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by abrupt diversity crashes, indicate how fluctuating physical conditions, and particularly rapid extinction, played an important role in guiding the evolutionary history of the clade.

OK, they are cute, but why should a developmental biologist care about them? Onset of calcification early in ontogeny coupled with gradual, progressive morphological development permits the recognition of growth sequences for over a hundred trilobite species. Striking variation in the number of trunk segments at maturity across ontogeny and phylogeny, coupled with the curious pattern of segment exchange between the pygidium and thorax during early development, provides opportunities to explore the co-evolution of different aspects of segmentation and body patterning. Recent results suggest an evolutionary trade-off between the ability to vary the overall number of thoracic segments and the advantages of regional specialization along the body axis. The striking, general decrease over time in the degree of intraspecific variation in the aftermath of the Cambrian radiation offers an opportunity to assess the roles of regulatory evolution and palaeoenvironmental change in shaping the evolutionary trajectory of the clade as a whole.

What else are they good for? Because they evolved rapidly they provide the finest resolution of geological time available in rock strata of Cambrian age and are used as index fossils to date the strata. The spatial distribution of species also constrains ancient geography and patterns of plate movement. Trilobites also look well on bolo ties and other fashion accessories.

Where can I find out more?

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http://www.trilobites.info/

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Lipid droplets

Laura L. Listenberger and Deborah A. Brown

What are lipid droplets? Lipid droplets are intracellular storage depots for neutral lipid. They are also known as lipid bodies (or oil bodies in plants, and lipid particles in yeast) and recently as adiposomes. The mature lipid droplet consists of a neutral lipid core (primarily triacylglyceride and/or cholesteryl ester) surrounded by a phospholipid monolayer (Figure 1). A number of proteins are specifically targeted to the lipid droplet surface, where they can regulate lipid droplet dynamics and turnover of stored lipid.

What do they do? Lipid droplets serve as energy reservoirs, sources of lipid for membrane biosynthesis, and storage sites for potentially toxic lipid species. Specific uses can vary between cell types. For example, adipocytes are highly specialized for lipid storage, and contain large (25–200 μm diameter), triacylglyceride-rich lipid droplets that are hydrolyzed to provide energy for peripheral tissues. Cells in the adrenal cortex, testes, and ovaries have smaller (1 μm) lipid droplets that store cholesteryl esters for use in steroid hormone biosynthesis. Hepatocytes use lipid stored in lipid droplets for assembly of very low density lipoproteins. Some plants accumulate lipid droplets in their seeds as a source of energy for germinating embryos.

How are lipid droplets made? The final steps in the synthesis of triacylglycerides and cholesteryl esters are catalyzed by enzymes (diacylglycerol acyltransferases (DGATs) and acyl-CoA: cholesterol acyltransferases (ACATs), respectively) that reside in the endoplasmic reticulum (ER) membrane. ACATs and DGATs do not appear to be highly regulated, and the rate of neutral lipid synthesis usually reflects substrate availability. According to a widely-held (but still unproven) model, newly-synthesized neutral lipids coalesce into a disc in the interior of the ER bilayer. Continued lipid synthesis causes the disc to swell into a sphere that eventually buds into the cytosol, surrounded by an ER-derived phospholipid monolayer (Figure 1). However, reports that the phospholipid composition of the lipid droplet surface monolayer is distinct from that of the ER suggest that lipid droplets may bud from specialized ER subdomains, or perhaps even be made by an entirely different mechanism. Following their synthesis, lipid droplets may change in size. It has been suggested that additional neutral lipids are delivered directly to lipid droplets, even after the lipid droplets have budded from the ER. Lipid droplets may also grow by fusing with each other: lipid-droplet-associated

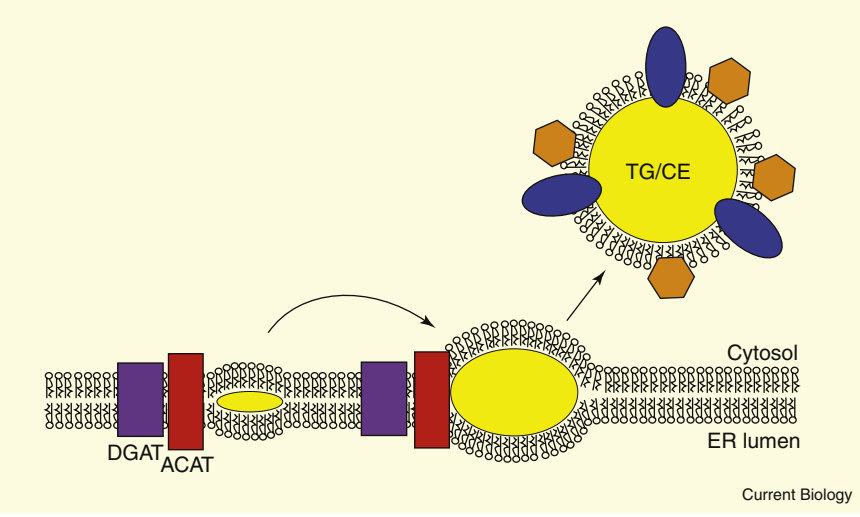

Figure 1. Model of lipid droplet formation. Lipid droplets may form via coalescence of newly synthesized neutral lipids in the interior of the ER membrane and subsequent budding into the cytosol. Mature lipid droplets consist of a neutral lipid core surrounded by a phospholipid monolayer and associated proteins, mostly recruited from the cytosol. ACAT, acyl-CoA: cholesterol acyltransferase; CE, cholesteryl ester; DGAT, diacylglycerol acyltransferase; TG, triacylglyceride.

SNAREs were recently reported. Conversely, in adipocytes, large lipid droplets can fragment as an early response to hormonal stimulation.

How do lipid droplets interact with other structures? Not yet clear! Lipid droplets in many cells are dynamic, and move in a microtubule-dependent manner. However, in other cases they seem to stay associated with the ER. In yeast, lipid droplets can snuggle up to peroxisomes, delivering fatty acids for β-oxidation. Proteins involved in membrane trafficking, such as Rab18, can be present on lipid droplets, and the trafficking regulator Arf1 binds ADRP, an abundant lipid droplet protein in many mammalian cell types. Interaction of lipid droplets with organelles of the secretory and/or endocytic pathways could function in lipid delivery.

How are stored fats released from lipid droplets? Triacylglycerides are catabolized by sequential cleavage of acyl chains from the glycerol backbone, releasing free fatty acids and generating diacylglyceride and monoacylglyceride intermediates along the way. Lipid turnover in adipocytes is highly regulated by hormonal stimulation. Abundant lipid droplet surface proteins called perilipins regulate the association of the cytosolic enzyme hormone-sensitive lipase (HSL) with lipid droplets. Under basal conditions, perilipins inhibit HSL binding to lipid droplets, slowing triacylglyceride hydrolysis. By contrast, perilipins greatly stimulate lipolysis following hormonal stimulation by recruiting HSL to lipid droplets, and/or by activating the lipase once on the lipid droplet surface. Protein kinase A mediates these effects by phosphorylating both perilipins and HSL in response to hormonal stimulation. Because HSL is so highly regulated, it was surprising to learn recently that another enzyme, adipose triglyceride lipase (ATGL), actually catalyzes the first step in triacylglyceride turnover in adipocytes, generating diacylglycerides. HSL turns out to work downstream, hydrolyzing diacylglycerides generated by ATGL. Unlike HSL, ATGL is widely expressed among mammalian cell types and other eukaryotes. ATGL orthologs play key roles in triacylglyceride turnover in *Drosophila* and yeast. ATGL is not phosphorylated by protein kinase A, but is instead activated by CGI-58, which is structurally similar to lipases but lacks catalytic activity. Mutations in genes encoding ATGL and CGI-58 cause distinct neutral lipid storage diseases, highlighting the key role of these proteins in lipid metabolism.

What about other cell types? Hormonal control of lipolysis is largely restricted to adipocytes, and the tissue distribution of HSL and perilipins is also highly restricted. However, modulation of the activity and association of cytosolic lipases with lipid droplets is likely to be a general strategy for regulating lipid turnover. Other proteins in the same family as perilipins are abundant on lipid droplets in many mammalian cell types. Two of these (ADRP and TIP47) are ubiquitously expressed, while the others have more restricted expression patterns (S3-12 is mostly in adipocytes, and MLDP/OXPAT in oxidative tissues, especially heart and slow-twitch muscle). These proteins may regulate access of lipases to the lipid droplet surface, just as perilipins do in adipocytes under basal conditions. Lipid droplets in the seeds of oil seed plants are coated with oleosins, unique proteins with extended hydrophobic domains that penetrate deep into the lipid droplet core. Oleosins prevent lipid droplet aggregation under drought conditions.

Why do pathogens like lipid droplets? Two very different human pathogens — *Chlamydia trachomatis* and hepatitis C virus — rely on host cell lipid droplets. *C. trachomatis* recruits aberrant lipid droplets to the intracellular inclusion that surrounds the bacteria. Inhibition of lipid droplet synthesis severely inhibits bacterial replication. On the viral front, hepatitis C core protein is targeted to lipid droplets, where it nucleates virus particle assembly. Disruption of lipid droplet targeting inhibits virus production. In both cases, the basis of the surprising requirement for lipid droplets remains a puzzle.

Where can I find out more?

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Primer

Hedgehog signalling

Philip W. Ingham

Secreted signals play a central role in the development of animals, coordinating the growth and patterning of the cellular assemblies of which they are composed. Identifying these signals and elucidating their mechanisms of action has been a major focus of developmental biology over the past two decades. It is now clear that the development of most metazoans is underpinned by just a few families of secreted signalling molecules, one of which comprising the Hedgehog (Hh) proteins. Originally identified in the fruit fly, *Drosophila melanogaster*, genes encoding Hh proteins have subsequently been characterised in a multitude of species, ranging from sponges to humans. Not surprisingly, given their key role in developmental processes, the aberrant activity of the pathway that transduces Hh signals has been implicated in a variety of cancers, making it a prime target for therapeutic interventions.

Hh signalling mediates a plethora of processes during embryonic development and, subsequently, in tissue homeostasis. In some instances, Hh acts to control a binary cell-fate decision, in others Hh specifies multiple cell fates across an entire field of cells. In the zebrafish embryo, for instance, the Hh homologue, Sonic hedgehog (Shh), is secreted by the axial midline structure known as the notochord and acts on immediately adjacent muscle progenitor cells, programming them to differentiate into slow-twitch muscle fibres rather than the fast-twitch fibres to which the remaining myogenic progenitors will give rise. By contrast, the same notochord-derived Shh protein becomes distributed in a gradient across the ventral half of the neural tube where it acts in a dosage-dependent manner to specify a range of distinct neuronal cell types (Figure 1). In the former context, the signal often needs to be spatially restricted close to its source, whilst in the latter it must spread over many cell diameters. The execution of the wide repertoire of processes controlled by the same Hh proteins depends upon