (4).

Many of the useful chemical modifications in
unusual fatty acids arise from catalysis by
specialized, evolutionarily diverged fatty acid
desaturases. Introduction of hydroxyl groups
into fatty acids allows these molecules to be di-
rectly bonded as lubricants to surfaces of high-
performance engine parts. Castor bean,
the main source of hydroxy fatty acids,
produces more than 90% hydroxy fatty
acid (relative to total fatty acid content) but
is also a natural source of the infamous
poison ricin. Introducing the hydroxy fatty
acid trait into GM crops has frequently led
to deleterious side effects— for instance,
a 20% reduction in total seed oil and
poor seed germination (15). Combinato-
rial studies of hydroxylases introduced
into Arabidopsis and GM plants have led
to steady increases in hydroxy fatty
acid production over time (Fig. 2). The
highest levels of hydroxy fatty acids in
Arabidopsis and Camelina were reported
at 29% and 21% of total fatty acid con-
tent, respectively (5, 16). A comparison
of global gene expression profiles from
closely related Camelina to hydroxy fatty
acid-accumulating developing seeds of Physaria fendleri suggested coevolu-
tion of many lipid biosynthetic genes and
others associated with the production of
hydroxy fatty acids (17). Furthermore,
multiple differences in developmental timing of gene expression, substrate promiscuity by enzymes, allelic variation, ploidy, etc., likely contribute to differences in lipid composition among host systems. Consequently, a strategy for further increasing unusual fatty acid levels might require engineered plants with coexpression of a larger number of genes with targeted precision than previously assumed. In synthetic biology terms, the appropriate chassis makes a difference.

Up to 65% of the total fatty acids in Camelina seeds have been converted to ω7 monounsaturated fatty acids, a sustainable precursor for 1-octene used in the production of polyethylene (2). Punicic acid, an 18:3 conjugated fatty acid from pomegranate (Punica granatum) thought to contribute to its antiatherogenic health benefits, was produced in amounts up to 21% of total fatty acids when introduced into a high linoleic (18:2) Arabidopsis background (18). By co-producing a cyclopane fatty acid synthase and a cyclopane-specific lysophosphatidate acyltransferase, up to 35% cyclopane fatty acids, which serve as natural insecticides, of total fatty acids were produced in Arabidopsis seeds, although they showed reduced germination rates (19).

**Increasing energy density and nutritional value**

Diversity among land plants is also evident in the wide range of lipid content in storage and specialized tissues. Many domesticated crops such as palm, soy, and canola produce lipid-rich seeds with extractable seed oils, the primary source of commercial vegetable oils. Even modest increases in the total seed oil content will increase the crop's value. Because yield increases by conventional breeding of high oil-producing natural varieties are expected to reach a limit, attempts have been made to improve performance of these crops through targeted engineering. For example, a 16% relative increase in soybean seed oil was achieved by introducing specialized amino acid residues into the main soybean diacylglycerol acyltransferase, DGAT1 (20). In canola, constitutive overexpression of the Arabidopsis transcription factor gene LEAFY COTYLEDON1 acting upstream of the WRINKLED1 transcription factor produced a range of relative seed oil increases up to 16% (21). Alternatively to targeting anabolism, the suppression of SUGAR-DEPENDENT1, a triacylglycerol lipase, by RNA interference (RNAi) increased relative canola seed oil content up to 8% (22).

Energy density and nutritional value of vegetative plant tissues can also be increased by diverting photosynthetically fixed carbon into triacylglycerols. An integrated strategy for increasing triacylglycerol levels in vegetative leaves has been applied through simultaneous alterations that increase the production of fatty acids by overexpressing WRINKLE1, in addition to driving the incorporation of fatty acids through increasing diacylglycerol acyltransferase abundance, and by protecting accumulated triacylglycerols by reducing lipase-mediated breakdown, as well as by directly altering carbon partitioning (7, 8, 23). Applying this approach to Arabidopsis roots, stems, and leaves resulted in accumulated triacylglycerol levels from 5 to 8% dry weight (23). In crop systems, tobacco leaf triacylglycerol levels increased up to 15% of dry weight (7), whereas triacylglycerol levels in sugarcane leaves and stems increased up to 1.5% of dry weight (8). Ectopic expression of a green algal diacylglycerol acyltransferase type II encoding cDNA in Arabidopsis increased leaf triacylglycerol content by a factor of 10, such that caterpillar larvae feeding on transgenic tissue gained 45% more weight, thereby demonstrating the nutritional enhancement of this GM plant (24). However, there remain challenges for further increasing oil in some vegetative tissues, as demonstrated by overexpressing WRINKLE1 in the grass Brachypodium distachyon, where local cell death is likely due to a doubling of free fatty acid levels (25).

One of the most striking successes for the nutritional enhancement of seed oil, while at the same time providing a solution for the protection of natural resources, is the production of fish oil–like vegetable oils in GM crops. The daily intake of ω3 long-chain polyunsaturated fatty acids by most humans—especially consumers of the Western diet, rich in saturated animal fats—falls short of recommendations despite well-documented health benefits, in particular those of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) (26, 27). The current global supply of naturally produced EPA and DHA in the form of marine fish oils is insufficient to meet increasing demand. Although many plants accumulate another ω3 fatty acid that is readily available in the human diet, α-linolenic acid (18:3), its conversion to EPA and DHA in humans is inefficient. Therefore, introducing these fish oil–like vegetable oils into GM crops provides a feasible, sustainable avenue for the production of ω3 long-chain polyunsaturated fatty acids for human consumption (9, 10). This synthetic biology–based engineering feat was achieved in Camelina by redirecting the endogenous production of 18:3 through a series

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**Table 1. Examples of engineering GM crops and model plants to accumulate desirable fatty acids.**

<table>
<thead>
<tr>
<th>Fatty acid (FA)</th>
<th>Natural high-accumulating source</th>
<th>GM plant</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type</strong></td>
<td><strong>Structure</strong></td>
<td><strong>Species</strong></td>
<td><strong>Tissue</strong></td>
</tr>
<tr>
<td>Short chain</td>
<td>2:0</td>
<td>Euonymus alatus</td>
<td>Seed</td>
</tr>
<tr>
<td>Medium chain</td>
<td>8:0</td>
<td>Cuphea pulcherrima</td>
<td>Seed</td>
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<tr>
<td></td>
<td>10:0</td>
<td>Cuphea viscosissima</td>
<td>Seed</td>
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<tr>
<td></td>
<td>12:0</td>
<td>Oil palm</td>
<td>Seed</td>
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<td></td>
<td></td>
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<tr>
<td>Very long chain</td>
<td>22:1∆13</td>
<td>Crambe abyssinica</td>
<td>Seed</td>
</tr>
<tr>
<td></td>
<td>24:1∆15</td>
<td>Lunaria annua</td>
<td>Seed</td>
</tr>
<tr>
<td>Hydroxylated</td>
<td></td>
<td>Castor bean</td>
<td>Seed</td>
</tr>
<tr>
<td>ω7</td>
<td></td>
<td>Dolichandra unguis-cati</td>
<td>Seed</td>
</tr>
<tr>
<td>ω3</td>
<td>DHA</td>
<td>Bulk fish oil</td>
<td>Fish</td>
</tr>
<tr>
<td></td>
<td>EPA</td>
<td>Bulk fish oil</td>
<td>Fish</td>
</tr>
<tr>
<td>Conjugated</td>
<td>Punic acid</td>
<td>Pomegranate</td>
<td>Seed</td>
</tr>
<tr>
<td>Cyclic</td>
<td></td>
<td>Litchi chinensis</td>
<td>Seed</td>
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</tbody>
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*Percent acetyl-triacylglycerols of total triacylglycerols.
of unusual desaturases and elongases derived from different microalgae and fungi. In seeds, up to 12% EPA and 14% DHA of total fatty acids accumulated when targeted for cosynthesis, or to 12% EPA and 14% DHA of total fatty acids.

Unlinking triacylglycerol biosynthesis and cell division

Interest in microalgae has surged because of their high capacity for high-energy compound production in culture systems not competing with food crops. However, one of the biggest conundrums has been that microalgae accumulate triacylglycerols in lipid droplets when they are nutrient-deprived and cease growth. That is, triacylglycerol accumulation and biomass production are inversely correlated. Conceptually, cells must progress from the cell division cycle to the quiescent state, when cells are metabolically active but do not divide, to produce high amounts of triacylglycerol. How this transition is controlled is not yet known, but one possible regulatory factor, COMPROMISED IN THE HYDROLYSIS OF TAG 7 (CHT7), has been identified in *Chlamydomonas* (37). This protein is a component of a presumed large nuclear transcriptional complex not unlike the retinoblastoma tumor suppressor protein complex governing the cell division cycle in *Chlamydomonas* (38).

Understanding how the nutritional state of cells affects quiescence and cell division will provide a solution to the conundrum hampering algal feedstock engineering. Although many studies suggest that nutrition determines the metabolic state of human cells and can thereby affect the outlook for the development of cancer, mechanistic insights are scarce. *Chlamydomonas* provides a single-celled, easily manipulated model system that has the same basic machinery governing cell division and cellular quiescence as found in human cells. Hence, basic research in algae on cell cycle regulation and triacylglycerol formation during nutrient deprivation–induced quiescence, and research into mechanisms by which the nutritional state of human cells affects cell division for better or worse, may converge in the near future. As such, fundamental insights gained by studying the regulation of algal lipid metabolism promise to allow us to address health and environmental issues of concern to current and future generations.

Conclusions

Measurable progress in engineering the plant lipidome has been made, but additional advances will require a holistic approach. Versatile “omics” approaches aided by bioinformatics will be needed to address several areas of lipid metabolism, including complexities within acyl exchange and lipid remodeling, characterization of orthologous enzymes for lipid modification, availability and localization of multiple lipid substrate pools within subcellular compartments, and trafficking of these lipid constituents between plant purposes. As an example, human fibroblast growth factor 9 fused to oleosin and produced in *Arabidopsis* cells has been targeted to lipid droplets (36). Challenges include the short half-life of some lipid droplets, substrate availability and competition within competing pathways, and incompatibility of proteins targeted to the same membrane.

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Plant metabolism, the diverse chemistry set of the future

Eleanore T. Wurtzel1,2,* and Toni M. Kuchen3,4

New technologies are redefining how plant biology will meet societal challenges in health, nutrition, agriculture, and energy. Rapid and inexpensive genome and transcriptome sequencing is being exploited to discover biochemical pathways that provide tools needed for synthetic biology in both plant and microbial systems. Metabolite detection at the cellular and subcellular levels is complementing gene sequencing for pathway discovery and metabolic engineering. The crafting of plant and microbial metabolism for the synthetic biology platforms of tomorrow will require precise gene editing and delivery of entire complex pathways. Plants sustain life and are key to discovery and development of new medicines and agricultural resources; increased research and training in plant science will accelerate efforts to harness the chemical wealth of the plant kingdom.

From the ancient valleys of Mesopotamia to the Amazonian rainforests, mankind has sought plants for food and nutrition, biomaterials for living, and treatment of pain and disease. Traditional medicine worldwide has relied on the medicinal properties of plants, such as the opium poppy, Papaver somniferum, first cultivated by the Sumerians in 3400 B.C.E. Plant extracts or provided physiologically active chemicals, such as henna from Lawsonia inermis, in use today, and the essential oils such as rose oil have provided sensual pleasure since antiquity. Cotton fibers from Gossypium species werefirst woven into clothing thousands of years ago, and papyrus used for writing in ancient Egypt evolved into the paper industry of today. Selected examples of this structural diversity and for which use humanity has exploited it is given in Fig. 1.

The chemical diversity of plants is enormous. Plants evolved the biosynthesis of a cornucopia of novel chemicals to survive and communicate in a complex ecological environment. Although some plant chemicals are sharp or bitter tasting (glucosinolates and pyrrolizidine alkaloids) to deter herbivory, others such as anthocyanins and carotenoids are brightly colored flower pigments that attract pollinators. Chemicals that are cytotoxic or otherwise physiologically active in mammals are used, for example, as pain-killers, chemotherapeutics, and other drugs. All of these plant chemicals are made through species-specific, specialized biochemical pathways that modify metabolites of primary metabolism. A plethora of new chemicals and metabolic pathways are likely hidden in plant genomes awaiting discovery. Although structures for 200,000 natural products are known, only 15% of the estimated 350,000 plant species have been investigated for their chemical constituents (I). This estimate suggests that a relatively small percentage of the chemical space present in the plant kingdom has been discovered. With every new enzyme and underlying gene discovered, there is potential for a biochemical reaction that can improve modern medicine, human and animal health, bioenergy, and agriculture.

In this review, we present recent examples of selected exciting technologies that are transforming how we study plant metabolism and how we implement these discoveries to develop the plants and microbes of tomorrow. Although the pace of progress during the past several years has accelerated, there are still challenges to be met in order to fully harness the chemical wealth of the plant kingdom. Accelerating pathway discovery

Inexpensive DNA sequencing, together with computational tools for genome assembly, have revolutionized pathway discovery in plants. The relatively small number of sequenced genomes revealed a surprising distribution of genes encoding specialized biochemical pathway enzymes (2). For a growing number of pathways, enzymes are encoded in clustered genomic regions (2) having shared chromatin signatures to coordinate expression (3). Pathways are also encoded by unlinked genes or a combination of linked and unlinked genes. Specialized plant chemicals function to communicate with the ecological environment, and environmental cues are likely necessary to regulate expression of certain pathways, whether organized in clusters or randomly throughout a genome. The breadth of the chemical space of plants is not known, in part because of reliance on environmental signals for the expression of some pathways. This clustered genome feature can be exploited to identify silent pathways or pathways expressed at levels so low that the metabolites that they produce accumulate below our current levels of chemical detection and have remained undiscovered. Development of computational methods that link chromatin signatures with transcript and metabolite profiles will accelerate discovery of unknown pathways encoded by gene clusters. Development of facile heterologous expression platforms will enable

REFERENCES AND NOTES

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