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EDITOR'S COMMENTARY

Disentangling the spermatozoon's transcriptome

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Woody Allen's cult film classic, "Everything You Ever Wanted to Know about Sex," iconizes the fate of epididymal sperm, while awaiting the moment of ejaculation. As his angst accumulates, while fighting to get into a better position (first in, first in the egg race), he recognizes that unlike real estate, location is not all that matters when it comes to gaining access to the oocyte's investments lurking in the hollows of the distal fallopian tube. Instead, in typical Allenesque form, the litany of worries includes his dwindling fuel supply, how fast he will swim, and how will he beat his competitors in the race to the finish line.

This comedic rendition of the plight of the sperm in waiting is prescient, in ways that would have been unpredictable, as little as 2 years ago. For example, even in the 1970s, as Allen conceived this anthropomorphic model, the notions of fuel supply and hyperactivity in sperm performance were appreciated from the foundations of reproductive medicine, etched by the likes of Fawcett, Setchell, Hunter and others. Indeed, what sperm required in design principles, in order to effect fertilization was widely recognized and it was only a matter of time before male infertility could be posited in the context of sperm anatomy and physiology. But what about the insecurity shown by Allen's spermatological character—the entangled psyche that emerges after sizing up his quantitatively superior competition, while feverishly pacing the hallways of the epididymis?

That intangible element that determines fertilizability for a given sperm may not meet metaphorical standards, in the psychological sense, but there is certainly room for speculation when one considers advances in the field of sperm transcriptomics, as highlighted in this issue of JARG. What Montjean and colleagues report in our lead article this month is the detection of mRNA expression patterns that distinguish the transcriptome of sperm from healthy fertile individuals from those diagnosed with idiopathic infertility. While far from lending themselves to any therapeutic intervention that could ameliorate this condition, the results raise important new questions, with respect to the significance of sperm bearing a host of mRNAs and how might failures to translate the spermatogenic genome appropriately impact fertility as a function of age or occupational exposure?

It came as quite a surprise to many when, in 1999, Miller and colleagues first demonstrated the existence of mRNAs in human spermatozoa (Gene. 1999;237:385–92.). After so many years of contending with the notion that once testicular spermatogenesis was complete, the now inert male genome would have completed the job of differentiation by cleaning house of any residual RNAs, finalizing most—if not all—post-translational modifications in proteins, and otherwise entering a lulled state of metabolism, that would be managed during epididymal storage. The viewpoint that, at an RNA level, there was little to be added to the male dowry of a nuclear genome, a centrosome, and mitochondria destined for destruction received support for many years because there was little consensus as to what it meant for sperm to be hanging onto RNAs that were probably left over from the rush through spermatogenesis. Even if there were a chance for survival or translation of lingering mRNAs, the hostile confines of the ooplasm would surely have assured the demise of these freeloaders, given its own robust RNA degradation machinery, activated after fertilization. So along comes the paper by Montjean that has now adopted the power of the transcriptomic platform to edge us closer to identifying the underlying causes of male infertility.

Capsule The mismanagement of gene expression is revealed in the transcriptome of oligospermic patients shedding new light on the causes of male infertility.

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While almost too much to process, the results from this paper indicate significant reductions in several groups of genes aligned with the condition of oligospermia. That genes affecting spermatogenesis and motility were identified in these patients points immediately—and not surprisingly—to the ancestral roles of gene expression that would impair, but not stop, the process of spermatogenesis from progressing. In addition, diminished expression of genes that participate in the processes of DNA damage repair and the regulation of oxidative stress is itself a disturbing sentinel, as it implicates impairment of mechanisms designed not only to limit exposure to free radicals but, perhaps, also to limit the ability to keep up with mounting threats to DNA integrity, likely incurred during or after the completion of spermatogenesis. Finally, and most interestingly, many of the genes that encode for epigenetic modifiers were impacted in oligospermic patients. Unfortunately, the major limitations implicit in this kind of approach cannot be overlooked, despite the provocative nature of the data.

We know little at this point about the relationship between mRNA profiling and protein expression but, hopefully, efforts in the area of proteomics will soon begin to close this important gap; moreover, functional consequences have yet to be directly implicated from studies of sperm that would bear the pathological RNA signatures identified by this and future studies. And while the epigenetic stability of the male genome is receiving more attention of late—especially with respect to environmental exposures—few studies have directly characterized either specific alterations in imprinted genes, or the relationships these chromatin modifications would contribute to abnormal sperm function.

One of the more telling sidelights raised by this work remains the clarification of why these mRNAs are embedded into the sleek confines of sperm cytoplasm. Could these infuse the newly appointed zygote with a burst of amplification in proteins that would share responsibilities among the likes of histone modifiers or DNA repair players? Or contrarily, do these mRNAs amount to a vestige of what was, during the final stages of spermatogenesis, empowering gametes from some individuals with the advantage of both numbers and quality? With much anticipation, we now await resolution of these and related questions, as the genetic and epigenetic determinants of sperm quality come into focus.