

Fat, wonderful fat

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Fat is not a passive depository of grease. Fat is, in effect, quite precious and fulfils multiple functions in our bodies. Now there's a thought in a day and age where the slightest lipid bump is deemed ungracious! It cushions our fingertips and eye sockets, and acts as a shock absorber in our knee joints and heels. It blankets our internal organs and lines our bellies, seals perforations within internal organs and may well play a role in local immune responses. Adolescents need fat to mature sexually, young women need fat to cope with pregnancy and, in older women, fat protects bones from the effects of menopause.

As always, extremes are dangerous. Too little fat spells infertility problems and a diminished immune response. Too much can be the source of cancer, diabetes and heart disease. Some overweight men can even become slightly feminised and prone to losing facial hair. If fat can do all that, it must be quite talented and one protein that participates in this talent is perilipin. But first: what is fat?



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Fat is not particular to humans. It is found throughout the animal and plant kingdom. Fat is fuel. Without it we would feel continuously run down. It is spread throughout our body in specialised fat-producing cells called adipocytes. Adipocytes are bulging full of grease balls, scientifically known as lipid

droplets. Some adipocytes reach the size of 50 micrometers, almost the diameter of a human hair!

Each lipid droplet is a highly organised minute entity, probably globular in shape. The inside is packed full of triacylglycerol (TAG): fat itself. TAG is held within a monolayer of phospholipids, which is then coated by perilipin. This is not much of a scoop since similar proteins (oleosins and oleosin-like proteins), which form a capsule around the oil bodies in seeds and other plant cells, have been known for quite some time now. However, perilipin may give important clues as to how fat is used, or not used, in humans. Ultimately, it will contribute to a better understanding of illnesses related to fat.

So far, it is thought that perilipin may act as a barrier against unnecessary degradation of TAG. Indeed, it is becoming more and more apparent that the production and breakdown of our fat stores are part of sophisticated machinery regulated by hormones. That is why scientists are beginning to think that fat is an organ *per se*. Lipid droplets in pre-adipocytes are not coated with perilipin but with another protein: adipose differentiation-related protein (ADRP). Once the adipocyte has matured, ADRP bows out and perilipin moves in. Surprisingly though, if lipid droplets continue to form, they are immediately coated by perilipin. Some believe that perilipin may initially serve as a nucleation site for lipid deposit and then move onto its role as a barrier.

What is perilipin obstructing? This is a key question. When energy is needed, TAG is

hydrolysed to both fatty acids and glycerol in response to hormonal stimulation. For TAG to be hydrolysed, perilipin has to let a hydrolytic enzyme – hormone-stimulated lipase (HSL) – into the droplet.

How is the barrier dropped? Probably via phosphorylation of perilipin. Phosphorylated perilipin induces a change in the lipid droplet surface thus giving way to HSL. When the perilipin gene was disrupted in mice, the adipose stores decreased by 70-80%...even on a high-fat diet (lots of chocolate and peanuts). The good news is that transgenic mice that do not produce perilipin do not have the nasty side effects of insufficient adipose tissue such as elevated plasma insulin, glucose and lipids, or fatty livers.

Is this the beginning of a solution to Christmas dinner or other such feasts? Obviously, understanding the exact role of perilipin could lead to the creation of an anti-obesity drug, on a planet where 1.2 billion people are estimated to be overweight. In the USA only, about \$98 billion is spent per year on health care directly attributable to obesity, as well as weight-reduction programmes and special foods. However, many questions remain unanswered. Do perilipins have a structural role? Do they dock lipolytic enzymes? Do they interact with other proteins that may be integrated on lipid droplet surfaces? What is more, a mouse is not a human and the “fat system” is such a complex one that it seems unlikely that pharmaceuticals or surgery based upon a single component – such as perilipin – could lead to the resolution of illnesses related to fat. But despite all this, is it not encouraging to be told that fat is wonderful?

Cross-references to Swiss-Prot

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Love that fat
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