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Nanotechnology-Future Prospects of Sperm-Driven Therapy in Oncology - A Review Article

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ABSTRACT

Cancer is a major fatal disease worldwide, with millions of new cases and deaths each year. While treatments like chemotherapy and immunotherapy have saved many lives, they often come with severe side effects. A better solution being developed targeted drug delivery, which aims to deliver medication directly to cancer cells, which increasing the effectiveness of the treatment and reducing harmful side effects. One fascinating approach under development is sperm-loaded nanotherapy. This innovative method uses sperm cells as natural carriers for cancer drugs. Because sperm can move efficiently through the reproductive system, they're ideal for targeting gynaecological cancers like cervical and ovarian tumors. By attaching anticancer drugs to sperm, researchers have created "spermbots" that navigate to tumors, deliver medication, and minimize harm to surrounding healthy tissues. This therapy takes advantage of nanotechnology to improve how drugs are delivered, including optimizing the size and shape of nanoparticles for better tumor penetration. While still experimental, this approach has shown promise in reducing cancer cell growth in lab studies. However, challenges like ensuring safety, improving drug loading efficiency, and addressing ethical concerns remain. Sperm-driven nanotherapy represents an exciting leap forward in cancer treatment, offering the potential for more precise, effective, and less toxic therapies. With further research, it could become a powerful tool not only for gynaecological cancers but also for other hard-to-reach tumors.

Keywords: Cancer therapy, Nanotechnology, Targeted drug delivery, sperm-loaded nanotherapy, Enhanced permeability and retention (EPR), Spermbots.

INTRODUCTION

Cancer is one of the fatal diseases globally. In 2020, there were about 19.3 million new cases and nearly 10 million deaths caused by cancer. Over the next 20 years, the number of cancer cases is expected to rise significantly due to factors like aging populations, pollution, and unhealthy lifestyles. This highlights the urgent need for better treatments to lower cancer-related deaths. [2-4]

Traditional treatments such as surgery, chemotherapy, and radiotherapy have helped many patients survive, but they often don't work well for advanced cancers that have spread. Newer treatments like immunotherapy show promise, but they don't work for everyone. Both chemotherapy and immunotherapy are non-

specific treatment that often damage healthy cells along with cancer cells, leading to serious life-threatening side effects. [2-4]

A better solution being developed is tumor-targeted drug delivery.[5] This method focuses on delivering medicine directly to cancer cells, avoiding harm to healthy cells, and increasing the effectiveness of treatment. This approach could make cancer treatments safer and more effective in the future.

ENHANCED PERMEABILITY AND RETENTION (EPR) EFFECTS:

Nanomedicines are designed to target tumors by taking advantage of the way tumor blood vessels and drainage systems work. These features allow small particles to build up in tumors through a process called the enhanced permeability and retention (EPR) effect, discovered in 1986. This approach has led to the development of several cancer treatments, including Doxorubicin and Taxol. However, the EPR effect doesn't work the same way for everyone or for all types of tumors, meaning these treatments can be less effective in some cases. To address this, scientists are working on other ways to improve how these medicines reach tumors, such as targeting tumor blood vessels, using immune cells to deliver drugs, and directly injecting the medicine into the tumor.[5,6]

Tumors grow quickly and need more oxygen and nutrients than nearby blood vessels can provide. To keep growing, they force the formation of new, abnormal blood vessels, which are leaky and allow large molecules or nanoparticles to enter the tumor. This is called the Enhanced Permeability and Retention (EPR) effect. [5,6]

HOW THE EPR EFFECT WORKS:

The EPR effect is a natural advantage in cancer treatment, allowing nanoparticles to target tumors specifically. However, differences in tumor structure and patient biology can affect how well it works, so ongoing research is focused on improving nanoparticle design for better drug delivery. [5,6]

1. **Leaky Blood Vessels:** Tumor blood vessels are poorly built, with gaps that let nanoparticles and drugs seep into the tumor tissue.
2. **Poor Drainage:** Tumors lack a proper lymphatic system to remove excess fluid. While small molecules can leave, larger particles (like nanoparticles) get trapped and stay in the tumor for longer.

Factors Influencing the EPR Effect:

The tumor environment, including proteins and molecules like VEGF and prostaglandins, makes blood vessels more-leaky and affects drug delivery. [5,6]

The design of nanoparticles is crucial for successful delivery:

- **Size:** Nanoparticles between 50–150 nm work best. Smaller ones are quickly removed by the kidneys, and larger ones can't enter the tumor easily.
- **Shape:** Rod- or worm-shaped particles circulate longer and accumulate better in tumors than round ones.
- **Surface Charge:** Particles with neutral or slightly negative charges are ideal. Positive charges get stuck in blood vessel walls, while negative charges are cleared by the liver or spleen.

Various types of nanocarriers used to enhance the EPR effect include:

- **Liposomes:** Lipid-based vesicles that encapsulate drugs, improving their delivery and stability.
- **Polymeric nanoparticles:** Biodegradable and versatile carriers for targeted drug delivery.
- **Dendrimers:** Highly branched, nanoscale polymers used for efficient drug loading and targeting.
- **Micelles:** Amphiphilic molecules that can solubilize hydrophobic drugs for delivery.
- **Nanostructured lipid carriers:** Hybrid carriers that combine lipids and

surfactants for better drug release profiles. [5,6]

SPERM-LOADED NANOTHERAPY FOR CANCER TREATMENT:

Sperm-loaded nanotherapy is emerging as a promising platform for treating cancers within the reproductive system. Sperm cells, with their unique ability to traverse the female reproductive tract, offer a natural vehicle for delivering drugs to hard-to-reach tumors.

Mechanism of Action:

In sperm-loaded nanotherapy, sperm cells are loaded with anticancer agents (Fig.1) [1] such as

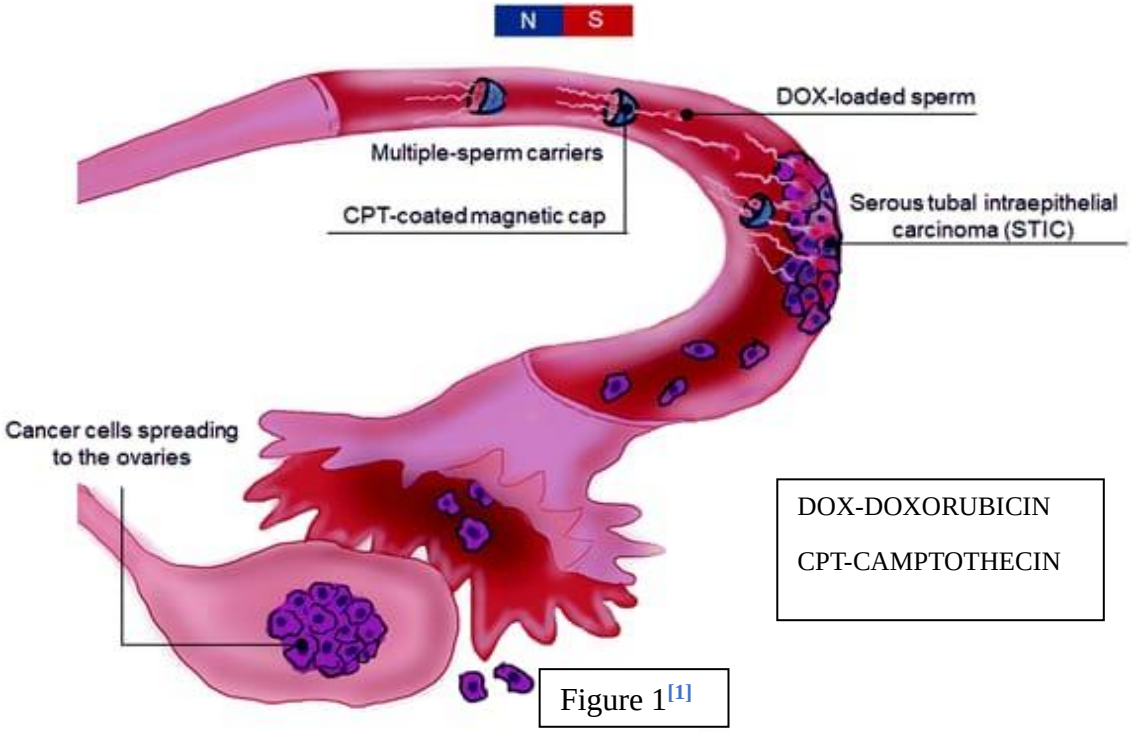

Figure 1[1]

DOX, a widely used chemotherapy drug. [1,7,8] These "spermbots" are engineered to:

1. Drug Loading onto Sperm Cells:

- **Attachment of Nanoparticles or Drugs:** Drugs like doxorubicin (DOX) are either chemically conjugated to the sperm membrane or physically loaded into the sperm head. This can be achieved using methods like:
  - Electrostatic interactions
  - Encapsulation of the drug within liposomal or polymeric nanoparticles.
- **Stability and Release:** The drugs are formulated to remain attached during transportation and to release at the tumor site, often triggered by environmental factors like pH or enzymatic activity. [1,7,8]

2. Sperm Navigation to Tumor:

- **Natural Motility:** Sperm cells naturally move through biological fluids using their flagella, allowing them to traverse the female reproductive tract and target gynecological tumors such as ovarian or cervical cancers. [1,7,8]
- **External Guidance Systems:** Magnetic microcapsules can be attached to sperm cells to direct them toward tumors using magnetic fields.
- **Biochemical gradients** (e.g., chemotaxis) may also guide sperm to specific tumor environments.

3. Penetration of Cancer Tissue:

- **Binding to Cancer Cells:** Sperm cells are capable of adhering to tumor cell surfaces, aided by the interaction between the sperm membrane and tumor-specific markers or receptors. [1,7,8]

- **Drug Release Mechanism:**
  - Once bound to cancer cells, the drug payload is released through:
  - **Diffusion:** Drugs like DOX diffuse out of the nanoparticles or sperm.
  - **Enzymatic Action:** Tumor microenvironment enzymes trigger the breakdown of drug-loaded coatings, ensuring localized release.
  - **Fusion:** Sperm cells may fuse with cancer cells, allowing intracellular delivery of the therapeutic agents.

4. Therapeutic Effects:

- **Localized Chemotherapy:**
  - Drugs like DOX enter the cancer cell and bind to DNA, inhibiting topoisomerase II and interfering with DNA replication and transcription.
  - This results in apoptosis (programmed cell death) of the cancer cells while sparing healthy tissues due to the targeted delivery.

- **Improved Drug Efficacy:**
  - Studies show that DOX-loaded sperm deliver three times more effective anticancer action compared to free drug solutions, particularly in 3D cancer models. [1,7,8]

5. Tumor Microenvironment Interaction:

- Minimized Systemic Toxicity: Sperm's biocompatibility and natural barriers reduce the likelihood of immune rejection or off-target effects. [1,7,8]
- Tumor-Specific Localization: Nanoparticle coatings and sperm's targeting capabilities ensure drug release primarily in the tumor microenvironment, minimizing exposure to non-cancerous cells. [1,7,8]

PREVENTION OF UNINTENDED FERTILIZATION:

To develop sperm-based drug delivery systems while preventing fertilization, researchers have explored multiple strategies. A primary method involves modifying sperm with physical or biochemical barriers to ensure they only serve as carriers for therapeutic agents without risking pregnancy. For instance, sperm can be paired with magnetic or nanostructured harnesses to control their movement and direct them toward cancer cells, reducing the likelihood of encountering an egg. These systems can also employ sperm inactivated by chemical (glutaraldehyde) or UV treatments to maintain motility while preventing fertilization capabilities. [13,14]

In recent studies, bovine sperm cells were loaded with chemotherapy drugs like doxorubicin and guided using magnetic fields to cervical cancer spheroids. This approach allows sperm to fuse with cancer cells, delivering drugs effectively without interacting with reproductive cells in vivo. Researchers are also developing targeted delivery mechanisms using antibodies or coatings that block sperm's interaction with eggs. [13,14]

APPLICATIONS:

1. Gynaecological Cancers:

Studies have shown promising results in treating cervical and ovarian cancers. Sperm loaded with DOX demonstrated superior tumor penetration compared to free drug solutions, significantly reducing cancer cell viability in 3D models. [9,10]

2. Combination Therapies:

Sperm cells can be co-loaded with multiple drugs or combined with other therapies, such as photodynamic therapy, to enhance treatment outcomes. [9,10]

Advantages:

- Targeted Delivery: Sperm's natural motility ensures precise delivery to tumor sites, minimizing damage to healthy tissues.

- Reduced Toxicity: By localizing the drug's action, systemic side effects are significantly decreased.
- Biocompatibility: Sperm cells are non-immunogenic, reducing the risk of adverse immune responses.

CHALLENGES AND FUTURE DIRECTIONS:

Despite its potential, sperm-loaded nanotherapy faces several challenges:

- **Loading Efficiency:** Optimizing drug loading without impairing sperm motility.
- **Guidance Systems:** Developing reliable external control mechanisms, such as magnetic fields.
- **Regulatory Approval:** Addressing ethical and safety concerns for clinical applications. [11,12]

CONCLUSION

The role of nanotechnology in drug delivery for cancer therapy. It describes how nanoparticles improve the precision of anticancer drugs, allowing them to target tumor cells while sparing healthy tissues. This approach reduces toxicity and enhances therapeutic efficacy. Various nanocarriers, such as liposomes and polymeric nanoparticles, are explored for their ability to improve solubility, control drug release, and overcome multidrug resistance. The integration of these systems with existing treatments shows promise for advancing personalized and effective cancer therapies. Currently, spermbot therapy is in the experimental stage and has not yet been approved for clinical use. Future research aims to expand this technology beyond gynaecological cancers, exploring applications in other hard-to-reach tumors and integrating advanced nanomaterials for enhanced drug delivery.

Declaration by Authors

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