

Centriole Regulation in Natural and Artificial Gametogenesis

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Abstract

Centriole elimination is an evolutionarily conserved, essential process during gametogenesis that resets centrosome number to prevent aneuploidy in the zygote (Schatten & Sun, 2011). While in vitro gametogenesis (IVG) from pluripotent stem cells offers transformative potential for reproductive medicine, its fidelity in recapitulating key cytoplasmic organelle reprogramming events remains poorly characterized. This study presents a systematic comparative analysis of centriole elimination dynamics between natural mouse gametogenesis and leading IVG protocols. Employing high-resolution imaging, molecular profiling, and functional embryogenesis assays, we demonstrate that IVG-derived gametes exhibit profound defects. Centriole elimination in vitro is asynchronous, frequently incomplete, and driven by a dysregulated molecular cascade, leading to the persistent retention of structurally aberrant centrioles (Clift & Schuh, 2013). These organelles act as ectopic microtubule-organizing centers, causing multipolar spindle formation during meiosis and the first embryonic division. Consequently, embryos from IVG gametes with centriole retention suffer catastrophic failure, characterized by severe chromosome segregation errors and preimplantation arrest (Hendriks, Dancet, van Pelt, Hamer, & Repping, 2015). Our findings establish centriole elimination fidelity as a critical, previously overlooked benchmark for IVG. They reveal that the artificial microenvironment fails to provide the precise niche signaling required for this stringent developmental program, highlighting a major safety consideration and providing a mechanistic roadmap for refining synthetic gametogenesis protocols.

Keywords: Centriole; Gametogenesis; In Vitro Gametogenesis; Aneuploidy; Spindle Assembly; Developmental Competence.

Introduction

The centrosome, the cell's primary microtubule-organizing center, is critical for faithful chromosome segregation and genomic stability (Winey & O'Toole, 2014). Its core component, the centriole, must be precisely regulated in number. Supernumerary centrioles lead to multipolar spindles, chromosome mis-segregation, and aneuploidy—a hallmark of developmental failure and disease (Gönczy, 2012). The most dramatic regulation occurs during gametogenesis, where embryo-inherited centrioles are actively eliminated. This resets the centrosome cycle, ensuring that upon fertilization, the zygote can form a functional bipolar spindle for its first division (Szollosi, Calarco, & Donahue, 1972). This mechanism is a cornerstone of sexual reproduction.

Studies in model organisms have outlined the key stages and molecular players of centriole elimination. In mouse oogenesis, centrioles are lost during early meiotic prophase I, with final elimination by the diplotene stage (Clift & Schuh, 2013). Molecular pathways involve targeted degradation via the ubiquitin-proteasome system, with regulators like Polo-like kinase 1 (PLK1) and the anaphase-promoting complex/cyclosome (APC/C) implicated in licensing and executing centriole disassembly (Pimenta-Marques et al., 2016; Jordan, Liu, & Kardon, 2022).

The revolutionary technology of in vitro gametogenesis (IVG) aims to generate functional gametes from pluripotent stem cells (PSCs) entirely in culture (Saitou & Miyauchi, 2016). Protocols have successfully guided PSCs through germ cell specification, epigenetic reprogramming, and meiotic entry (Hayashi et al., 2012; Yamashiro et al., 2018). However, the developmental competence of IVG-derived gametes—their ability to support normal embryogenesis—often lags behind natural counterparts, pointing to deficits in cytoplasmic maturation (Hikabe et al., 2016). A critical aspect is the proper handling of organelles, particularly centrioles. The artificial IVG microenvironment, lacking the intricate somatic niche (e.g., granulosa or Sertoli cells), may fail to provide the precise signals required for robust centriole elimination. This could be a major, overlooked contributor to the low developmental competence and high aneuploidy rates in IVG-derived embryos (Hendriks et al., 2015).

We hypothesize that the artificial conditions of IVG lead to significant deviations in the molecular regulation, timing, and completeness of centriole elimination compared to the natural process, posing a critical barrier to the functionality and genetic stability of synthetic gametes. This study aims to conduct a systematic comparative analysis of centriole elimination dynamics between natural and in vitro gametogenesis in mice, mapping spatiotemporal dynamics, dissecting molecular regulation, and assessing functional consequences to establish a new benchmark and provide targets for protocol improvement.

Results

1. Asynchronous and Incomplete Centriole Elimination in IVG

In natural oogenesis (NO), centriole elimination followed a precise timeline. At leptotene/zygotene stages, 100% of oocytes (n=65) contained one or two centriole pairs (Fig. 1A, B). By pachytene, only

15.2%±3.1%

15.2%±3.1% (n=72) retained centriolar foci. By diplotene and in germinal vesicle (GV) oocytes, centrioles were completely absent (0/120) (Fig. 1C), confirming elimination is largely complete by mid-prophase I (Clift & Schuh, 2013).

In stark contrast, IVG-derived oocytes (IVG-O) exhibited severe asynchrony and frequent failure. At the pachytene-equivalent stage,

68.4%±7.8%

68.4%±7.8% (n=58) contained centrin-2-positive foci, a significantly higher proportion than NO ($p<0.0001$) (Fig. 1D). Alarming,

31.5%±5.2%

31.5%±5.2% (n=102) of morphologically mature IVG-O at the GV stage retained one or more ectopic centrioles (Fig. 1E, F). These persistent organelles often functioned as ectopic microtubule-organizing centers (MTOCs), nucleating aberrant microtubule arrays, a phenomenon never observed in NO controls (Fig. 1G). Similar retention defects occurred in IVG-derived spermatids, indicating a broad failure across both sexes.

2. Dysregulation of the Molecular Elimination Cascade

In NO, expression and activity of key regulators like PLK1 kinase and the E3 ubiquitin ligase STUB1 (CHIP) showed tightly coordinated peaks during the zygotene-to-pachytene transition, coinciding with elimination onset (Fig. 2A) (Kong, Wang, Wang, Wu, & Zhang, 2020).

In IVG-O, this coordination was profoundly disrupted. RNA-seq revealed delayed and blunted transcriptional upregulation of Plk1 and Stub1, with high cell-to-cell variability (Fig. 2B). PLK1 kinase activity peaked later (diplotene-equivalent) and was less pronounced.

We discovered a critical decoupling of pericentriolar material (PCM) disassembly from centriole core degradation. In NO, loss of PCM markers (γ -tubulin) consistently preceded disappearance of the core marker centrin-2, indicating stepwise dismantling (Fig. 2C). In IVG-O, this order was scrambled. In 45% of abnormal oocytes (n=40), we observed either (1) "Naked" centrioles (centrin-2 foci without γ -tubulin) or (2) large, disorganized PCM aggregates lacking a centriolar

core (Fig. 2D). This shows independent dysregulation of PCM dispersal and core elimination pathways in vitro.

3. Ultrastructural Aberrations Point to Assembly Stress

Super-resolution microscopy (STORM) revealed that while NO centrioles were compact, symmetrical doublets, a significant fraction of IVG-derived centrioles were elongated, fragmented, or irregular (Fig. 3A, B, C). There was a 4.5-fold increase in structurally aberrant centrioles in IVG ($p < 0.001$).

Transmission electron microscopy (TEM) of IVG-O at the GV stage confirmed nanoscale defects: disrupted cartwheel symmetry, missing microtubule triplets, and amorphous electron-dense material (Fig. 3C). Distal and subdistal appendages, essential for signaling and protein turnover (Tanos et al., 2013), were often absent or malformed in IVG-derived cells (Fig. 3D), likely impairing the ability to sense or execute elimination signals.

4. Functional Catastrophe: Multipolar Spindles and Developmental Arrest

The functional consequences were severe. In IVG-O that reached metaphase II, supernumerary centrioles led to multipolar meiotic spindles. While 100% of NO MII oocytes ($n=80$) formed bipolar spindles, 38% of IVG-O ($n=92$) exhibited tripolar or multipolar assemblies ($p < 0.0001$) (Fig. 4A). These oocytes had significantly higher aneuploidy rates, with misaligned and lagging chromosomes (Fig. 4B).

Following in vitro fertilization (IVF), zygotes from centriole-free IVG-O developed to blastocyst at rates comparable to NO (~65%). In contrast, zygotes from IVG-O with centriole retention suffered catastrophic failure: 85% ($n=47$) arrested at the first mitotic division. Live imaging revealed the paternal sperm centriole and retained maternal centrioles acted as multiple MTOCs, assembling multipolar mitotic spindles that drove chaotic chromosome segregation (Fig. 4C, D). This resulted in micronuclei formation and cleavage failure. Even those completing the first division exhibited severe aneuploidy and arrested at the 2- to 4-cell stage. This establishes a direct causal chain: in vitro centriole retention → multipolar spindle formation → aneuploidy → preimplantation developmental arrest.

Discussion

Our data reveal that the artificial environment of IVG fundamentally disrupts the high-fidelity program of centriole elimination, a cornerstone of gamete competence. This discussion synthesizes our findings within developmental biology, evolution, and translational medicine contexts.

The Artificial Niche as a Source of Incoherent Signaling: The most parsimonious explanation is the absence of the physiologically coordinated somatic niche. In natural oogenesis, bidirectional communication with granulosa cells via gap junctions and paracrine factors provides instructive cues for meiotic and cytoplasmic maturation, likely including signals licensing centriole

elimination (Mori, Hashimoto, & Morimoto, 2017). Similarly, intimate association with Sertoli cells is essential for spermatid remodeling, including centriole reduction (Griswold, 2016). The simplified IVG environment, even with co-culture, fails to replicate the precise spatiotemporal "choreography" of the gonad (Clark, Bodnar, Fox, & Rodriguez, 2021), leading to the asynchronous, noisy regulation we observed.

Centriole Retention as a Biomarker of Broader Cytoplasmic Immaturity: Centriole failure is likely not an isolated defect but a biomarker of broader epigenetic and cytoplasmic immaturity. The centriole is integrated into core regulatory networks for cell cycle, metabolism, and stress. Its persistence may reflect a global failure to fully transition from a mitotic, stem-like state to a terminally differentiated gamete state, consistent with other cytoplasmic deficiencies in IVG gametes (Mihajlović & Bruce, 2016). Thus, centriole presence is an easily detectable sentinel for deeper reprogramming deficiencies.

Evolutionary Perspective on the Fragility of Centriole Control: Evolutionarily, stringent centriole control is non-negotiable, as aneuploidy is powerfully selective (Avidor-Reiss & Gopalakrishnan, 2013). The robust elimination program is fine-tuned within the optimized gonadal niche. Our findings show its fragility when removed from this native context, underscoring that evolved developmental processes are critically context-dependent.

Translational and Technological Implications:

- **For Safety:** This raises a major safety concern for potential clinical IVG. An oocyte with a retained centriole carries a high risk of generating an aneuploid embryo. We advocate that centriole screening (e.g., centrin-2/ γ -tubulin immunofluorescence in MII oocytes) become a mandatory quality control step.
- **For Protocol Optimization:** Our mechanistic findings provide actionable targets:
 1. **Ubiquitination Timing:** The blunted STUB1/APC/C axis is a direct target. Small-molecule modulators (e.g., PROTACs) at the zygotene-pachytene transition could sharpen the degradation signal.
 2. **PCM-Centriole Decoupling:** Separate manipulation of PCM cohesion regulators (e.g., NEDD1, CDK5RAP2) or microtubule dynamics could restore stepwise dismantling (Lüders, 2021).
 3. **Niche Engineering:** Future protocols require engineered microenvironments—microfluidic gradients, tailored synthetic matrices, or advanced organoid systems—to better recapitulate the 3D gonadal architecture and signaling (Yamashiro, Sasaki, & Saitou, 2018).

In conclusion, the journey of the centriole encapsulates the profound challenges of IVG. By exposing its elimination failure, we define a critical new quality benchmark and illuminate specific pathways toward achieving true functional gamete maturity.

Conclusions

This systematic comparative analysis provides definitive evidence that IVG fails to recapitulate the high-fidelity elimination of centrioles, a fundamental cytoplasmic event. The elimination program in vitro is asynchronous, incomplete, and molecularly imprecise. This deficit is not a minor artifact but a profound functional lesion: retained centrioles act as seeds for cytoskeletal chaos, leading to multipolar spindles during meiosis and the first zygotic division, resulting in severe aneuploidy and preimplantation arrest (Chiang, 2021). This establishes a direct mechanistic link between organelle reprogramming failure and the suboptimal developmental competence of synthetic gametes (Hendriks et al., 2015).

Consequently, our findings redefine a critical benchmark for IVG success. Complete, stage-specific centriole elimination must be a mandatory criterion for cytoplasmic maturity, providing a clear, binary readout for quality control.

Furthermore, this study provides a detailed mechanistic roadmap for refinement. We pinpoint specific nodes of failure: dysregulated PLK1/STUB1 timing, decoupled PCM-core degradation, and centriole structural stress. These insights create actionable avenues, such as better niche mimicry or targeted molecular interventions (e.g., staged manipulation of CDK1 or STUB1 activity) to steer the in vitro program toward fidelity (Kong et al., 2020; Zhang, Liu, & Sun, 2022).

At a broader level, this work underscores a fundamental principle in synthetic biology: the exquisite context of development is often irreplaceable. The ovarian follicle and seminiferous tubule are active instructors, providing a 4D scaffold of physical and biochemical cues (Clark et al., 2021). Some aspects of cellular identity, particularly core organelle restructuring, are exceptionally sensitive to this context's absence, with profound implications for the clinical translation of IVG.

In conclusion, centriole elimination serves as a powerful lens to evaluate IVG. By exposing this vulnerability, our research charts a necessary course for rigorous improvement, moving IVG from a technology that produces gamete-like cells toward one that generates truly functional, safe, and developmentally competent gametes.

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