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Commentary

A Nanoplatform for Hypoxia-Responsive Co-delivery of an NQO1 Enzyme-responsive Pterostilbene Prodrug and Phenanthriplatin for Multi-Mechanistic Cervical Cancer Therapy

Zuoping Li[1,2]*

[1]School of Medicine, Xinjiang College of Science & Technology, Korla, 841000, Xinjiang, China

[2]Key Laboratory of Xinjiang Endemic Phytomedicine Resources Ministry of Education, Shihezi University College of Pharmacy, Shihezi, 832003, Xinjiang, China

***Corresponding authors:** Zuoping Li, Xinjiang College of Science & Technology, Korla, China

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Abstract

This commentary discusses a recent study that developed a hypoxia-responsive nanoplatform PAP 3.5/Phen-Pt/PTS-433 for co-delivering phenanthriplatin (Phen-Pt) and an NQO1-activated prodrug of pterostilbene (PTS-433) in cervical cancer. The system exploits tumor hypoxia and NQO1 overexpression to achieve targeted drug release, enhance platinum-induced DNA damage, and restore natural killer (NK) cell activity. This commentary highlights the dual-responsive design, the immunological benefits, and the translational potential, while also discussing limitations such as NQO1 expression heterogeneity and the need for more advanced hypoxia models.

Keywords: *Cervical cancer, Hypoxia-responsive nanoplatform, NQO1 prodrug, Phen-Pt, Pterostilbene, Immunotherapy*

Introduction

Platinum-based chemotherapy remains a cornerstone for treating advanced cervical cancer, but its efficacy is severely limited by tumor hypoxia and acquired resistance [1]. In a recent article published in *BBA-Molecular Cell Research*, we present an elegant nanoplatform that addresses these challenges through a triple-action design: a hypoxia-sensitive size-switchable dendrimer (PAP 3.5) co-delivers the monofunctional platinum agent Phen-Pt together with a novel quinone-locked PTS-433, which is selectively activated by NQO1 overexpressed in cervical cancer cells [2]. We demonstrate that released pterostilbene acts as a histone deacetylase inhibitor (HDACi) to sensitize cancer cells to Phen-Pt, while also reversing the hypoxic immunosuppression of NK cells. This commentary evaluates the study's strengths, potential limitations, and implications for future nanomedicine and immune-oncology.

Summary of Key Findings

We synthesized PTS-433 by modifying the phenolic hydroxyl of pterostilbene with a trimethyl-locked Quinone Propionic Acid (QPA) moiety, which is cleaved by NQO1. PTS-433 showed negligible toxicity in normal cells (low NQO1) but potent activity in HeLa and SiHa cells (high NQO1), with IC_{50} values around 30 μM. The combination of PTS-433 and Phen-Pt produced strong synergistic effects (combination index < 0.2 at optimal ratios), increased histone acetylation, enhanced γ-H2AX phosphorylation, and induced apoptosis [2].

The PAP 3.5 nanocarrier (PAMAM-AZO-PEG) was 97 nm in normoxia but shrank to 10 nm under hypoxic conditions ($Na_2S_2O_4$ treatment), due to azobenzene (AZO) reduction and PEG detachment. This size switch promoted cellular uptake and tumor accumulation. Drug release was strictly dependent on both acidic pH (6.8) and hypoxia, achieving 80-90% release within 90 min. Importantly, PTS-433 upregulated major histocompatibility complex class I chain-related gene A and B (MICA/B) on cervical cancer cells (via PI3K/AKT) and downregulated NRP-1, TGF-β, and IDO, thereby restoring NKG2D expression and NK cell cytotoxicity in co-culture models. In a HeLa xenograft model, PAP 3.5/Phen-Pt/PTS-433 achieved a 3.26-fold higher tumor inhibition than the negative control, with no significant body weight loss [2].

Strengths and Novelty

The study has several noteworthy strengths. First, the dual stimuli-responsiveness (hypoxia and acidic pH) ensures that the cytotoxic payloads are released preferentially in the tumor microenvironment (TME), minimising premature drug leakage. The hypoxia-triggered size reduction from 97 nm to 10 nm is a clever design that combines the EPR effect (via PEG shielding) with deep tumour penetration after size collapse. Second, the NQO1-activated prodrug strategy adds a second layer of selectivity: PTS is released only in cancer cells that overexpress NQO1, sparing normal tissues. This is particularly important because PTS acts as an HDACi, which could otherwise cause

unwanted epigenetic changes. Third, the immunomodulatory function of PTS-433 distinguishes this platform from conventional platinum nanotherapies. By upregulating MICA/B and downregulating TGF-β/IDO, it counteracts the immunosuppressive TME and restores NK cell activity-a feature that could synergise with immune checkpoint inhibitors [3].

Limitations and Open Questions

Despite these advances, some limitations warrant discussion. NQO1 expression heterogeneity-while high in many cervical cancers, NQO1 levels vary considerably among patients and even within tumour regions [4]. We used HeLa and SiHa cells as NQO1-high models, but clinical translation would require patient stratification or a theranostic approach to confirm prodrug activation. Second, the hypoxia model relied on $Na_2S_2O_4$ as a chemical reducing agent, which does not fully replicate the complex, chronic hypoxia in solid tumours (e.g., gradients of O_2, nutrient deprivation, and acidic metabolites). Future studies should validate the system in more physiological hypoxic cultures (e.g., 1% O_2 incubators for extended periods) and in orthotopic or patient-derived xenograft models. Third, while the nanoplatform showed excellent biocompatibility in the short term, long-term toxicity and biodistribution studies (e.g., accumulation in the reticuloendothelial system) are needed before clinical consideration. Finally, the combination of Phen-Pt and PTS produced strong synergy (CI = 0.14-0.20), but the optimal dosing ratio and scheduling in vivo require further refinement, especially because PTS-433 release kinetics differ from those of Phen-Pt.

Conclusion

We have developed a sophisticated nanoplatform that leverages two tumor-specific cues (hypoxia and NQO1) to deliver a synergistic combination of Phen-Pt and a PTS-433. The work convincingly demonstrates enhanced cytotoxicity, apoptosis, and NK cell activity in vitro, along with superior tumor inhibition in a xenograft model. Although certain gaps remain, this study provides a strong proof-of-concept for multi-mechanistic, microenvironment-responsive drug delivery in cervical cancer. Future refinement of the carrier design and more rigorous immune evaluation will determine its potential for clinical adoption.

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