transfer was increased in mice subjected to fasting, and these effects were reversed upon re-feeding, which involved membrane trafficking from adipocytes to other WAT cells, prominently endothelial cells. Furthermore, EV secretion from endothelial cells in vitro was promoted by the fasting-associated hormone glucagon. Thus, EV secretion in WAT is linked to feeding patterns and systemic glucose metabolism.

In summary, endothelial cells in WAT communicate with adipocytes through EVs, which transmit intracellular signalling molecules and extracellular components such as nutrients. This communication may relay metabolic information from the circulation to adapt adipocyte function to changing metabolic needs.

Paulina Strzyz

ORIGINAL ARTICLE Crewe, C. et al. An endothelial-to-adipocyte extracellular vesicle axis governed by metabolic state. *Cell* https://doi.org/10.1016/j.cell.2018.09.005 (2018)
FURTHER READING van Niel, G., D'Angelo, G. & Raposo, G. Shedding light on the cell biology of extracellular vesicles. *Nat. Rev. Mol. Cell Biol.* **19**, 213–228 (2018)

Credit: Nicola Hawes/ Springer Nature Limited

Furthermore, cGAS expression is upregulated in non-small-cell lung carcinomas. Thus, these data suggest that nuclear cGAS has a role in generating genomic instability that fuels tumorigenesis.

This newly uncovered role of nuclear cGAS as a suppressor of homologous recombination-mediated DNA damage repair may offer novel targets for cancer therapy.

Grant Otto

ORIGINAL ARTICLE Liu, H. et al. Nuclear cGAS suppresses DNA repair and promotes tumorigenesis. *Nature* https://doi.org/10.1038/s41586-018-0629-6 (2018)

Journal club

SELENIUM CYSTEINE AND EPILEPTIC SEIZURES

In 1822, the French Egyptologist Jean-François Champollion announced the complete deciphering of the hieroglyphs carved around 200 BC into a block of granodiorite, the so-called Rosetta stone. This was an impressive intellectual achievement, as it established the basis for reconstructing ancient Egyptian history. Another decoding effort, however, had far more profound consequences for humanity: the cracking of the genetic code in the laboratories of Marshall Nirenberg and Har Gobind Khorana during the early 1960s, which explained how a language made of four bases of DNA can be translated into a language of 20 amino acids in proteins. The genetic code turned out to be universal: once you know the DNA sequence of the genome of any organism, you can derive the amino acid sequences of its proteins.

As for most rules, there are a few exceptions to the universality of the genetic code. Perhaps the most interesting one is the stop codon UGA, which in a very small subset of mRNAs encodes selenium cysteine (Sec), known as the '21st amino acid'. In humans only 25 Sec-containing proteins (selenoproteins) have been identified, and it was unclear whether they have essential functions.

The mouse genome harbours a single Sec tRNA gene, and thus the inactivation of this gene prevents the synthesis of all selenoproteins. Mouse embryos lacking Sec tRNA die during the first few days in utero. Therefore, at least some selenoproteins have essential roles during embryogenesis, but which ones?

> “Cys-GPX4 reduces the levels of toxic lipids much less efficiently than Sec-GPX4”

It turned out that the inactivation of the gene encoding the selenoprotein glutathione peroxidase 4 (GPX4) phenocopies the disruption of the Sec tRNA gene. Thus, GPX4, which in animals is the only enzyme capable of reducing toxic lipid peroxides, must have a crucial function during embryogenesis.

A recent study beautifully dissected the role of Sec in GPX4. Mice in which in *Gpx4* the Sec codon TGA had been replaced with the Cys codon TGC were born and, depending on the genetic background, survived until about 2 weeks after birth. Thereafter, they either had to be euthanized because of dramatic weight loss or they died of lethal brain seizures.

In fact, the mice lacked a specific set of GABAergic inhibitory interneurons, which had succumbed to ferroptosis. Ferroptosis is a special kind of cell death that is caused by toxic lipid peroxides formed in the presence of ferrous iron (Fe^{3+}). Cys-GPX4 reduces the levels of toxic lipids much less efficiently than Sec-GPX4, because, unlike the selenol group of Sec, the sulfhydryl group of Cys cannot be regenerated after the reduction of lipid peroxides.

Nevertheless, the weak activity of Cys-GPX4 seems to be sufficient for bringing embryos to term. Likewise, fibroblasts derived from Cys-GPX4 mice proliferate normally, but are exquisitely sensitive to hydrogen peroxide (H_2O_2).

In addition to elucidating the rate-limiting function of Sec, the paper by Ingold et al. constitutes a formidable example of how a mutation — Sec to Cys in GPX4 — that would have been anticipated to cause general dysfunction in a variety of cells and tissues, manifests itself in a quite specific and unexpected phenotype: death by epileptic seizures.

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ORIGINAL ARTICLE Ingold, I. et al. Selenium utilization by GPX4 is required to prevent hydroperoxide-induced ferroptosis. *Cell* **172**, 409–422 (2018)