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EDITOR'S COMMENTARY

On becoming accepting of the imperfections in mammalian embryogenesis

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Commentary

Despite growing evidence to the contrary, the human embryo has been accorded special status assayable with advancing technologies aimed at ascertaining morphological, genetic, and cell biological parameters believed to be predictive of implantation and term development potential. That these indices of embryo quality perceived during the propagation of the blastocyst ex vivo are reliable and predictive is a major tenet of the practice of ARTs in clinical settings. The seasoned, but not widely acknowledged, notion that early embryogenesis in mammals shares features not unlike those exhibited by cancer cells has been challenging to contextualize and compounds our efforts to objectify in a meaningful way the perfections and imperfections of this dynamic process.

So it comes as no surprise that more recent studies on human and mouse embryos add clarity and depth to our understanding of preimplantation morphogenesis as was considered in our previous issue highlighting the degree of autonomy human embryos are capable of.

In this issue, Munch and colleagues report that among the genes expressed in human preimplantation embryos that may be involved in blastocyst formation and implantation, two leading candidates are identified that are typically found in neoplasms of certain kinds [1]. As shown on our cover this month, S10014A exhibits widespread distribution in the trophectoderm, and as the authors of this work propose, factors like this may underpin the emergence of anchoring and/or invasiveness required to initiate and sustain implantation.

Whether these or comparable studies searching for biomarkers released into culture medium or accumulated within the blastocoel provide clinically useful indices for developmental potential remains an area of active inquiry. More importantly though, this work adds to the mounting discourse surrounding the curious and unavoidable conclusion that human embryos have adopted properties of cancer cells, begging the question: are these "perfections or imperfections" in the grand design of things?

Reaching consensus on this topic with respect to clinical significance remains problematic. In part, our clinical norms have taken poetic license in assuming that what we measure during embryo culture equates to live birth rates, a matter requiring refinement and standardization as noted within by the article of Baker and colleagues from Stanford [2]. More proximal to the present discussion are the matters of why would the early embryo engage the many "imperfections" exemplified by the biology of neoplastic transformation, and what exactly constitutes the molecular characteristics of such cellular behaviors?

It is well beyond the purview of this commentary to be comprehensive in coverage; but to provide our readership with a glimpse of why this topic deserves recognition in the context of human ARTs, the following items serve as an entrée.

Some years ago, the notion that cancer cells acquire genetic instability in their sojourn to frank tumorigenicity to gain a survival advantage over host tissues was discussed [3]. While much is known about the molecular basis for such

Capsule While our obsession with identifying suitable technology and biomarkers of human embryo developmental competence continues, the litany of molecular imperfections engendered in early mammalian embryogenesis appear much more likely to confound and impair embryo selection strategies, all the while reinforcing the resemblance of human embryos to tumors.

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transformations in cancer cells, it was Ann Kiessling who first suggested that the human embryo may follow a similar course during its preimplantation development [4, 5]. The biological foundations for this work drew upon the widely conserved imperative among eukaryotic organisms to proceed through a series of cell cycles as quickly as possible—something that most of our sexually reproducing and heterogametic evolutionary counterparts do with 100 % fidelity on their way to 100 % fecundity! What these initial findings from Kiessling demonstrated was that human embryos—we being of the less fecund—appear to overexpress the molecules promoting cell cycle progression, and most surprisingly lack expression of cell cycle checkpoint genes! This latter category of genes, which leads to genetic instability during tumor progression, gives rise to protein products instrumental in sensing errors in the cell cycle that have to do with DNA replication fidelity, chromosome missegregation, and centrosome balance—all accepted properties of cancer cells that contribute to their survival and growth.

Clues adding substance to the idea that mammalian embryos are bestowed with an array of "imperfections" are appearing with great regularity even in the murine model system. These include the recent studies from Bolton and colleagues portraying the iatrogenic aneuploidy embryo as one instilled with a degree of plasticity that closely monitors the ratio of euploid to aneuploid cells that is compatible (not incompatible) with further development [6]. And reports from the Fitzharris laboratory in Montreal add credence to the concept of opportunistic and risky behaviors with investigations showing that as a matter of principle, regulating nuclear size and mitotic spindle organization follow more the guidelines accorded to cancer cells than those of a "normal" somatic cell [7, 8].

In closing, given the tenor of ongoing discussions regarding the use of PGS, time-lapse imaging, and omics-based technologies, and the shared incentives driving the quest for tractable and meaningful embryo selection strategies, tempered enthusiasm is in order until the meaning of the cancer cell embryo parallel can be further deciphered. As Aristotle noted, "It is the mark of an educated mind to entertain a thought without accepting it."

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