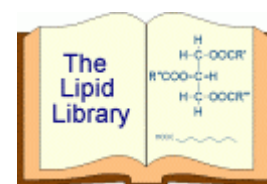


TRIACYLGLYCEROLS

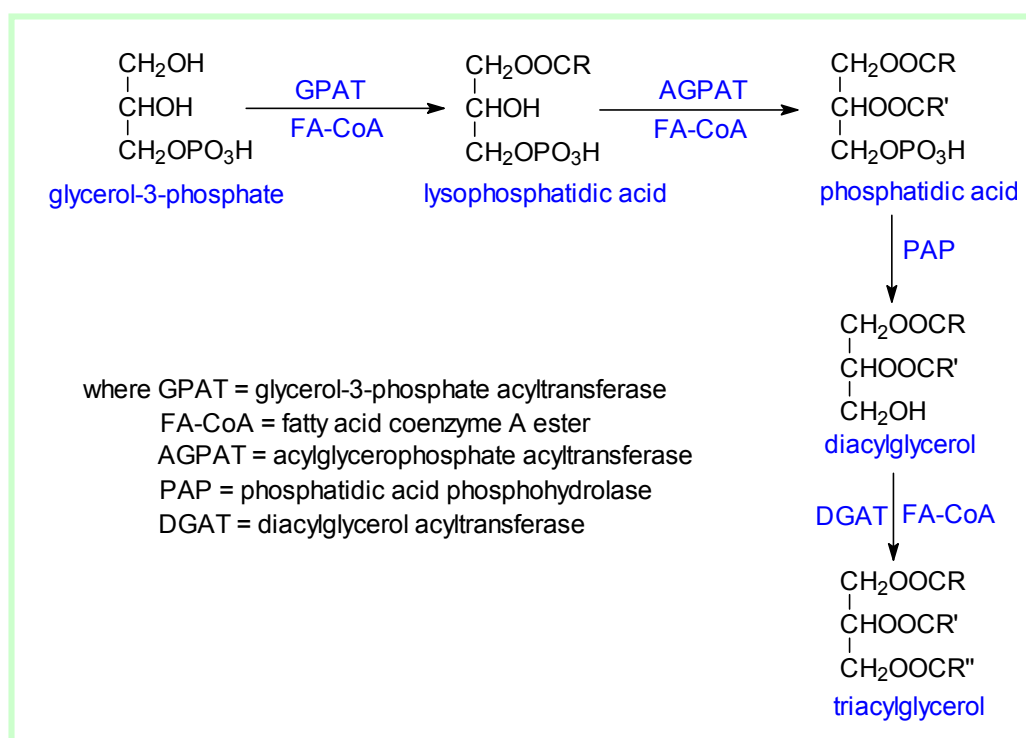
PART 2. BIOSYNTHESIS AND METABOLISM



1. Biosynthesis of Triacylglycerols

All eukaryotic organisms and even a few prokaryotes have the ability to synthesise triacylglycerols, and the process has been studied intensively in plants and animals especially. Many cell types and organs have the ability to synthesise triacylglycerols, but in animals the liver and intestines are most active, although most of the body stores of this lipid are in adipose tissue. Within all cells, even those of the brain, triacylglycerols are stored as cytoplasmic '**lipid droplets**' (also termed 'fat globules', 'oil bodies', 'lipid particles', 'adiposomes', etc) enclosed by a monolayer of phospholipids and hydrophobic proteins, such as the perilipins in adipose tissue or oleosins in seeds. These lipid droplets are now treated as distinctive organelles, with their own characteristic metabolic pathways and associated enzymes – no longer boring blobs of fat. They are not unique to animals and plants as Mycobacteria and yeasts have similar lipid inclusions. The lipid serves as a store of energy and a reserve of essential fatty acids, but it may also exist as a protective measure to remove any excess of biologically active and potentially harmful lipids such as free fatty acids, diacylglycerols, cholesterol (as cholesterol esters) and coenzyme A esters.

Two main biosynthetic pathways are known, the *sn*-glycerol-3-phosphate pathway, which predominates in liver and adipose tissue, and a monoacylglycerol pathway in the intestines. In maturing plant seeds and some animal tissues, a third pathway has been recognized in which a diacylglycerol transferase is involved. The most important of these is the *sn*-glycerol-3-phosphate or Kennedy pathway illustrated below, first described by Professor Eugene Kennedy and colleagues in the 1950s, by means of which more than 90% of liver triacylglycerols are produced.



In the *sn*-glycerol-3-phosphate or α -glycerophosphate pathway, the main source of the glycerol backbone has long been believed to be *sn*-glycerol-3-phosphate produced by the catabolism of glucose (glycolysis) or to a lesser extent by the action of the enzyme glycerol kinase on free glycerol. However, there is increasing evidence that a significant proportion of the glycerol is produced *de novo* by a process known as glyceroneogenesis via pyruvate. Indeed, this may be the main source in adipose tissue.

Subsequent reactions occur in the endoplasmic reticulum. First, the precursor *sn*-glycerol-3-phosphate is esterified by a fatty acid coenzyme A ester in a reaction catalysed by a glycerol-3-phosphate acyltransferase (GPAT) at position *sn*-1 to form lysophosphatidic acid, and this is in turn acylated by an acylglycerophosphate acyltransferase in position *sn*-2 to form a key intermediate in the biosynthesis of all glycerolipids **phosphatidic acid** (see our webpage on this lipid).

The phosphate group is removed by the enzyme phosphatidic acid phosphohydrolase (PAP or 'phosphatidate phosphatase' or 'lipid phosphate phosphatase'). PAP is also important as it produces diacylglycerols as essential intermediates in the biosynthesis of phosphatidylcholine and phosphatidylethanolamine. In contrast to the activity responsible for phospholipid biosynthesis in mammals, much of the phosphatase activity leading to triacylglycerol biosynthesis resides in three related cytoplasmic proteins, termed lipin-1, lipin-2, and lipin-3, which were characterised before the nature of their enzymatic activities were determined. The lipins are tissue specific, and each appears to have distinctive expression and functions, but lipin-1 (PAP1) accounts for all the PAP activity in adipose tissue and skeletal muscle. While it occurs mainly in the cytosolic compartment of cells, it is translocated to the endoplasmic reticulum in response to elevated levels of fatty acids within cells. Lipin-1 activity requires Mg^{2+} and is inhibited by *N*-ethylmaleimide, whereas the membrane-bound activity responsible for synthesising diacylglycerols as a phospholipid intermediate is independent of Mg^{2+} concentration and is not sensitive to the inhibitor.

Perhaps surprisingly, lipin-1 has a dual role in that it operates in collaboration with known nuclear receptors as a transcriptional coactivator to modulate lipid metabolism and the expression of genes involved in lipid metabolism. Abnormalities in lipin-1 expression are known to be involved in human disease states that may lead to the metabolic syndrome. Lipin 2 is a similar phosphatidate phosphohydrolase, which is present mainly in liver and is regulated dynamically by fasting and obesity (in mice).

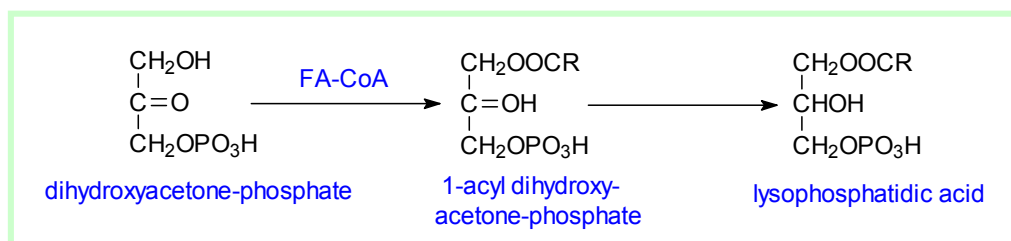
The resultant 1,2-diacyl-*sn*-glycerol is acylated by a diacylglycerol acyltransferase (DGAT) to form the triacyl-*sn*-glycerol. As the glycerol-3-phosphate acyltransferase has the lowest specific activity of these enzymes, this step may be the rate-limiting one. On the other hand, DGAT is the dedicated triacylglycerol-forming enzyme, and this is seen as a target for pharmaceutical intervention in obesity and attendant ailments.

In fact there are two DGAT enzymes, which are structurally and functionally distinct. DGAT1 is expressed in skeletal muscle, skin and intestine, with lower levels of expression in liver and adipose tissue. Perhaps surprisingly, it is the only one present in the epithelial cells that synthesise milk fat in the mammary gland. DGAT2 is the main form of the enzyme in hepatocytes and adipocytes, although it is expressed much more widely in tissues. Both enzymes are important modulators of energy metabolism, although DGAT2 appears to be especially important in controlling the homeostasis of triacylglycerols *in vivo*.

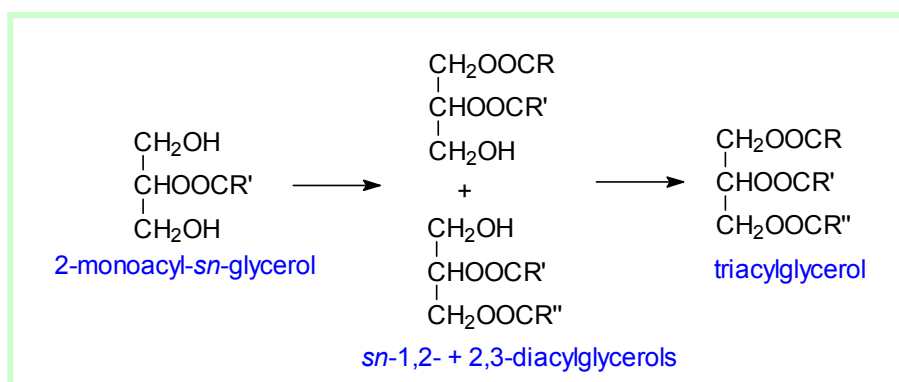
Among other potential routes to the various intermediates, lysophosphatidic acid and phosphatidic acid can be synthesised in mitochondria, but must then be transported to the endoplasmic reticulum before they enter the pathway for triacylglycerol production. 1,2-Diacyl-*sn*-glycerols are produced by the action of phospholipase C on phospholipids.

In addition, dihydroxyacetone-phosphate in peroxisomes or endoplasmic reticulum can be acylated by a specific acyltransferase to form 1-acyl dihydroxyacetone-phosphate, which is reduced by

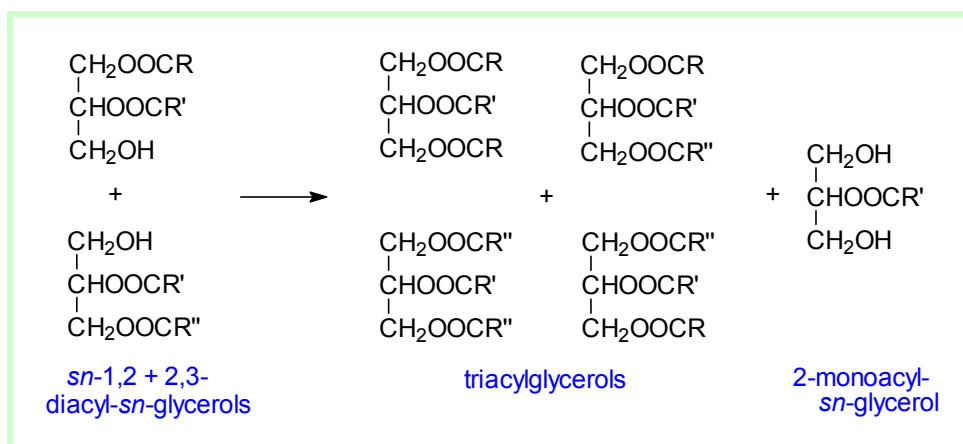
dihydroxyacetone-phosphate oxido-reductase to lysophosphatidic acid (part of the biosynthetic route to **plasmalogens**), which can then enter the pathway to triacylglycerols.



In the enterocytes of intestines after a meal, up to 75% of the triacylglycerols are formed via a monoacylglycerol pathway. 2-Monoacyl-*sn*-glycerols and free fatty acids released from dietary triacylglycerols by the action of pancreatic lipase within the intestines are taken up by the enterocytes. There, the monoacylglycerols are first acylated by an acyl coenzyme A:monoacylglycerol acyltransferase with formation of *sn*-1,2-diacylglycerols mainly as the first intermediate in the process, though *sn*-2,3-diacylglycerols are also produced, and then by acyl coenzyme A:diacylglycerol acyltransferase (DGAT1) to form triacylglycerols. DGAT1 can also acylate monoacylglycerols.



In the third biosynthetic pathway, which is less well known, triacylglycerols are synthesised by an acyl-CoA independent transacylation between two racemic diacylglycerols. The reaction was first detected in intestinal microvillus cells and is catalysed by a diacylglycerol transacylase. Both diacylglycerol enantiomers participate in the reaction with equal facility to transfer a fatty acyl group with formation of triacylglycerols and a 2-monoacyl-*sn*-glycerol. A similar reaction has been observed in seed oils.



It has been suggested that the enzyme may function in remodelling triacylglycerols post synthesis, especially in oil seeds, and it is possible that it may be involved in similar processes in liver and adipose tissue, where extensive hydrolysis/re-esterification is known to occur. There is evidence

for selectivity in the biosynthesis of different molecular species in a variety of tissues and organisms, which may be due to the various biosynthetic pathways. Also, fatty acids synthesised *de novo* appear to be utilized in different ways from those entering tissues from external sources.

In prokaryotes, the glycerol-3-phosphate pathway of triacylglycerol biosynthesis only occurs, but in yeast both glycerol-3-phosphate and dihydroxyacetone-phosphate can be the primary precursors and synthesis takes place in cytoplasmic lipid droplets and the endoplasmic reticulum. In plants, the glycerol-3-phosphate pathway is most important, but many questions remain concerning the nature and compartmentalization of the process, as many different isoenzymes have been characterized in different organelles for each of the acylation steps. The terminal acylation step is catalysed by microsomal diacylglycerol acyltransferases with broad substrate specificities. However, little is yet known of how the membrane and storage lipids acquire their very different fatty acid compositions and positional distributions.

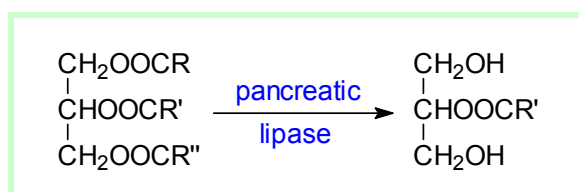
In the glycerol-3-phosphate and other pathways, the starting material is of defined stereochemistry and each of the enzymes catalysing the various steps in the process is distinctive and can have preferences for particular fatty acids (as their coenzyme A esters) and for particular fatty acid combinations in the partially acylated intermediates. It should not be surprising, therefore, that natural triacylglycerols exist in enantiomeric forms with each position of the *sn*-glycerol moiety esterified by different fatty acids (as discussed in another document in this website).

Although the topic has been the subject of much research, the mechanism for the production of lipid droplets within animal cells is poorly understood. However, the available evidence suggests that large droplets grow by merger of smaller droplets in regions adjacent to the endoplasmic reticulum in animal cells at least. Recent work suggests that diacylglycerols accumulate on the surface of lipid droplets and are utilized for synthesis of triacylglycerols in a reaction catalysed by DGAT2, the key enzyme for the production of storage triacylglycerols. This appears to explain how droplets can grow in the apparent absence of a physical connection to the endoplasmic reticulum.

While triacylglycerols are essential for normal physiology, an excessive accumulation in human adipose tissue and other organs results in obesity and other health problems, including insulin resistance, steatohepatitis and cardiomyopathy. Accordingly, there is considerable pharmaceutical interest in drugs that affect triacylglycerol biosynthesis and metabolism.

2. Triacylglycerol Metabolism in the Intestines, Liver and Mammary Gland

Fat comprises about 40% of the energy intake in the human diet in Western countries, and a high proportion of this is triacylglycerols. The process of fat digestion is begun in the stomach by acid-stable gastric or lingual lipases, the extent of which depending on species but may be important for efficient emulsification. However, this is insignificant in quantitative terms in comparison to the reaction with the colipase-dependent pancreatic lipase, which occurs in the duodenum. Entry of triacylglycerol degradation products into the duodenum stimulates synthesis of the hormone cholecystokinin and causes the gall bladder to release bile acids, which are strong detergents and act to emulsify the hydrophobic triacylglycerols so increasing the available surface area. In turn, cholecystokinin stimulates the release of the hydrolytic enzyme pancreatic lipase. The process of hydrolysis is regiospecific and results in the release of the fatty acids from the 1(3) positions of the triacylglycerols and formation of 2-monoacyl-*sn*-glycerols. Isomerization of the latter to 1(3)-monoacyl-*sn*-glycerols occurs to some extent, and these can be degraded completely to glycerol and free acids.



The free fatty acids and 2-monoacyl-*sn*-glycerols are rapidly taken up by the intestinal cells, via specific carrier molecules but possibly also by passive diffusion, and they are esterified into triacylglycerols as described above. There is evidence that the regiospecific structure of dietary triglycerides has an effect on the uptake of particular fatty acids and may influence further the lipid metabolism in humans. In particular, incorporation of palmitic acid into the position *sn*-2 of milk fat may be of benefit to the human infant (as a source of energy for growth and development), although it increases the atherogenic potential for adults.

Within the intestines, triacylglycerols are incorporated into lipoprotein complexes termed chylomicrons. These consist of a core of triacylglycerols together with some cholesterol esters, which is stabilized and rendered compatible with an aqueous environment by a surface film consisting of phospholipids, free cholesterol and one molecule of a truncated form of apoprotein B (48 kDa). These particles are secreted into the lymph and thence into the plasma for transport to the peripheral tissues for storage or structural purposes. Adipose tissue in particular secretes appreciable amounts of the enzyme lipoprotein lipase into the surrounding blood vessels, where it rapidly hydrolyses the triacylglycerols at the cell surface, releasing free fatty acids, most of which are absorbed into the adjacent adipocytes and re-utilized for triacylglycerol synthesis within the cell.

The chylomicron remnants eventually reach the liver, where the remaining lipids are hydrolysed and absorbed. The fatty acids within the liver can be utilized for a variety of purposes, from oxidation to the synthesis of structural lipids, but a proportion is re-converted into triacylglycerols, and some of this is stored as lipid droplets within the cytoplasm of the cells (see next section). Excessive accumulation of storage triacylglycerols is associated with fatty liver, insulin resistance and type2 diabetes.

Most of the newly synthesised triacylglycerols are exported into the plasma in the form of very-low-density lipoproteins (VLDL), consisting again of a triacylglycerol and cholesterol ester core, surrounded by phospholipids and free cholesterol, together with one molecule of full-length apoprotein B (100 kDa), apoprotein C and sometimes apoprotein E. These particles in turn are transported to the peripheral tissues, where they are hydrolysed and the free acids absorbed. Eventually, the remnants are returned to the liver. These processes are discussed in greater detail in our webpage dealing with [lipoproteins](#).

In the mammary gland, triacylglycerols are synthesised in the endoplasmic reticulum and large lipid droplets are produced with a monolayer of phospholipids derived from this membrane. These are transported to the plasma membrane and bud off with an envelope comprised of the bilayer membrane to form milk fat globules as food for the newborn. The process is thus very different from that involved in the secretion of triacylglycerol-rich lipoproteins.

3. Triacylglycerol Metabolism in Adipocytes and Lipid Droplets

Within animal cells, a proportion of the fatty acids taken up from the circulation is converted to triacylglycerols as described above and incorporated into cytoplasmic lipid droplets with a surrounding protective monolayer that includes phospholipids, cholesterol and hydrophobic proteins, such as perilipins, caveolins and the Adipose Differentiation Related Protein (ADRP or adipophilin). Such droplets can be compared in their micellar structure to the plasma lipoproteins. The phospholipid component of the monolayer contains significant amounts of phosphatidylcholine with a fatty acid composition distinct from that of the endoplasmic reticulum and plasma membrane. Lipid droplets of adipocytes are enriched in triacylglycerols as an energy store, while defending cells against lipotoxicity. They also provide structural components, including cholesterol, for membrane synthesis and repair. Many cell types, even ganglia in the brain, can contain small lipid droplets, but in adipocytes these can range to up to 100 μm in diameter. Cytosolic lipid

droplets with similar metabolic activities are found in yeasts, such as *Saccharomyces cerevisiae*, and the fly *Drosophila melanogaster*.

Lipid droplets have a close association with the endoplasmic reticulum, the main site of lipid synthesis, and there are suggestions that active knots of this membrane may be physically entrapped within droplets. There appears to be communication also with the mitochondrial, peroxisomal and endosomal compartments.

Some of the surface proteins on lipid droplets can extend long helical hairpins of hydrophobic peptides deep into the lipid core. For example, perilipin is a member of a family proteins that bind to lipid droplets in animals and share a common region, the so-called 'PAT' domain, named for the three original members of the family including perilipin and ADRP. Proteins related evolutionarily to these are found in more primitive organisms, including insects, slime moulds and fungi. Other proteins are enzymes intimately involved in triacylglycerol metabolism. There is even a suggestion that cytoplasmic droplets may act as a storage organelle for hydrophobic proteins whose function is elsewhere in the cell.

On the basis of profiling of the surface proteins and phospholipids, it has been argued that lipid droplets in cells should be considered as complex, metabolically active organelles that also function in the supply of fatty acids for various purposes, including membrane trafficking and possibly in the recycling of both simple and complex lipids. For example, within the liver, triacylglycerols are stored as lipid droplets in the cytoplasm adjacent to the endoplasmic reticulum, where a triacylglycerol hydrolase can effect lipolysis to di- and monoacylglycerols that are more soluble in the membrane, which they are able to cross. They are then available for re-synthesis into triacylglycerols by lumenally oriented acyltransferases before assembly into nascent lipoprotein complexes. Similar organelles can be found in most eukaryotic cells and in bacteria, and they provide a reservoir not only for triacylglycerols, but also for esterified cholesterol and in some specialized cells of retinol esters, for example.

This process is especially important in adipose tissue, which is the major energy-dense store of lipids in animals. When fatty acids are required by other tissues for energy or other purposes, they are released from the triacylglycerols by the actions of three enzymes, hormone-sensitive lipase, adipose triacylglycerol lipase and monoacylglycerol lipase. Hormone-sensitive lipase is stimulated by the action of the hormones insulin and noradrenalin by a mechanism that ultimately involves phosphorylation of the enzyme by cAMP-protein kinase, thereby increasing its activity and causing it to translocate from the cytosol to the lipid droplet. Perilipin has been described as "the gatekeeper of the adipocyte lipid storehouse". Thus, the lipolytic process is regulated by perilipin, which acts as a barrier to lipolysis in non-stimulated cells, but on stimulation as during fasting is phosphorylated by the cAMP-protein kinase also. This changes its shape and reduces its hydrophobicity, and in the process activates lipolysis. In addition to its activity towards triacylglycerols, hormone-sensitive lipase will rapidly hydrolyse diacylglycerols, monoacylglycerols, retinyl esters and cholesterol esters. In fact, diacylglycerols are hydrolysed ten times as rapidly as triacylglycerols. Within the triacylglycerol molecule, hormone-sensitive lipase preferentially hydrolyses ester bonds in the *sn*-1 and *sn*-3 positions, leaving free acids and 2-monoacylglycerols as the main end products.

Less is known of the properties of the adipose triacylglycerol lipase, which was discovered relatively recently, but it is structurally related to the plant acyl-hydrolases in that it has a patatin-like domain in the NH₂-terminal region (patatin is a non-specific acyl-hydrolase in potato). It is specific for triacylglycerols yielding diacylglycerols and free fatty acids as the main products. It has low activity only towards diacylglycerols, and none to monoacylglycerols, retinyl esters and cholesterol esters, although it also has transacylase and phospholipase activities. It is located on the surface of the lipid droplet both in the basal and activated states. Adipose triacylglycerol lipase is now believed to be rate limiting for the first step in triacylglycerol hydrolysis. Regulation of the enzymatic activity is believed to involve hormonal factors, but these have yet to be characterized.

However, a lipid droplet protein, designated 'CGI-58' or 'ABHD5', is known to be an important activating factor. In the resting state this protein binds to perilipin, but on phosphorylation of the latter, it is believed to dissociate and interact with adipose triacylglycerol lipase to activate triacylglycerol hydrolysis. Mutations in adipose triacylglycerol lipase or CGI-58 are believed to be responsible for a syndrome in humans known as 'neutral lipid storage disease'.

The monoacylglycerol lipase is believed to be the rate-limiting enzyme in monoacylglycerol hydrolysis, i.e. the final step in triacylglycerol catabolism releasing free glycerol and fatty acids, and is found in the cytoplasm, the plasma membrane, and in lipid droplets. It is specific for monoacylglycerols and has no activity against di- or triacylglycerols. As it is the enzyme mainly responsible for deactivation of the endocannabinoid **2-arachidonoylglycerol**, and is highly active in malignant cancers, it is attracting pharmaceutical interest.

Free fatty acids released by the combined action of these enzymes are exported into the plasma for transport to other tissues in the form of albumin complexes. The glycerol released is transported to the liver for metabolism by either glycolysis or gluconeogenesis. Eventually, the whole organelle can disappear, including the proteins, the fate of which is uncertain.

Not only does the adipocyte provide a store of energy but it manages the flow of energy through the formation of the hormone leptin, which secretes various factors that communicate with other tissues including cytokines, adiponectin and resistin. The synthesis of leptin is tightly controlled by adipocytes and its main function is believed to be the provision of information on the state of fat stores to other tissues. Lipid droplets may play a role in this process, since perilipin is required for the sensing function. A potential involvement of **caveolae**, which contain the proteins caveolins (and presumably sphingolipids) and are particularly abundant in adipocytes, is still a matter of conjecture. They may modulate the flux of fatty acids across the plasma membrane, or they may be involved in signal transduction and membrane trafficking pathways. Thus, adipose tissue metabolism has profound effects on whole-body metabolism, and defects in these processes can have severe implications for the pathogenesis of diabetes and obesity in humans.

One specialized form of adipose tissue, brown fat, is highly vascularized and rich in mitochondria, which oxidize fat so rapidly that heat is generated ("non-shivering thermogenesis"). This appears to be especially important in young animals and in those recovering from hibernation.

4. Other Functions of Triacylglycerol Depots

Subcutaneous depots serve as insulation against cold in many terrestrial animals, as is obvious in the pig, which is surrounded by a layer of fat, and it is especially true for marine mammals. In the latter and in fish, the lipid depots are less dense than water and so aid buoyancy with the result that less energy is expended in swimming. More surprisingly, perhaps, triacylglycerols together with the structurally related glyceryl ether diesters and wax esters are the main components of the sonar lens used in echo-location by dolphins and some whales. The triacylglycerols are distinctive in that they contain two molecules of 3-methylbutyric (isovaleric) acid with one long-chain fatty acid. It appears that the relative concentrations of the various lipids in an organ in the head of the animals (termed the 'melon') vary in such a way that they are able to focus sound waves.

5. Triacylglycerol Metabolism in Plants

In the seeds of plants, fatty acids are stored in the embryo or endosperm tissues as triacylglycerols in lipid droplets, which exist in close proximity with glyoxysomes (peroxisomes). These are the membrane-bound organelles that contain most of the enzymes required to oxidize fatty acids derived from the triacylglycerols via acetyl-CoA to four-carbon compounds, such as succinate, which are then converted to soluble sugars to provide germinating seeds with energy to fuel the

growth of the seedlings and to produce shoots and leaves. In addition, they supply structural elements, before the seedlings develop the capacity to photosynthesise.

Triacylglycerols in the developing seeds are synthesised in the endoplasmic reticulum by the Kennedy pathway described above. Oil droplets then accumulate in the endoplasmic reticulum by mechanisms that are only poorly understood, and are surrounded by a monolayer of phospholipids and proteins, which in *Arabidopsis* include oleosins, a caleosin, a steroleosin, a putative aquaporin and a glycosylphosphatidylinositol-anchored protein. Upon germination, lipases are activated and the process of lipolysis begins at the surface of oil bodies, where the oleosins, which are the most abundant structural proteins, are believed to serve to assist the docking of lipases. A number of lipases have been cloned from various plant species and are typical α/β -hydrolases, with a conserved catalytic triad of Ser, His, and Asp or Glu, which are able to hydrolyse triacylglycerols but not phospho- or galactolipids. The most important of these is believed to be the 'sugar-dependent lipase 1 (SDP1)', which is a patatin-like lipase similar to the mammalian adipose triacylglycerol lipase discussed above, and is located on the surface of the oil body. This is active mainly against triacylglycerols to generate diacylglycerols, but presumably works in conjunction with di- and monoacylglycerol lipases to generate free fatty acids and glycerol. How these products are transported to the peroxisomes for further metabolism has still to be determined.

Also in plants, oil droplets in the anthers of flowers provide the lipids and oleosins that coat and stabilize pollen.

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