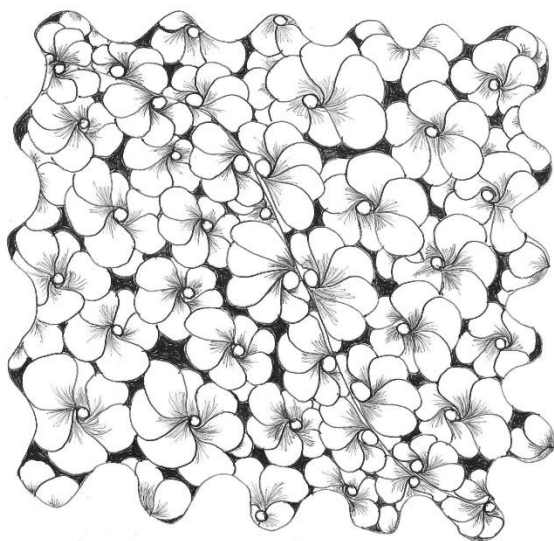


elusive

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My grandmother had a lovely pantry. It was a small room next to the kitchen, dedicated to the accumulation of ‘non-perishables’, i.e. mainly jam, rice, flour, sugar, dried potato, packets of biscuits and noodles. In some dark corner, you would invariably find a tin or two of powdered eggs or milk – a reminder of the days when fresh eggs and milk were hard to come by. My grandmother never really lost the habit of hoarding food, of storing the basics to provide sustenance to the family if needed. Cells, too, have their pantries. Germ cells, in particular. Plant germ cells have vacuoles. Birds’ eggs have yolk. And mammalian oocytes have cytoplasmic lattices. All of which are used to bank nutrients for the embryonic development. Oocyte cytoplasmic lattices were discovered in the 1960s but we are only beginning to understand their molecular structure – and hence how they work. It seems, now, that cytoplasmic lattices are a place where maternal proteins accumulate to provide nutrients for developing embryos. Once thought to be composed of strings of ribosomes or keratin, we now know that cytoplasmic lattices consist of several components, one of which is a puzzling protein known as peptidyl arginine deiminase 6 or PADI6.



ZENTANGLE by Nicola Lindsay

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Cytoplasmic lattices, or CPLs, are only observed in oocytes and were discovered in the late 1960s. First depicted as ‘whorls’ in an oocyte’s cytoplasm, their nature and their purpose remained a mystery for many years. Some suggested that they were formed by strings of ribosomes – creating a sort of ribosomal reservoir awaiting the onset of embryonic development. Others

suggested that they were filaments of keratin and probably had a structural role. With time and technology, scientists began to see that CPLs did not, as initially thought, line the cytoplasmic edge of a cell’s membrane but that they were present throughout the cytoplasm. Visually, a cytoplasmic lattice looks like a bundle of fibres in a lattice-like arrangement, where each fibre resembles a twisted potato noodle known as a *schnupfnudel*. Thick in the centre, each twisted fibre narrows out towards both of its extremities. CPL fibres are in fact composed of an average of 22 filaments that are stacked and twisted relative to each other, which gives them a helical appearance. Their role? CPLs appear to act as small scaffoldings onto which latch maternal proteins that are needed for the very first stages of embryonic development.

For over 20 years, scientists have known that peptidyl arginine deiminase 6 (PADI6) is important for embryonic development. They just didn’t know in which way. To be honest, its precise role remains elusive, but we do know much more about it. PADI6 belongs to the peptidyl arginine deiminase (PAD) family of which there are 5 members in humans: PADI1-4 and PADI6. Where is PADI5, you may wonder? Human PADI5 turned out to be an orthologue of mouse PADI4, so it was renamed PADI4 – which left a gap in the nomenclature. The first four members of the PAD family are enzymes and are present in a variety of tissues. They act as homodimers, where one monomer binds to the other in a head-to-tail conformation. Once

bound to their substrate, Ca^{2+} , PADI1-4 catalyse the conversion of arginine to citrulline: citrullination. The process, though still poorly understood, must cause significant changes in downstream proteins since the absence of PADI activity is associated with a range of pathologies such as rheumatoid arthritis, multiple sclerosis and cancer.

PADI6 is very similar to PADI1-4. It is built in the same way: each monomer has two N-terminal immunoglobulin-like (IgG) domains followed by a C-terminal α/β propeller domain – that is a group of beta sheets assembled into a toroidal structure. Like its siblings, PADI6 seems to act as a homodimer. ‘Seems to act’ because so far PADI6 has shown no catalytic activity whatsoever. In PADI1-4, the catalytic site is found at the C-terminal end where their substrate, Ca^{2+} , lodges in a pocket formed by the homodimer. But PADI6 doesn’t seem to bind Ca^{2+} . Or if it does, it doesn’t do it like the other family members. Why? Because its active site has been modified and its substrate, Ca^{2+} , can’t squeeze in anymore; a structural loop seems to be impeding its entrance. Is PADI6 a dead enzyme? Does it bind Ca^{2+} in a different way to its siblings? Or does it have a completely different role altogether?

PADI6 does indeed seem to have lost its capacity to convert arginine into citrulline. It is the only PADI present in oocytes – in very generous amounts, and its presence in other tissues is negligible. So surely it must have an important role in germ cells. Perhaps, over time, PADI6 lost its capacity to bind to its substrate because germ cells are drenched in calcium immediately after fertilization to induce cascades of downstream developmental changes. Torrents of calcium may have thrown PADI6 into confusion. So, in time, the system may have been switched off. It’s a hypothesis.

What we have found out is that PADI6 seems to be linked to a structure known as the subcortical maternal

complex, or SCMC. Together, PADI6 and SCMC are among the most abundant proteins in oocytes. SCMC is a complex composed of maternal proteins that are used in the very first stages of embryonic development, until the embryo can make its own components. SCMCs are just another kind of pantry, really, and are only found in mammalian oocytes and early embryos. Together, PADI6 and SCMC seem to drive the accumulation of yet other maternal proteins required for development. How do they do this? PADI6 and SCMC are intimately linked to CPLs. So, do PADI6 and SCMC direct the assembly of lattices? Which then act as platforms that prompt the binding of yet other maternal proteins important for embryonic development? Or do PADI6 and SCMC simply regulate the assembly of CPLs? PADI6 is not telling.

Nevertheless, it seems that PADI6 and SCMC are at the heart of a storage platform – a massive pantry – where proteins accumulate to promote the very early stages of embryonic development. Concomitantly, the maternal proteins on hold, so to speak, are stabilised and protected from degradation or even prevented from assembling into ribosomes, for instance, which could cause mayhem. When PADI6 is absent, embryo development is checked. This is hardly surprising if PADI6 is at the heart of the place where maternal proteins are stored – each of which is involved in fundamental events such as meiotic spindle formation, genome activation, mitochondria and ER localization and so on. Mutations in PADI6 are a well-established cause of human infertility, as are mutations in the SCMC. Mutations in cytoplasmic lattice genes could also be the cause of recurring early pregnant loss – and one of the reasons some women don’t seem to benefit from *in vitro* fertilization for example. PADI6 continues to baffle scientists. It may well have lost its enzymatic activity, but it certainly provides a fascinating field of research. And one that nurtures hope.

Cross-references to UniProt

Inactive protein-arginine deiminase type-6, *Homo sapiens* (Human) : Q6TGC4

Inactive protein-arginine deiminase type-6, *Mus musculus* (Mouse) : Q8K3V4

References

1. Jentoft I.M.A., Bäuerlein F.J.B., Welp L.M., et al.
Mammalian oocytes store proteins for the early embryo on cytoplasmic lattices
Cell 186:5308-5327(2023)
PMID: 37922900
2. Williams J.P.C., Mouilleron S., Trapero R.H. et al.
Structural insight into the function of human peptidyl deiminase 6
Computational and Structural Biotechnology Journal 23:3258-3269(2024)
PMID: 39286527