

Synthesis of WRG-decorated Nanogels as combo therapy for ovarian cancer

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Ovarian carcinoma is one of the most lethal gynecological cancers due to asymptomatic progression, late diagnosis, and chemoresistance. Research has focused on the biological and genetic factors driving tumor development, highlighting two main strategies against metastasis: smart drug delivery systems to enhance intracellular drug release, and the modulation of both the tumor cells and the tumor microenvironment through inhibition of specific cell receptors.

In this work, we propose the development of a hyaluronic acid and linear polyethyleneimine nanogel-based platform integrating dual functionality: extracellular receptor inhibition and enhanced intracellular chemotherapeutic delivery. The nanogel (NG) synthesis proceeds through a surfactant-free, mixed emulsion/evaporation method where a water-in-oil emulsion of activated hyaluronic acid is prepared, followed by the addition of a second aqueous dispersed phase containing Cy5-labeled PEI [1]. Through exploiting the interface interactions and coalescence phenomena, polymer crosslinking occurs, forming NGs. To achieve receptor-specific targeting, we functionalize the NGs with novel resorufin-based derivatives inspired by WRG-28, a small molecule known to inhibit discoidin domain receptor 2 (DDR2), which is overexpressed in high-grade serous ovarian carcinoma (HGSOC), and it is involved in the signaling pathways of its metastatic progression [2]. Specifically, we synthesize two WRG analogs: i) WRG-A, a coupling-ready WRG-28 derivative, and ii) WRG-B, a newly designed amino-aliphatic resorufin compound.

Both versions of the decorated NGs present an average size lower than 250nm (220nm for NG-A and 240nm for NG-B), and WRG grafting densities of ca. 0.67 mgWRG/mgNG for NG-A and ca. 0.60 mgWRG/mgNG for NG-B. WRG-functionalized NGs demonstrated selective inhibition of DDR2-mediated tumor cell interactions with the extracellular matrix, thereby interfering with metastatic signaling pathways. Furthermore, these NGs are validated as cisplatin delivery system, ensuring a drug encapsulation efficiency of ca. 70% and a sustained drug release up to 13 days. Their administration to ovarian cancer cells resulted in significantly enhanced therapeutic effects, with Δ viability of -15% for NG-A and -20% for NG-B relative to free drug administration. This work presents a novel approach within the field of both molecular design and polymer chemistry, reinforcing the potential of multifunctional nanogels for next-generation oncology therapies.

Keywords: nanogels; mixed emulsion; WRG; DDR2; cisplatin; ovarian cancer.

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2. Grither, W. R. & Longmore, G. D. *Proc Natl Acad Sci U S A* **115**, E7786–E7794 (2018).