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> ONE MONTH, ONE PROTEIN <

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a motherly mesh

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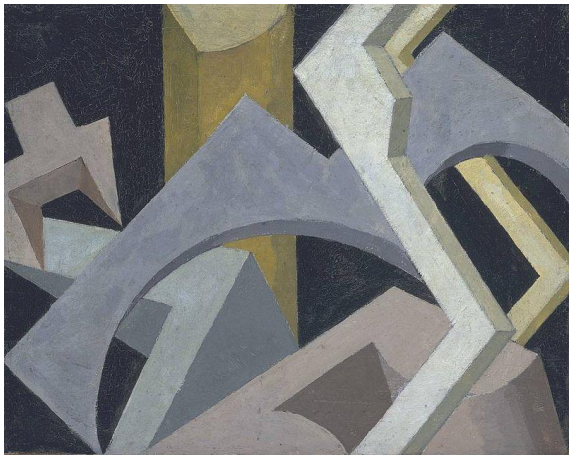
Toxic waste. Since the 19th century, our species has had to find ways of scrapping industrial detritus which is frequently dangerous. So, we dig deep down into the earth and leave the nasty stuff there or we build thick crusts of cement around it. We then count on time to do the rest. Cells also produce refuse which, unless degraded or somehow set aside, will end up by being harmful to them. So they, too, have devised ways of dealing with it – namely with all kinds of degradative systems lodged within the cells themselves. Some cells, however, are not able to get rid of their scrap material in a timely fashion. Take oocytes, for example. Most mammalian oocytes are arrested at a certain developmental stage as they await ovulation – which may take several decades. During this rather long period, oocytes are kept in a sort of lethargic state and are unable to deal with degradation. So how do they cope with their waste? The answer is ELVAs, or endo-lysosomal vesicular assemblies. Much like fishnets, ELVAs trap noxious scrap within a proteinaceous mesh whose formation is initiated by a protein known as RUFY1.



Jessica Dismorr (1885-1939)

How humans are made has been debated for thousands of years. The beginnings of an answer truly began to emerge in the 1660s when Melchisedec Thévenot, a French patron of the sciences, asked two of his protégés – Niels Stenson from Denmark and Jan Swammerdam from the Netherlands – to find out what it is in animals that gives rise to other animals. By the 1670s, after many dissections, experiments and discussions, Stenson suggested that all animals come from eggs, and that eggs are also found in women. It so happens that another student, the Dutch physician Rainier de Graaf, reached the same conclusion at about the same time. He, however, was the first to publish his results. Somewhat ruffled, Swammerdam promptly published his own understanding of the issue – and both men asked the Royal Society to judge which of the two had priority over the theory.

Much to their amazement, no doubt, the Royal Society (UK) told them that neither of them had priority. According to the Society's understanding, it was Niels Stenson who had been the first to say that animals come from eggs. Despite this, the history of biology has written things down differently and a follicle – the cellular aggregation in which nests an egg cell – is known today as a Graafian follicle. By the time the decision was taken, and perhaps disappointed by the outcome of things, Niels Stenson had left the realm of science to become a bishop of the Catholic Church – and no one knows if he was ever told about what had been going on. In any event, by the 1670s, scientists had accepted the notion that women store eggs in their ovaries. Although it took another 150 years for the German naturalist Karl Ernst von Baer to actually observe one, in 1827.

Oocytes are one of these rare cells that are long-lived – unlike spermatozoa, their male counterparts, which are created on the spot, when they are needed and from puberty onwards. Girls are born with their a life's stock of oocytes. Dependent first on sexual

maturity and then monthly ovulation, the "chosen" oocytes have to survive at least one decade before they get a chance to mature and ovulate. In humans, most of them will have lived for two decades, if not three or even four, before they get the rare opportunity to be fertilised. This is a very long time for one cell to survive, especially as – like any other cell – mal-formed or damaged proteins accumulate forming aggregates that, unless degraded, become harmful. These protein aggregates form in the cell's cytoplasm, and it is crucial that an oocyte's cytoplasm remains healthy since it contains all an embryo needs for the very first divisions. Why, you might be thinking, do oocytes not degrade these aggregates as they form? Much in the way other cells do? That is because, before ovulation, oocytes are kept in a sort of low energy-cost state, and degradative organelles, such as lysosomes, are energy-consuming. So protein aggregates are left to accumulate.

Researchers recently observed that mouse oocytes ensure that harmful protein aggregates accumulate in guarded places, i.e. endo-lysosomal vesicular assemblies, or ELVAs. ELVAs are super organelles which have no distinct boundary and are scattered throughout the oocyte's cytoplasm. They can be compared to a fishing net in which are trapped not fish but degradative organelles such as endo-lysosomes, autophagosomes and proteasomes – and also protein aggregates. The organelles are not bound to one another but to a filamentous net. Upon ovulation, when the oocyte matures, the ELVAs migrate – some of them merging into one another as they do so – to the egg's cortex. At the same time, the degradative organelles are activated and the protein aggregates are cleared. By the time an embryo has reached its two-cell stage, no protein aggregates are left. Possibly because they are dangerous for the embryo's development but also because they may provide the embryo with raw building material, such as amino acids.

ELVAs are sort of liquid super organelles, which, like fishing nets, adopt no particular shape while trapping protein aggregates in their wake. The net is made up of microfilaments, a proteinaceous matrix, to which the degradative organelles bind and in which the aggregates are caught. Researchers discovered a protein that is directly involved in forming ELVAs: a protein known as the RUN and FYVE domain-containing protein 1, or RUFY1. RUFY1 has three distinct structural domains: an N-terminal RUN domain which is required for membrane association, a central coil-coiled domain which is needed for self-assembly, and a C-terminal domain which binds phosphatidylinositol 3-phosphate, necessary for the protein's activity. RUFY1 is known to be an effector protein which self-assembles and is involved in the formation of early endosomes. In the case of ELVAs, RUFY1 seems to initiate and drive the formation of the proteinaceous matrix to create a kind of biological glue, the net, which holds everything together: both the degradative organelles and protein aggregates.

It is a wonderful solution for a situation that, at one point, is bound to become critical for a long-lived cell. Oocytes have developed a way to remain in a state which does not cost them too much energy while stashing away harmful molecules that form as they await maturation – at which point they will have the wherewithal to deal with their waste, while also providing material as they break it down. Discoveries such as these could help scientists understand certain forms of infertility and why some embryos do not reach the two-cell stage. Could it be because the oocyte's noxious aggregates have not all been cleared? Perhaps. Certainly, the more you learn about life and how it is organised, the more you are amazed at how it manages to keep a very fragile – yet sturdy – balance as it tiptoes along a pretty slim tightrope.

Cross-references to UniProt

RUN and FYVE domain-containing protein 1, *Mus musculus* (Mouse): Q8BIJ7

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