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EDITOR'S COMMENTARY

Somatic offloading during sperm maturation: shining light on the extragenomic paternal dowry

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Much of what we give credit to the embryo for—conversing with the endometrium, elaborating pregnancy signals to extend the CL lifespan, and supporting fetal growth and development under the guidance of the placenta—is based in our common belief how the conceptus' genetic and epigenetic constitution sets and maintains the course for term pregnancy. Despite our *embryocentric* tendency to find the embryo (or perhaps because of it), what gametes bring to the party has received considerably less attention with exception to a cadre of *oocentrists* who would boldly argue that all you need to make a baby is a good egg!

In past years, the theme of how an organism's general health status influences fecundity has gained traction as the importance of the soma—both proximal to gametes within the specialized gonadal compartments overseeing maturation and distal systemic components including those of the reproductive tract—becomes better defined. Getting out of the traditional genetic mindset as the reaper of causality for all matters infertility has been challenging despite suggestions to the contrary. One thing that is clear is the necessity to broaden our thinking with respect to the physiological interface between gametes and soma that lends itself subject to direct manipulations so central to the current principles and practices of human ARTs.

This month, we take aim at male reproduction. From a current perspective on the genetic determinants of male fertility (See Okutman and colleagues, *Genetic evaluation of patients with non-syndromic male infertility*, https://doi.org/10.1007/s10815-018-1301), to the rapidly growing field of chromatin domain structure in the sperm head (See Sarrate et al., *Chromosome positioning and male infertility: it comes with the territory* https://doi.org/10.1007/s10815-018-1313), and closing with a critical assessment of how paternal components drive embryogenesis (See Colaco and Sakkas, *Paternal factors contributing to embryo quality* https://doi.org/10.1007/s10815-018-1304), we offer our readership a balanced treatment of the physiology of male reproduction.

Procuring two healthy gametes for purposes of embryo production is a mainstay of ARTs. Today there is a greater awareness that somatic cells from within the gonads or other segments of the reproductive tract convey instructional signals for embryonic development. The form and substance of these signals acting as drivers of embryogenesis remains obscure. But the notion that gametes acquire specific cargoes of somatic origin that are essential for fertilization and later events is finding support in recent studies as described below.

Bearing the signature of their somatic heritage is becoming a matter of greater and greater concern when speaking of gamete quality as appears to be the case during sperm development and maturation.

Negotiating the niche defined by the properties of the seminiferous epithelium and the blood–testis barrier [1] is step one, but what downstream portions of the tract contribute to developmental attributes is less clear. Acquiring motility by putting the finishing touches on the axoneme is one important attribute [2] that typically reflects non-genetic influences during sperm maturation, unlike many of the known intrinsic genetic factors that could impact motility [3]. And lessons from studies on endangered species have uncovered variations in the contributions made by the male reproductive tract to the ability of ejaculated or extracted sperm to support later embryo development [4]. In fact, one study published this year in JARG shows how the epididymis releases exosomes that appear to be essential for fertilization in a cat model system [5]. Exosomes have become targets of investigation as transportation devices between somatic cells and their role as integrators between the soma and germ line is becoming increasingly apparent.

Recent work from the Rando laboratory at the University of Massachusetts Medical Center illustrates this using the mouse as a model system. They have shown that small RNAs acquired during epididymal maturation are clearly of somatic origin and play a role in directing early stages of

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embryo development [6]. Besides demonstrating important roles for these RNAs in development, they go on to report that embryos produced by ICSI develop only if derived from the cauda (not caput) epididymis and embryonic lethality could be rescued when the RNA derived from cauda is injected into zygotes. Just how does this potent somatic-derived RNA get transported into maturing sperm? To address this question, Sharma and colleagues in an accompanying paper provide compelling evidence for the biosynthesis and release of said RNAs within epididymosomes that can deliver the small RNAs to testicular sperm under in vitro conditions. Together, two clear-cut messages emerge from this work. First, the growing notion that somatic cells from within the gonads or other segments of the reproductive tract convey instructional signals for embryonic development must be taken in context as drivers of embryogenesis that result from specific cargo embellishments integrated prior to fertilization. Second, the perceived autonomy ascribed to the zygote once it has activated its genome presents shortcomings that could have an obvious impact on the way ARTs are practiced today.

Next month, our issue will be focused on monozygotic twinning in ARTs and the renewed interest in this topic owing to the dynamics being explored at the earliest stages of human development.

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