proteinspotlight
> ONE MONTH, ONE PROTEIN <

Issue 261, Septembre 2023
www.proteinspotlight.org

in good time

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When my daughter was born, I could not help but realise that she already had inside her what would participate in giving life, if she so chose, to a daughter or a son of her own. Given a little thought, it is an extraordinary state of affairs. My daughter's ovaries were already filled to the brim with a life-time's stock of egg cells, albeit not quite mature. As it so happened, my next child was a baby boy, and I knew he would only begin to produce germ cells at puberty and cease to produce them when his life comes to an end. It is a fundamental difference between the two sexes, which obviously entails very distinct physiological makeups. Notably, and at the very least in these parts of the world, egg cells must remain healthy during the best part of two decades before one, or two, or perhaps several more are actually fertilised. Fertility is hugely dependent on egg-cell fitness, which is why many mechanisms exist to protect not only an egg's integrity but also elemental macromolecules and organelles whose activities are temporarily arrested. One protein known as ZAR1, from Zygote ARrest 1, is at the heart of such a mechanism.

illustration by Andrea Bonnet, 2011

For the sake of simplicity, let us talk about human germ cells only. Mature human egg cells, like sperm cells, carry inside them half of the genetic makeup of what may one day become a human being. At the very beginning, that is before puberty and the onset of ovulation, egg cells are immature and the great majority of them will remain in this state until the onset of menopause. At puberty, however, usually one by one and every month, a minority of these immature egg cells will be swept from the ovaries into the Fallopian tubes fully expecting to bump into a sperm cell. While on this trip, the chosen egg cells mature into full-blown oocytes, ready to be fertilised.

What is meant by egg-cell maturation? What are oocytes? To cut a long story short, egg cells go through two distinct types of division, called meiosis I and meiosis II. Meiosis I is the dividing mechanism by which germ cells swap bits of their DNA, thus creating novel DNA which will be unique to every germ cell. It is a source of genetic richness and how Nature, with the help of evolution, manages to produce such a variety of organisms, even within a given species. Meiosis II is the dividing mechanism that follows meiosis I to produce mature egg cells, or oocytes, each of which carries only one copy of the novel DNA. Immature egg cells are stuck between meiosis I and II until puberty, and only a selected few will fully mature upon ovulation. By bonding with a mature sperm cell, the fertilised egg – or zygote – recovers the requisite two copies of DNA. A zygote thus represents the very first cell we all begin as.

Egg cell maturation is not only a question of DNA. Egg cells are full of other macromolecules and organelles, all of which are essential for their survival. Two examples are maternal mRNAs and mitochondria. Maternal mRNAs are mRNAs that belong to both the immature and the mature egg cell and are translated into required protein until the newly formed zygote can transcribe its own mRNAs. Maternal mRNAs are involved in essential roles such as translation and mitochondrial function. In a way, they constitute the yoke of germ cells.

Maternal mRNAs are kept dormant in immature egg cells – as are mitochondria that have little need to produce energy for cells whose activity has been arrested.

What holds egg cells in their immature state? And what shifts them into maturity? Part of the answer is protein ZAR1. ZAR1 is responsible for generating a sort of jelly that traps mitochondria and dormant maternal mRNAs into gelatinous bubbles that are found throughout the egg cell's cytoplasm. Such a membraneless structure provides stability to translationally repressed maternal mRNAs – a minority of which are only triggered into action twenty, thirty perhaps even as much as forty or fifty years later. Besides giving rise to the gel, ZAR1 also acts as a ribonucleoprotein by binding to maternal mRNAs. This jelly-like bubble full of mitochondria and maternal mRNAs has been given the name Mitochondria-Associated Ribonucleprotein DOmain, or MARDO. ZAR1 is thus one of the major players in MARDO assembly.

ZAR1 sculpts MARDOs while also acting as a ribonucleoprotein (RBP). Indeed, ZAR1 has a conserved C terminus, a zinc-binding motif typically found in RBPs like transcriptional activators, repressors or cofactors. A disordered region, on the other hand, is found in ZAR1's N-terminal region. These recently discovered regions in protein sequences are known to adopt varied 3D conformations according to the environment – an observation which shattered the ongoing 'structure-function' paradigm that had prevailed up until the eve of this century*. In ZAR1, this disordered region forms the scaffold for MARDO assembly. When an egg cell matures, and if it is further fertilised, maternal mRNAs will continue to be translated until the zygote begins to transcribe its own – ZAR1 is then completely degraded, the MARDOs disrupted, and their mitochondria released to resume function. The remaining maternal RNAs, now redundant, are broken down.

Other RBPs are found in MARDOs as are other macromolecules, many of which are no doubt involved in building up and strengthening the protective gelatinous bubbles. But ZAR1 is central in their architecture since without it, MARDOs are unable to form. Many questions remain to be answered. Why, for instance, does the membrane potential of mitochondria increase during MARDO formation? Why are there numerous mitochondrial clusters distributed throughout the cells and not just one huge one? Understanding MARDOs in detail will no doubt help to grasp problems related to female infertility. It is not hard to see that if ZAR1 is dysfunctional one way or another, there is little chance that egg cells will mature. A humbling thought.

**Protein Spotlight issue 238*

Cross-references to UniProt

Zygote arrest protein 1, *Mus musculus* (Mouse): Q80SU3
Zygote arrest protein 1, *Homo sapiens* (Human): Q86SH2

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