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Sperm Capacitation and Programmed Cell Death: A Journey Beyond Survival

Alberto J. Cardenas-Padilla[1*], Alfredo Medrano[1]

[1] Departamento de Ciencias Pecuarias, Facultad de Estudios Superiores Cuautitlan, Universidad Nacional Autonoma de Mexico, Cuautitlan Izcalli 54714, Mexico.
* acardenasp@cuautitlan.unam.mx;

ABSTRACT
In sexually reproducing species, life originates from the union of two haploid gametes, each contributing half of the genetic material necessary to form a diploid zygote. The male gamete, the spermatozoon, not only fulfills its role in fertilization through capacitation and the acrosome reaction but also follows a path closely associated with cellular death. This commentary explores the intersection of sperm capacitation and programmed cell death, questioning the boundaries between life, function, and extinction at the cellular level. Is the sperm cell merely a vehicle for genetic transfer, or is it a biological entity with its own regulated death path, carefully orchestrated to ensure species preservation?

Key words: Spermatozoon; capacitation; apoptosis; fertilization.

Lay Summary
Before a sperm cell can fertilize an egg, it must undergo a process called capacitation. This process prepares the sperm to reach and fuse with the egg, but interestingly, it also triggers changes in the sperm that resemble early signs of cell death. These changes may help sperm function better for a short time, but they also make the cells more fragile.
Scientists have found that sperm cells show some surprising behaviors: they respond to chemical signals like nerve cells, work together at first, and then compete to reach the egg. However, modern fertility treatments, like intracytoplasmic sperm injection, may bypass natural selection, allowing sperm that wouldn't normally fertilize an egg to do so. This raises questions about how our technologies might be affecting future generations.
Understanding the balance between sperm survival, function, and death could help improve fertility treatments and spark important discussions about the ethics of assisted reproduction.

Introduction

Sexual reproduction relies on the contribution of two haploid cells, one from each parent, which upon fertilization, generate a diploid zygote capable of developing into a new individual. The spermatozoon is produced within the seminiferous tubules of the testis, where Sertoli cells directly support spermatogenesis, and Leydig cells indirectly regulate this process via testosterone synthesis. The reactivation of the hypothalamic–pituitary–gonadal (HPG) axis at puberty initiates the division of spermatogonia—first through mitosis, then meiosis (spermatocytogenesis), and ultimately through spermiogenesis, culminating in immature spermatozoa [1].
Following spermiation, spermatozoa mature as they transit through the epididymis, gaining fertilizing potential. These mature sperm cells are exposed to seminal plasma at ejaculation, which contains decapacitating factors that preserve viability until the right time and place for capacitation occurs [2]. This process is classically described as a prerequisite for successful fertilization and involves profound structural and biochemical changes including increased membrane fluidity, ion fluxes, and protein phosphorylation [3].
Interestingly, many of these changes overlap mechanistically with early events in programmed cell death (PCD), particularly apoptosis. For example, the externalization of phosphatidylserine—a hallmark of apoptosis—is also observed during capacitation, raising the provocative question: **Is capacitation a regulated prelude to sperm death?** [4] This duality leads us to consider whether capacitation and PCD are not opposing processes, but rather interconnected branches of the same biological pathway—one that prepares the sperm for a function it will not survive.
The sperm cell, once considered a simple motile carrier of paternal DNA, is increasingly seen as complex and responsive to biochemical cues. Meizel famously referred to the spermatozoon as a "neuron with a flagellum," due to the diversity of neurotransmitter receptors it expresses and its sensitivity to environmental signals [5]. The cellular response may depend on neurotransmitter concentrations, receptor expression levels, and the signal transduction feedback mechanisms. Furthermore, receptor dimerization and ligand specificity modulate downstream effects, introducing a level of regulatory sophistication often underestimated in gametes.
Capacitation is a multifactorial and highly dynamic event. Cryopreservation, for instance, can alter capacitation status depending on osmotic, physical, and chemical stressors [6]. Following natural mating, seminal plasma initially facilitates cooperative sperm transport via smooth myometrial contractions mediated by prostaglandins. However, as the sperm progress towards the oviduct, seminal plasma is diluted, triggering a transition from cooperation to competition—much like the transformation of migratory birds flying in formation to sprinters in a race nearing the finish line.
Once in the oviduct, capacitation is triggered by the removal of seminal plasma components. This prepares the sperm for hyperactivation, acrosome reaction, and interaction with the oocyte. Despite being structurally identical, a spermatozoon

in the cauda epididymis differs functionally from one near the uterotubal junction. The former is in a suspended state of potential; the latter is actively progressing towards self-destruction in pursuit of fertilization.

This raises a philosophical and evolutionary question: **Does the sperm cell prioritize species preservation over its own survival?** Since LUCA (Last Universal Common Ancestor), life has been defined by the drive to survive. Yet, spermatozoa seem biologically committed to die once they fulfill their singular purpose: genetic delivery. Their chromatin is so tightly packed with protamines that it inhibits transcriptional activity, classifying them as terminally differentiated cells [7]. However, recent studies have identified sperm-borne microRNAs and residual protein synthesis capacity, indicating that sperm cells retain limited post-transcriptional regulatory capabilities [8].

What then, of sperm cells that fail to fertilize? Assisted reproductive technologies (ARTs) such as ICSI bypass natural selection mechanisms, raising questions about the long-term implications of circumventing sperm competition and cooperation. While this serves human objectives—enhancing fertility, improving livestock production—it also interferes with evolutionary pressures that historically shaped reproductive efficiency and species resilience.

In the future, advances in molecular biology and cancer research may reveal deeper insights into sperm cell death pathways and capacitation events. Understanding these fine mechanisms will be essential, not only for improving ART outcomes but also for ensuring that conservation strategies respect the physiological diversity among species. Sperm capacitation, as it turns out, is not only a technical step in reproduction—it is an elegant biological sacrifice, a cell's final journey toward giving life.

Conflicts of interest

Authors state no conflict of interest.

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Author contribution

A.J. C.-P, was responsible for conceptualization, writing original draft, reviewing and editing the final manuscript.
A. M. was responsible for reviewing and editing the final manuscript.

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