Supercilious cell cycles in the human embryo

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The 1980s and 1990s were witness to advances in our ability to comprehend the mysteries of the cell cycle; these advances continue to change and impact the face of contemporary biomedical research. Notwithstanding the immediate effects that this Nobel Prize-bearing topic (2004) has had on the understanding of cancer and the impetus it has provided for novel approaches to prevention and treatment, the cell cycle has assumed center stage in the field of human reproduction. This is true for three reasons: First is the issue of what distinguishes the meiotic cell cycle in gametes from that of their somatic cell counterparts. Even between the sexes, there is mounting evidence to suggest that while progressing through the rigors of spermatogenesis, a ruthless series of cell cycle checkpoints eliminates most all defective sperm. Second, the long acknowledged preponderance of aneuploidies exhibited by human oocytes, especially with advancing maternal age, has called into question the integrity of the controls responsible for eliminating chromosomally imbalanced ova. And finally, if suspicions exist as to the fidelity of chromosome balance in the female gametes, then what of the conceptus and its ability to monitor and dispense of blastomeres that harbor errors in chromosome segregation during the mitotic divisions of the preimplantation embryo? With over 30 years of ARTs experience and the evaluation of genetic integrity of human embryos under our belts, there is little left to the imagination—human embryos constitute an unusually striking example of cell cycles gone wrong! Why would this be?

Here enters the paper by Kiessling and coworkers in this issue of *JARG*; studies that take a major step forward in elucidating the causes and consequences of genetic stability in human embryos. This report forecasts and illustrates the power of bioinformatics and, as in other disciplines of biomedical research, brings into focus one of the most confounding and disconcerting properties of human embryos: their propensity toward chromosome imbalance.

Using microarrays of 8 cell human blastomeres, as well as array data from two human embryonic stem cell lines and human fibroblasts (both before and following iPS), the expression of transcripts relevant to cell cycle control was analyzed from a database of over 3,000 human genome mRNAs. What makes this work most provocative and insightful is that the ontology analyses were based upon genes known to play a central role in cell cycle progression from functional siRNA knockdown databases for two human cell lines: HeLa and U2OS. Based on the analysis of over 1,000 transcripts for each of these cell types, strong inferences were deduced relative to the levels of specific gene products detected in the human 8 cell blastomere arrays. In the broadest sense, 35 genes were identified as being overexpressed, including transcripts encoding for cell cycle “drivers,” while ten genes were identified as being underexpressed that notably included key checkpoint control gene products. Among the implications of these findings is the reinforcement of the notion that when it comes to cell cycle checkpoint surveillance, human embryos appear rather cavalier in their approach to achieving chromosome balance. What might speeding up the cell cycle with worn brakes accomplish? The authors argue that speed may be of the essence in order to drive development to the stage of compaction when reliance on growth factors to sustain embryogenesis assumes a central

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role coincident with the activation and deployment of the embryo's genome. Kiessling and coworkers speculate further that drawing upon oscillators for gene expression to encourage timely gene duplication may come at a cost, as accelerating the cell cycle could lead to asynchrony between the processes of karyokinesis and cytokinesis in the absence of trident checkpoints that are normally deployed during the G1 and G2 phases of the cell cycle.

So how will these findings influence the future of reproductive medicine? From a technical point of view, this work sets the stage for research into the precise molecular mechanisms that distinguish somatic cells, cancer cells, gametes and embryos from each other. Candidate genes are identified but there still exists the imperative to transform these leads into functional studies at the protein level. Two weaknesses of this approach are that the inferences drawn are solely based on mRNA expression data (not protein), and secondly, that neither of the cell lines used for siRNA functional studies are “normal” somatic cells. This means that the databases are suspect in their own right and may not provide an appropriate baseline for comparisons to human embryos and are likely incomplete given the nature of the cell cycle screens used to derive these databases. A recent paper in *Nature* (Neumann *et al.*, 2010, “Phenotypic profiling of the human genome by time-lapse microscopy reveals cell division genes”, 464:721, doi:[10.1038/nature08869](https://doi.org/10.1038/nature08869)) provides enhanced impetus for solving this problem. In what can only be described as a *tour de force*, an siRNA library

designed to screen the approximately 21,000 protein-coding genes that grace the human genome was used to earmark cell division genes by time-lapse microscopy to assign specific phenotypes. The prize at hand? A data set derived from about 190,000 time-lapse movies that encoded 19 million HeLa cell divisions! This extraordinary feat, made possible through the international Mitocheck consortium, brings to the surface a public database from which studies like those of Kiessling *et al.* can now apply to their own work—at a level of functional and proteomic resolution that was not previously imaginable. The take-home message of the Neumann *et al* contribution inspires promise and awe. Not only is there now an exploitable library of gene products suspected to be involved in cell cycle control, with which we can interrogate the rich network databases in hand for human gametes and embryos, but this work uncovered many gene products of unexpected relevance that will also have to be explored.

While it is difficult to know where we stand as a species in the spectrum of quality control for genome integrity, there is a lingering consensus within the field of ARTs that human embryos are at best woefully inept at handling the rigors of early cell divisions. Given the pace at which ARTs have moved from the bench to bedside over the past 30 years, perhaps it is time to slow down—instead of following the example of the human embryo's approach to the cell cycle (“faster is better”). Maybe we should step back and take the time to carefully monitor our progress and status, like a good cell cycle!