Mitomania and Human ARTs: micromanaging the mitochondrial genome and metabolome

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New-wave historians have a habit these days of forecasting events of today or in our future through the eyes of the commoners, rather than those of royalty. By focusing on the hard-working middle class and laborers toiling in the fields, the true story behind the origins of seminal contributions in technology, government, and economics that led to advances in the overall health and well-being of society is being told by uncovering the often sequestered efforts and experiences from deep within the story of civilization. Should it come as any surprise that by uncovering the nitty gritty details of what makes a human embryo surpass the obstacles encountered on the road to implantation and beyond, the “players” behind the scenes finally get the recognition they so richly deserve? Enter the mitochondrion!

Long known for their indispensability as energy-generating powerhouses, co-opted during the evolution of eukaryotes, to fuel the most demanding of cellular activities, there is an ongoing burst of excitement in and exploitation of the role of the mitochondrion in the quest for optimizing the practice of human ARTs.

The attention of late derives from two broad considerations: First, these worm-like critters that move about the cytoplasm, discharging their fuel reserves in response to oxygen consumption, are now appreciated to subserve many other vital functions within cells; for example, the matter of life and death is now viewed in terms of the balance of processes aimed at committing suicide (programmed cell death/apoptosis) or withstanding the challenges of stress,

induced by a lack of nutrients. In the latter case, much has been revealed about the process of autophagy as a mechanism of cell survival during moments of severe environmental stress, such that when a cell is signaled to activate autophagy, it will likely “look within” and self-digest organelles like mitochondria (mitophagy), both to temper metabolism through oxidative phosphorylation and look forward to a time when these by-products will be re-used to make a new set of mitochondria. Clever, for sure, and the ultimate statement of recycling for survival at the subcellular level! As for apoptosis, the long sought after explanation for the timely or not-so-timely demise of a cell through a cascade of enzymatic changes that chew up our genomes, it turns out that here too, mitochondria take center stage in effecting the death-wish pathway to its completion. So, mitochondria hold court at the intersection of life and death that speaks directly to the health and metabolism of our gametes and embryos throughout our reproductive lifespan.

Consideration Number Two has to do with our mitochondrial genomes. No surprise to specialists in reproductive medicine, nor students of high school biology, inheriting our mitochondrial genome from mother is but one of the more significant legacies of oogenesis and embryogenesis that we pay homage to on Mother’s Day each year. In fact, not only do our oocytes (eggs) take full responsibility for generating a healthy complement of mitochondrial soma, with enclosed circular genomes, they must see to it that the mitochondrion delivered from the midpiece of the fertilizing sperm is tacitly destroyed with the bravado and acumen of a stealth weapon. Interestingly, though the elimination of male mitochondria is understood to be mediated by a process involving enzymatic ubiquitination and thus labeled for destruction, there is recent evidence that this process is finalized within the zygote by means of autophagy. Stay tuned as this prospect, if demonstrated more widely, is likely to change the way we view parameters of

Capsule The maternal legacy embodied within our mitochondrial genomes and metabolomes requires a re-examination of the impact of modern human ARTs on this often overlooked and underappreciated organelle and its seminal role in the continuity of our life cycle.

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oocyte quality that have been desperately seeking better definition.

The matter of acquiring a sufficiently pure and abundant population of mitochondria is a matter of life and death for the embryo. As has been much discussed since the first attempts to use heterologous mitochondrial transfer for improving the quality of aged human oocytes, mixing mitochondrial genotypes creates a condition known as heteroplasmy that may compromise offspring health at different stages along the human life cycle. Moreover, and in turning the focus on this topic to the present issue of JARG, many of the steps we now take to generate oocytes for embryo production in the management of human infertility may compromise mitochondrial fitness with unforeseeable consequences.

One example of this is shown in the paper by Huang and colleagues. Human metaphase-2 oocyte cryopreservation by slow freezing or vitrification has become a widespread and expanding ART that offers patients and clinicians alike opportunities to maximize the chances of attaining a pregnancy within the traditional framework of clinical practice. Of the many well demonstrated applications, JARG has featured oocyte cryopreservation, both topically and in relation to fertility preservation strategies. But here comes the

rub. Most studies on the consequences of cryopreservation have understandably focused on the stability of the meiotic spindle, knowing full well that any long-term disturbances in spindle function would likely result in adverse chromosome segregation during the completion of meiosis-2, or during the initial mitotic cleavages in the conceptus. The studies by Huang and colleagues now point to an adverse effect of vitrification on the mitochondria of mature human oocytes. Turns out that an important reflection of mitochondrial membrane integrity is the maintenance of membrane potential that is linked to the metabolic functions these organelles will be required to sustain. Whether this effect is reversible over the long term, following vitrification, or whether a downstream consequence of membrane perturbation will be realized when active mitochondrial participation is required in the blastocyst is yet to be determined.

As we move more closely to setting the historical record straight for what finally makes an embryo achieve a high quality, and capable of producing healthy offspring, perhaps we should take a lesson from the words of Winston Churchill: “The farther back you can look, the farther forward you are likely to see.” Mitomania is likely to stay well within the sights of the future of human ARTs.