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a touch of warmth

Vivienne Baillie Gerritsen

We need heat. All warm-blooded animals know this instinctively because when life leaves us, the cold creeps in fast. Heat is produced in different ways inside us, and not only to keep our body temperature at a healthy level but also to keep it stable. After the fashion of small mobile furnaces, we carry adipose tissues that are full of stored fat waiting to be burnt down to release heat – a process termed thermogenesis. Researchers are becoming more and more interested in thermogenesis, especially adaptive thermogenesis which is the capacity an organism has to adjust its energy needs according to the environment, i.e. the amount of food that is available and the surrounding climate. Because where there is talk of food, there is talk of obesity and its direct cousin diabetes, two afflictions from which millions of people currently suffer worldwide. For some time already, scientists have known that molecules known as N-acyl amino acids, are important in biological processes such as thermogenesis, but they knew little more. Until they discovered an enzyme that is secreted by fat cells in adipose tissues, and that knows how to make them: peptidase M20 domain containing 1, or PM20D1.

Autumn Warmth, by Mary Pym

Courtesy of the artist

It is all very well to be told we are warm-blooded animals and that we need heat – ca. 37° Celsius – to keep us going. But why can our bodies not work at lower – or for that matter – higher temperatures without suffering from hypo- or hyperthermia? Well in theory they could. But to do so, over the millennia they would have needed to invent all sorts of systems to protect themselves from overheating, or freezing for that matter. Many creatures have developed such systems. There are varieties of fish, for instance, that are able to survive in freezing water, and bacteria that thrive in the vicinity of hydrothermal vents. It just so happens that 37° Celsius, or thereabouts, is the ideal temperature for the molecules that make us to function in an optimum way – like the hosts of metabolic pathways they are involved in. Take a protein: at 37°C, its 3D conformation is not denatured and therefore its activity unhindered. Organisms that live in extreme conditions have devised ways of protecting the smooth running of their metabolism. Two examples: antifreeze proteins and heat shock proteins.

One surprising fact is that humans are not comfortable at temperatures above 30°C, let alone 37°C. Our body prefers outside temperatures that are lower than the one it needs inside – and this is why we are condemned to create heat on an almost continuous basis. Some of the heat, we can access upon need, is stored in the form of fat in our adipose tissues, which are made up of adipocyte cells. There are two types of adipocyte cells: those that are bulging

with fat, and those that have less fat but are bulging with mitochondria and are known as brown fat cells. Mitochondria are a cell's powerhouse and are equipped to produce the currency of biological power known as ATP. Many different proteins are active in mitochondria. In those of brown fat cells, there is a protein which depends on PM20D1 and is intimately involved in thermogenesis. Its name: brown fat uncoupling protein 1, or UCP1.

UCP1 feasts on N-acyl amino acids, a process which generates heat. And PM20D1 synthesize N-acyl amino acids, thus providing UCP1 with its substrate. This, however, is a relatively recent finding. N-acyl amino acids are found in many different tissues, and for some time had been described by researchers and shown to have roles in many different biological pathways – from cell migration, cardiovascular function, memory and cognition to inflammation, pain and pathologies such as cancer, neurodegenerative diseases, diabetes and obesity. But how these metabolites are actually synthesized remained a mystery – until PM20D1 was discovered.

PM20D1 is a 500 amino-acid long enzyme. It is synthesized in fat cells in adipose tissue and subsequently secreted – thus able to influence neighbouring cells that are not necessarily specialized in making heat. PM20D1 is expressed upon exposure to cold, and catalyses the condensation of fatty acids and amino acids to form N-acyl amino acids. These N-acyl amino acids are then processed by UCP1 to create heat through the dissipation of chemical energy. Besides condensation, it turns out that PM20D1 is also able to hydrolyse N-acyl amino acids into their fatty acid and amino acid parts. This implies that PM20D1 probably has a role in regulating the levels of fatty acids and amino acids, and hence the production of heat. It could also be that the reaction leading to thermogenesis is actually driven by differences in the levels of fatty acids, or indeed N-acyl amino acids.

So PM20D1 has a role in regulating our body heat, and therefore in energy homeostasis. These are intriguing properties, because where energy homoeostasis is involved so are fat and sugar. It is a fact that when researchers administered N-acyl amino acids to mice, they not only increased energy expenditure – i.e. fat was burned to produce heat – but also improved glucose homeostasis. In the same way, there is a fair chance that a "therapeutic" increase in the expression of PM20D1 would also cause the level of N-acyl amino acids to rise. In a society where millions of people suffer from obesity and diabetes, these metabolites could be of great therapeutic value.

But things are not so straightforward. In order to lose weight, one might – and rightly so – imagine that if one eats less, the body will burn some of its own fat to keep itself going. The thing is, our body has this unique faculty of adapting to many situations, and it can very rapidly adjust its energy output by functioning on less energy per day. This is what is known as adaptive thermogenesis, which is not helpful in the fight against obesity for instance. What is more, PM20D1 and UCP1 are probably not the only proteins involved in thermogenesis and its regulation. Certainly, there seems to be therapeutic hope in N-acyl amino acids. And delving further into the molecular ways of PM20D1 will help pave the way.

Cross-references to UniProt

N-fatty-acyl-amino acid synthase/hydrolase PM20D1, *Homo sapiens* (Human) : Q6GTS8
Mitochondrial brown fat uncoupling protein 1 (UCP1), *Homo sapiens* (Human) : P25874

References

1. Long J.Z., Svensson K.J., Bateman L.A., Griffin P.R., Nomura D.K., Spiegelman B.M.
The secreted enzyme PM20D1 regulates lapidated amino acid uncouplers of mitochondria
Cell 166:424-435(2016)
PMID: 27374330

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