Research Summary – from genetics to epigenetics, and to a higher dimension

My past research, as it evolves, was driven by a load of curiosity, which I found to be the genuine source of creativity. My personal experience has now led me to believe that: *being a scientist, is somewhat like being a detective - you never know where the clues will lead you to, if you have the curiosity to follow*.

Navigating the embryos inside the uterus *(My starting project as a Ph.D. student)*

I began my research with a project studying mouse embryo-uterine interactions, a process that initiate mammalian pregnancy. I was intrigued by the phenomenon that mammalian embryos show remarkably consistent distribution pattern and embryo orientation with respect to the uterus. How a floating embryo, so small compared to the size of uterus, can be accurately navigated inside of the uterus? Driven by this question, we conducted a series of research on the molecular & biomechanical control of these events (*Mol Aspect Med 2013*), and found that a concerted uterine peristalsis (*J Biol Chem 2011*) and timely reabsorption of uterine fluid (*Cell Res 2015*) hold the key to control embryo's intrauterine location, and that a spatial-temporally controlled uterine Notch-RBPJ signaling is essential for correct embryo-uterine orientation (*Cell Res 2014*).

Discovery of AQP3 as the first membrane protein for rapid sperm osmoadaptation *(My Ph.D. thesis)*

As I began to study uterine fluid, I was fascinated by a fact that in the journey from the male to female reproductive tract, mammalian sperm experience a natural hypo-osmotic shock (e.g., in mouse, from ~415 mOsm in the cauda epididymis to ~310 mOsm in the uterine cavity). This hypotonic stress upon ejaculation is a 'double-edged sword', which can at one hand, activate sperm motility; but if uncontrolled, will damage the sperm structure by over-swelling of sperm. The specific sperm proteins responsible for this rapid osmoadaptation remain elusive. Under this background, we discovered Aquaporin-3 (AQP3), a water channel, as the first membrane protein for rapid osmoadaptation upon physiological hypotonicity, balancing the "trade-off" between hypotonic-induced sperm motility and cell swelling, thereby optimizing postcopulatory sperm behavior for fertilization (*Cell Res, 2011*). We suggest AQP3's role in this process as a mechanosensor, rather than being inert pores simply for water permeability (*Acta Pharmacol Sin 2011*).

Discovery of sperm tsRNAs *(Correspondence author)*

During my AQP3-sperm project, we sequenced the mature sperm RNAs with an original purpose to explain the incomplete penetrance of phenotype in knockout mice (an interesting but discontinued work). In this project, we serendipitously discovered that the mature sperm contain a unique subset of tRNA-derived small RNAs (tsRNAs), mainly from 5' transfer RNA halves and ranging in size from 29-34 nucleotides. tsRNAs are enriched in the sperm head and thus could be delivered into oocytes at the time of fertilization (*Cell Res 2012*). We also discovered that tsRNAs are enriched in vertebrate serum with evolutionary conservation (*J Mol Cell Biol, 2014*).

Sperm tsRNAs as epigenetic factor in transmitting paternally acquired traits *(Correspondence author)*

Parallel with the discovery of tsRNAs, we are fascinated about the increasing evidence that certain acquired traits during paternal exposure can be "memorized" in the sperm and inherited by the offspring - a resurrected idea of "Lamarckian inheritance". Yet, the underlining mechanisms remain unclear. Recently, we found changes in both expression profiles and RNA modifications in sperm tsRNAs of mice fed with a high-fat diet (HFD). By injecting various RNAs into normal zygotes, we found that sperm tsRNAs represent a novel type of 'epigenetic carrier' in mediating intergenerational inheritance of acquired metabolic disorders (*Science 2016*). I was interviewed by Science for this discovery (Leslie M, Science. 2016;351(6268):13).

RNA modifications in tsRNAs and their function in early embryos: a new frontier *(Correspondence author)*

In addition, we have identified more than 10 types of RNA modifications in sperm tsRNAs, some of which are sensitive to HFD, we also found that RNA modifications in tsRNAs are important for RNA stabilization (*Science, 2016*). These exciting discoveries demonstrated RNA modifications as an integral part of tsRNAs, and opened new questions regarding the regulative nature of these RNA modifications and their functional impact (*Nat Rev Genet 2016*, *Tends Mol Med 2016*). How RNA modifications affect tsRNAs' secondary structures and impact the trajectory of early embryo development, possibly via a 'butterfly effect' (*Nat Rev Genet 2016*) as early as before the first cell-fate decision (*Development 2015*), is now of keen interests in my lab.

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