SPERM CENTROMERES AND CENP-A

A review published by Štiavnická et al.[1] discusses the unique role and persistence of the centromeric histone variant CENP-A in mature sperm cells across different species, including humans, mice, cattle, and flies, and its implications for fertility and early embryonic development.

Importance of centromeres

Centromeres are critical chromosomal regions that ensure accurate chromosome segregation during cell division. While composed of repetitive DNA sequences, their functional identity is defined epigenetically by the presence of CENP-A, a variant of histone H3. CENP-A is central to kinetochore formation and chromosome stability.

Spermiogenesis and the histone-to-protamine transition

During spermiogenesis, most histones are replaced by protamines to tightly compact DNA. Despite this massive chromatin reorganization, CENP-A is retained at centromeres in mature sperm. This persistence is unusual, since histones are almost completely absent in sperm chromatin, raising important questions about biological function of CENP-A.

Historical insights and discovery

The first clues to centromeric proteins in sperm came from autoimmune sera (CREST) used to stain cells from patients with CREST syndrome. These sera identified CENP-A, -B, and -C. Later, bovine sperm was used to purify CENP-A due to its low histone content, facilitating the first cloning of the human CENP-A gene.

Retention of CENP-A in sperm

Initially, studies failed to detect centromere proteins in mature sperm, likely due to technical limitations imposed by extreme chromatin compaction. With the development of sperm decondensation protocols, researchers confirmed that CENP-A is indeed retained, whereas CENP-B and CENP-C are absent, at least in mouse and bovine sperm.

Comparative Species Data

- In flies, only CENP-A persists in sperm and its presence is essential for early embryonic development. Depleting sperm CENP-A results in embryonic lethality.
- In mice, more recent studies using genetic tagging and western blotting confirm CENP-A's exclusive presence in sperm. Its absence or reduction impairs centromere strength in embryos and compromises fertility.
- In humans and cattle, centromeric foci are observed, but comprehensive molecular confirmation of exclusive CENP-A retention is still under investigation.

Mechanisms of inheritance and function

In Drosophila, paternal CENP-A persists after fertilization and is gradually replaced by maternal CENP-A. It is essential for the correct incorporation of paternal chromosomes into the embryonic spindle. Moreover, insufficient paternal CENP-A cannot be rescued by maternal supply, highlighting a self-templating inheritance mechanism.

In mice, inheritance is more nuanced. Paternal CENP-A deficits can be partially compensated by maternal CENP-A, but asymmetries in parental CENP-A levels exist and are resolved post-fertilization. This suggests an epigenetic memory and a need for balancing centromere strength between parental chromosomes.

Future directions and open questions

The review emphasizes the need to understand:

- Why and how CENP-A is maintained in sperm despite global chromatin changes.
- The molecular structure of centromeric chromatin in protamine-bound sperm nuclei.
- The role of centromeric proteins in fertility and embryo development, especially in humans.
- How centromeres are spatially organized in the sperm nucleus and how this affects function.

The authors propose combining genome editing, super-resolution imaging, and long-read sequencing to map CENP-A positions and better understand centromere biology in reproduction.

1. https://link.springer.com/article/10.1007/s10577-025-09766-2