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EDITORIAL

Redefining Pediatric Surgical Oncology: Gene Therapy, Nanorobots & Theranostics

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Pediatric surgical oncology stands at the threshold of a technological revolution. The high burden of childhood cancer has made it an urgent priority for biomedical innovation. In the field of pediatric surgical oncology, the high prevalence of cancer in children makes their treatment a key priority for scientific research. Emerging approaches are offering new hope in improving outcomes for these young patients.

Among the most promising advancements are gene therapy, nanorobotics & theranostics, which are transforming our approach to detection, diagnosis, and treatment.

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Gene therapy is emerging as a powerful tool in the fight against childhood cancer. One notable breakthrough involves targeting glycosylation pathways closely linked to tumor progression. The MGAT5 gene, for instance, encodes an enzyme responsible for modifying carbohydrate chains that fuel tumor growth. Knockout strategies targeting MGAT5 are now being explored as viable therapeutic interventions. An example of the MGAT5 gene's involvement in pediatric surgical tumors is seen in neuroblastoma, a common extracranial solid tumor in children.

Neuroblastoma and MGAT5

In neuroblastoma, overexpression of the MGAT5 gene has been associated with increased tumor aggressiveness and poor prognosis. MGAT5 encodes a glycosyltransferase that enhances the branching of N-glycans on cell surface glycoproteins. These branched glycans facilitate:

- Enhanced tumor cell adhesion,
- Increased motility and invasiveness, and
- Immune evasion, by modulating how cancer cells interact with the surrounding environment.

By knocking out or silencing MGAT5, researchers have observed reduced tumor cell proliferation and metastasis in preclinical models, making it a promising therapeutic target in pediatric neuroblastoma.

As our understanding of the genome advances, such interventions will become increasingly personalized.

☐ Non-invasive diagnostics—Equally significant is the role of non-invasive diagnostics. Mutations in mitochondrial DNA—detectable from something as simple as saliva samples—are being linked to specific pediatric tumors. This opens new pathways for early screening and prevention, reducing the need for invasive biopsies and increasing diagnostic speed and accuracy.

A strong example of the role of non-invasive diagnostics using mitochondrial DNA (mtDNA) in pediatric tumors is found in medulloblastoma, the most common malignant brain tumor in children.

Medulloblastoma and Saliva-Based mtDNA Mutation Detection

Researchers have identified specific mitochondrial DNA mutations associated with medulloblastoma, particularly in oxidative phosphorylation (OXPHOS) genes, such as *MT-ND1* and *MT-CO1*. These mutations can alter energy metabolism in tumor cells and have been linked to tumor subtypes and prognosis.

Importantly, such mtDNA mutations have been detected in saliva-derived epithelial cells, enabling:

- Early, non-invasive detection,
- Molecular subtyping of tumors (which guides treatment), and
- Monitoring of recurrence or minimal residual disease over time without repeated invasive procedures.

This saliva-based approach holds promise for use in children, where traditional biopsies or repeated MRIs are either risky or logistically challenging.

☐ Therapeutics—Nanorobots equipped with biosensors advancing drug delivery and surgical precision in pediatric oncology:

1. **Neuroblastoma: Dual-Mode Nanoparticles for Imaging and Therapy**

Dual-mode nanoparticle probes combine magnetic resonance imaging (MRI) and fluorescence imaging to enhance tumor visualization in neuroblastoma. These nanoparticles target neuroblastoma cells, enabling precise imaging and potential therapeutic applications.

2. **Neuroblastoma: NIR-II Nanoprobes for Tumor Differentiation**

Matrix metalloproteinase 14 (MMP14)-activatable NIR-II nanoprobe has been designed to distinguish neuroblastoma tumor tissues from surrounding non-cancerous tissue. This nanoprobe emits fluorescence upon activation by MMP14,

which is overexpressed in neuroblastoma cells, aiding in precise tumor localization.

3. Theranostics

Theranostic agents are molecules or nanostructures designed to combine both diagnostic imaging and therapeutic treatment into a single entity. This approach allows for real-time monitoring of disease progression and treatment response, enabling more personalized and effective therapies.

Tumor-targeting theranostic agents are innovative, dual-function molecules or nanoparticles designed to both diagnose and treat cancer by specifically targeting tumor cells. They combine imaging capabilities with therapeutic agents, allowing for accurate tumor detection and treatment. This approach offers advantages over traditional therapies, including improved targeting, reduced toxicity, and enhanced efficacy. For example, use of radioisotopes to first image a patient's tumor for diagnostics and then therapeutically treat that tumor.

Neuroblastoma: Gene-Loaded Nanoparticles for Targeted Therapy

Ligand-modified, gene-loaded nanoparticles can serve as tumor-targeting theranostic agents. These nanoparticles are engineered to deliver therapeutic genes specifically to neuroblastoma cells while allowing optical imaging to monitor treatment efficacy.

- ☐ Chemotherapy toxicity- it remains a major concern in pediatric patients.

Nanorobots, equipped with biosensors, are redefining drug delivery and surgical precision. These devices use nanowire-based sensors to detect subtle biochemical changes, such as early markers of metastasis, enabling clinicians to act sooner and with greater confidence.

Perhaps most striking is the use of quantum dots—fluorescent nanoparticles that bind to tumor cells. Once tagged, these cells become visible under surgical imaging, allowing for more accurate tumor resection. Conjugating tumor-specific ligands to these nanocrystals transforms them into highly specific surgical beacons. Beyond detection, intelligent nanorobots can also navigate vascular networks, identify tumors, and deliver drugs directly to the disease site, minimizing systemic exposure and maximizing therapeutic effect.

Following are some examples where nanorobots equipped with biosensors are emerging to enhance drug delivery and surgical precision:

1. **Targeted Drug Delivery in Pediatric Neuroblastoma**

Nanorobots can be functionalized with tumor-targeting ligands (e.g., antibodies against GD2, a surface antigen overexpressed in neuroblastoma).

- These devices **navigate the bloodstream**, bind specifically to neuroblastoma cells, and **release chemotherapy drugs** locally, minimizing systemic toxicity.
- Biosensors detect **tumor-specific pH or enzymatic activity** to trigger drug release at the tumor site.

2. **Fluorescent Quantum Dots for Intraoperative Guidance in Wilms Tumor**

In Wilms tumor (nephroblastoma), fluorescent quantum dot-labeled nanoparticles tag tumor margins.

- During surgery, these labeled cells emit light under specific wavelengths, allowing surgeons to visually distinguish tumor tissue from healthy kidney tissue in real time.
- Biosensors in the nanorobots can detect biochemical signals (e.g., hypoxia or lactate) to further refine localization.

3. Smart Nanorobots for Medulloblastoma Monitoring

For pediatric brain tumors like medulloblastoma, nanorobots may be introduced into cerebrospinal fluid (CSF) to detect early biochemical markers of recurrence using biosensors (e.g., glioma-associated miRNA or protein fragments).

- These sensors transmit signals externally, offering real-time monitoring without repeated MRIs or lumbar punctures.

4. Multifunctional Gold Nanoparticles in Osteosarcoma

In osteosarcoma, gold-based nanorobots can serve both therapeutic and diagnostic (theranostic) roles.

- They carry doxorubicin or cisplatin, release it in response to tumor-specific cues (e.g., acidic pH), and simultaneously emit imaging signals detectable during surgery.
- Some platforms include magnetic targeting to direct the nanorobots to tumor locations preoperatively.

These technologies are still largely experimental or in early clinical research, but they are rapidly progressing and may soon become integral in pediatric surgical oncology.

Together, these advances suggest a future where pediatric cancer care is not only more precise and effective, but also far less invasive and traumatic for young patients. The integration of gene-editing tools, biosensor technologies, and surgical nanodevices represents more than innovation—it represents a paradigm shift.

In the race against pediatric cancer, these tools are not just helpful—they are essential.