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COMMENTARY

Fashioning sperm in vitro

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Anyone having the privilege to experience parenting takes special pause to the meaning of the word "maturation." Witnessing a child's precarious journey through adolescence and then adulthood carries with it the hopes and aspirations that their offspring will someday contribute something meaningful to society. While more and more parental patience seems needed these days before our children reach that mature stage of life, for our gametes, undergoing a final process of maturation leaves no room for tolerance when the goal of their *raison d'etre* is fertilization. One need only look back to our July issue (see "Desperately Seeking Embryos" JARG 27:345–346) to appreciate how critical it is for the oocyte to undergo maturation in the context of the ovulatory follicle if it is to obtain the tool kit needed to effect fertilization and embryonic development. As we do with our children in offering a niche conducive to them maturing, so does the testis in supporting the final maturative stages of spermatogenesis.

Our current issue offers new insights into the process of sperm maturation as revealed by the studies of Yukihiro Terada and his colleagues. With increasing focus being placed on utilizing the biology of stem cells to generate gametes as a potential means of treating infertility, this paper begins to unveil just what it takes for the mature sperm to ride the train of embryonic development in the context of ARTs. While there is much interest in identifying the characteristics, typically morphological, that make selection of the best sperm to use in IVF or ICSI practical, appearances continue to be deceiving. More important perhaps are the not so morphologically visible properties of mature sperm that allow them to make a significant contribution to the launching and sustainment of embryogenesis. Of these properties, the ability to generate acute and discrete patterns of calcium signaling in the zygote has been recognized as key to early development in mammals.

What is it about mature spermatozoa that activate oocytes at the time of fertilization? As readied as she is, stocked with organelles, RNAs, proteins and enough calcium to fortify milk, the oocyte awaits a spark from the sperm that comes in the form of an enzyme known as phospholipase C of the zeta variety (to distinguish it from the many forms of this enzyme found in many other kinds of cells; PLCz). Delivery of PLCz to the ooplasm triggers ionic havoc as stores of calcium are released into cytoplasm to effect alterations in metabolism needed for embryogenesis to ensue. In fact, not one, but multiple bursts of calcium encode a temporal imprint that will dictate the timing of subsequent cell cycles. Were it not for delivery of PLCz and a constipated nuclear genome, it seems likely that the contribution of sperm to the embryo would be unfairly minimized and devalued. Fear not spermists! Maturation does carry the day when we are talking about fashioning a functional sperm.

Here enters the studies of Terada and colleagues. They manually isolated round spermatids and sertoli cells from adult testes of mice and co-cultured these under conditions that included the addition of testosterone and FSH to the culture media. What they observed after 2 days of culture was nothing short of remarkable. The round spermatids underwent elongation and nuclear condensation, two complex processes that involve construction of the axoneme and profound changes in the compaction of chromatin. They

Capsule A recent paper in JARG shows that mouse sperm matured in vitro acquire the ability to activate oocytes.

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then tested the ability of in vitro elongated sperm to support development after ICSI. Their results indicate that these cells are clearly NOT ready for prime time as they had a limited ability to progress to the two cell stage and an even more impaired ability to support development to the blastocyst stage when compared to sperm that had experienced spermiogenesis in vivo. Possibly the most promising aspect of this study was the demonstration of a robust ability to induce calcium oscillations that were indistinguishable in form and frequency when compared to control sperm. The authors note that this result is suggestive of successful acquisition of a PLCz mediated means to explain the degree of egg activation that was achieved but this has yet to have been proven by more direct analyses. Moreover, they urge caution in noting that the embryonic deficiencies observed could very likely be due to the failure to process the male nucleus with respect to imprinting alterations normally occurring over this developmental window. Despite these shortcomings, this work takes on added significance in the context of stem cell biology.

Several reports have appeared that suggest that primordial germ cells, embryonic stem cells and spermatogonial stem cells acquire properties of sperm when they are allowed to develop after transplantation into the testis of mature mice. To date it appears that in some cases, cells taking this route of development may not have achieved a sufficient level of maturation to validate their ability to support fertility. Post-meiotic maturation seems to be the culprit underlying this inadequacy. The system reported here provides an experimental model for manipulating the final stages of spermatogenesis that will be useful to both the stem cell community and investigators focused on the molecular underpinnings of sperm maturation. This work also provides a point of departure for studies on human spermatids that have already gained usage in treatment of certain kinds of male fertility disorders. By cautious extension, it could open the gateway for using in vitro maturation of human sperm as an adjuvant therapy to ICSI. While contextualizing this work on the mouse for translational studies to human ARTs is precarious, it remains imperative to enact a discriminating program of research on such gametes before they would be considered useful in the treatment of male factor infertility. What may be fashionable may not be useful (or even dangerous)