

fuel

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We need fat. From bacteria and yeast to petunias, goldfish and humans, every single action an organism performs, whether conscious or not, requires some sort of fuel. Budding, photosynthesis, predation, digestion, hibernation, seeing, thinking, eating, breathing, immunity, sleeping, swimming, walking – the list is far too long to draw. Not everything works on fat, of course. Sugars and adenosine triphosphate (ATP) are also extensively used. It all depends on the metabolism and the biochemistry involved. The fact is, organisms are in constant need of energy, which is why they store it continuously. Triacylglycerol (TAG) is the main form of fat stored by animals and plants, and adipocytes are specifically dedicated to its accumulation. Within adipocytes, as is the case for most eukaryotic cells, TAG is confined to intracellular specialised bodies known as lipid droplets (LDs). Though ignored for years, more and more attention is being given to LDs. Once considered mere globs of fat, LDs have now been promoted to the status of full-blown organelles with their own dynamics. Lately, scientists discovered a protein intricately involved in their genesis and growth. They called it adipogenin.



'Number 4, Gray and Red' (1948)

Jackson Pollock (1912-1956)

You may have noticed small drops of fat floating on milk. These are known as milk fat globules and are secreted by mammary cells. Milk fat globules are similar in composition to lipid droplets in that they are full of triacylglycerol (TAG). LDs, however, are not visible to the naked eye. The first to have seen and describe these 'oil droplets' was Antonie van Leeuwenhoek when he took a look at milk under his microscope in 1674. No one gave any more notice to oil droplets for another 200 years, however, until the American zoologist and geneticist Edmund Beecher Wilson described them once again, this time in developing sea urchin eggs. Nothing came of that

either. Everyone continued to agree that oil droplets were simply very small storage facilities, or perhaps even sites of waste – despite their widespread presence in almost all cell types and across all kingdoms.

Things changed in the 1980s when a different understanding of obesity arose. Obesity was no longer seen as a marker of chronic disease, such as diabetes for example, but more as the dysregulation of energy stores. Adipose tissue, itself composed of adipocytes, was not just a place where fat accumulated anymore but a mature organ that synthesizes hormones and releases them. Consequently, researchers began to take a greater interest in the main components of adipocytes, namely lipid droplets and their constituents. Could LDs be more than just fat? Indeed, as the 1990s unfurled, it became apparent that LDs had all the characteristics of a metabolically active organelle. Not only were they composed of fat but also of several proteins, each with specific roles.

If you were around in the 1960s and 1970s, you will perhaps remember the craze many households had for lava lamps – these long slim glass tubes filled with water and colourful bubbles that floated along the tubes' length, budding and merging into one another as they did. In adipocytes, LDs behave in similar ways. Primarily spherical in shape, the membrane of LDs is composed of only one layer of phospholipids, as opposed to the more frequent bilayer found in other types of organelles. Several proteins are an integral part of the LD's membrane such as perilipin

(read *Protein Spotlight* issue 10), which was the first protein found to be associated with LDs. The droplet's lumen hosts yet other proteins and of course fat, mainly triacylglycerols (TAGs) but also cholesteryl esters (formed when cholesterol binds to a fatty acid).

LDs bud from the cell's endoplasmic reticulum (ER). The ER is an organelle *per se* and can be described as a sort of factory where the majority of membrane and extracellular proteins are synthesized. The ER membrane is a classic phospholipid bilayer. When an LD begins to bud, the two phospholipid layers of the ER ease apart locally to allow the formation of a nascent LD which only buds on the cytoplasmic side of the ER. TAGs are hurried into the lumen as the budding LD grows, and phospholipids are added to the expanding membrane, itself formed of one monolayer of phospholipids. At one point, a mature LD is released from the ER into the cell cytoplasm where it will continue to expand by merging with another LD, or more, for example.

How are TAGs injected into the lumen in the first place? How does an LD actually begin? And how exactly does it grow? Part of the answer is 'seipin'. Seipin is a protein that has been characterised for some time now. Until recently, it was known to exist as a decamer or an undecamer (a rather unusual aggregation of 11 monomers), and to be involved in the genesis of LDs, the aggregation of TAGs into the nascent lumen, and the actual budding of the droplet from the ER. But how it happened at the molecular level remained a mystery. Until recently, when adipogenin was discovered.

Adipogenin is a microprotein (80 amino acids long) and is intimately involved in the development of LDs. How? The microprotein promotes the oligomerization of a seipin dodecamer while also fostering its stability by slipping between every space created between two adjacent seipin monomers. Structurally, the dodecamer looks very like a doughnut and lies in the ER membrane along its flat axis. It is here that an LD will begin to form, and from where it will eventually bud. Its TAG constituents are synthesized within the ER membrane and cluster precisely where the seipin dodecamers (enriched with adipogenin) are located – which has led scientists to suggest that a certain concentration of TAG may actually trigger the onset of LD budding.

Much remains to be understood, but we are a long way away from the passive role LDs were first thought to have. Today, it is becoming more and more clear that LDs have an active role in an organism's overall energy homeostasis. What goes on in a world we are rarely aware of is bewildering and worthy of admiration. Molecules of all shapes and sizes come together to form, in this case, places to store energy we need to survive. Why store it and not make it only when it is required? Nature answered that question a long time ago. It takes time to make energy. It takes time to synthesize TAGs – as it does to synthesize other forms of energy. To avoid energy crises, our bodies stock fuel so that it's ready the moment we need it. And while we're using up that stock, our bodies will synthesize new stock. It's a clever system. One that has to do with survival.

Cross-references to UniProt

Adipogenin, *Mus musculus* (Mouse) : Q8R400

Seipin, *Mus musculus* (Mouse): Q9Z2E9

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