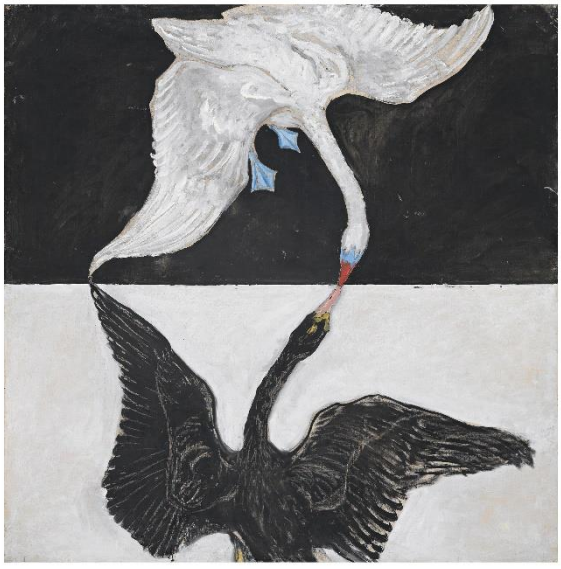
proteinspotlight
> ONE MONTH, ONE PROTEIN <

Issue 248, June 2022
www.proteinspotlight.org

two birds, one stone

Vivienne Baillie Gerritsen

All organisms depend on sets of vital connections, on parts that link to one another to form an intricate and organised whole. Without these connections, all things physiological and metabolic would simply fall apart. Consider animals – for the sake of simplicity. First of all, they require a membrane of sorts, such as skin, to hold everything together and in one place. Skeletons, if they have one, form a scaffold to which is attached muscle. In turn, muscles help to hold various organs in place as does their surrounding connective tissue. Connective tissue can be seen as a sort of biological glue-cum-support that fills in the 'empty' spaces and is composed of cells and 'extracellular matrix' – which, broadly speaking, is a collection of highly organized protein fibres. One of these fibres is fibrillin. Fibrillin is not new to researchers. However, what has recently come as a surprise is the destiny of the C-terminal end of one fibrillin sequence after maturation. Contrary to what had been thought until now, this end is not simply discarded but is actually the sequence of another protein: a protein hormone, since named asprosin.



The Swan

by Hilma af Klint (1862-1944)

As is frequently the case in science, asprosin was discovered quite by chance. Researchers were trying to understand the underlying cause of a disease known as neonatal progeroid syndrome (NPS) where patients endure facial disfigurements and extreme leanness in certain parts of the body. They also happen to suffer from glucose disorders. The researchers found that each of their patients had inherited mutated forms of the pro-fibrillin protein. This explains, in part, their malformations. Indeed, fibrillin is one of the major protein constituents of connective tissue – without it, the scaffold it forms caves in. But this is not all. Each mutation was located at the C-terminal end of pro-fibrillin, precisely where it is cleaved to produce its mature form, fibrillin. A closer look revealed the sequence of yet another far shorter protein, which they called asprosin. As it turns out, asprosin is a hormone involved in glucose homeostasis.

Hormones are secreted into our body fluids, such as blood, which they will use as motorways to reach their targets, namely organs. Once there, they bind to specific receptors thus launching set metabolic pathways. Asprosin was discovered in white adipose tissue, hence its name from the Greek *άσπρο* meaning 'white'. White adipose tissue is part of the body's greater adipose tissue whose main function is to store energy in the form of glycogen and release it as glucose depending on the body's needs. White adipose tissue is found throughout the body. Besides storing energy-rich lipids it also secretes a variety of hormones – or adipokines – among which the newly-discovered asprosin.

As discussed above, asprosin synthesis is linked to that of fibrillin – fibrillin-1 to be precise. Fibrillin comes in three isoforms: fibrillin-1 to -3. Forms 2 and 3 are preeminent in embryonic tissues while fibrillin-1 continues to be just as present in adult tissues. The FBN1 gene encodes a proprotein that is almost 3000 amino acids in length. The translated proprotein is cleaved at its C-terminus shedding 1), the very long fibrillin-1 and 2), asprosin which is barely 140 amino acids long. Fibrillin-1 is a large extracellular glycoprotein with a record-breaking number of calcium-binding sites – 43! It rapidly assembles into microfibrils whose predominant role is to act as a scaffold for the formation of elastic fibres such as those which form the basis of skin, lung and vessels. Meanwhile, asprosin prompts the release of glucose – an important source of energy for the body. Though fibrillin-1 and asprosin have very different functions, their syntheses and their activities are interdependent.

As fibrillin-1 is found throughout the body, there is reason to believe that asprosin is too – which does not really come as a surprise since glucose is a precious energy source and in demand everywhere. Certainly, asprosin seems to be present in the brain, the liver, the lung, the heart and the pancreas. This said, glucose production is not only ensured by asprosin; many other systems are equally involved in glucose regulation. What we know is that increased asprosin levels occur when the body is in need of glucose – at times of fasting for instance. Asprosin is secreted by adipocytes from where it travels to two places in particular: the liver and the brain. In the liver, it binds to a specific olfactory receptor – a G-protein coupled receptor – on the membranes of hepatocytes. This activates a pathway – for many of us, the famous CREB pathway – that leads to the production and release of glucose, which is then taken up by the cells that need it. In the central nervous system asprosin is thought to bind to receptors in the hypothalamus – the centre which deals with appetite. There, it stimulates neurons involved in promoting food intake thus regulating energy homeostasis.

Why would two genes for two proteins with very different roles be linked to one another? Why would their translation depend on one another? Certainly, putting two genes side by side and using all the machinery that is required to translate one sequence for the benefit of two is like spreading honey over two bits of toast in one go: it saves both time and energy. However, fibrillin-1 strikes one as being relatively 'static' as it is part of the extracellular matrix, while the release of glucose is more 'dynamic'. Why would Nature have opted for their linkage at the gene level? Chances are an underlying reason exists, which remains to be unveiled. However, researchers have already observed that FBN1 expression does fluctuate on a daily basis – and not only in white adipose tissue and the brain, but also in the lung, the heart and our kidneys – thus rendering it less 'static' than initially thought.

Because fibrillin is such an important part of connective tissue, mutated fibrillin is prone to cause serious diseases. Malfunctional fibrillin does indeed bring about syndromes – such as Marfan syndrome and NPS – that give rise to serious disfigurements and malformations in their victims. Highly dependent on fibrillin-1 synthesis and dealing as it does with glucose, asprosin too is involved in significant metabolic diseases, among them diabetes, obesity and cardiovascular disease. There is a chance that asprosin could act as a biochemical marker for the diagnosis of these diseases in the future, or even constitute a therapeutic target for treating them. Asprosin depletion could, for instance, help fight against type II diabetes, whose victims suffer from the presence of too much glucose in their blood because of insulin resistance. Time will tell. Nature's choice to link proteins whose nature is so unalike is as intriguing.

Cross-references to UniProt

Fibrillin-1, *Homo sapiens* (Human): P35555

References

1. Romere C., Duerrschmid C., Bournat J., et al.
   Asprosin, a Fasting-Induced Glucogenic Protein Hormone
   Cell 165:566-579(2016)
   PMID: 27087445

2. Muthu M.L., Reinhardt D.P.
   Fibrillin-1 and fibrillin-1-derived asprosin in adipose tissue function and metabolic disorders
   Journal of Cell Communication and Signaling 14:159-173(2020)
   PMID: 32279186