THE UNIVERSITY OF HONG KONG
SCHOOL OF BIOLOGICAL SCIENCES

Postgraduate Student Public Seminar

"Dendrimer Nanoparticles in Anticancer Treatment Applications"

Ms. ARTEMENKO Margarita
PhD Student, School of Biological Sciences, HKU
(Supervisor: Prof. Alice S.T. Wong)

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Abstract

Cancer is one of the leading causes of death worldwide. Epstein-Barr virus positive nasopharyngeal carcinoma (NPC), which is endemic NPC variant for South-Asian population, is characterized by a certain pattern of viral latent proteins expression, which are responsible for tumor development, progression, survival, chemoresistance, and recurrence. Latent membrane protein 1 (LMP1), an Epstein-Barr virus protein, is responsible for initiating multiple pathways in epithelial and B cell development, is especially important for NPC initiation and development on early stages. I demonstrated that polyamido amine dendrimer nanoparticles can be used as carriers for the siRNA molecules to knockdown the target gene LMP1 in NPC. Dendrimers formed stable complexes with siRNA, promoted cell uptake, protected siRNA from degradation, and induced LMP1 knockdown in stable and reactivated cell lines *in vitro*. LMP1 siRNA dendriplexes which were injected intravenously twice a week in C15 tumor bearing mice induced LMP1 knockdown resulting in tumor growth suppression.

Ovarian cancer, the leading cause of death among gynecological malignancies, is commonly diagnosed at late stages of development, which complicates its treatment. Cancer stem cells (CSCs), a small subpopulation of cancer cells that have the ability to self-renew, initiate new tumor formation and differentiate, are believed to be responsible for the tumor relapse, as being often resistant to conventional chemotherapy. Therefore, targeting CSCs is significant to improve disease outcome. Relatively new class of drugs, tyrosine kinase inhibitors, were first introduced in 2001 with the approval of imatinib mesylate that targets c-Kit. Ovarian CSCs are characterized by c-Kit expression, which triggers multiple stem-related pathways in CSCs, so imatinib could be a potential drug for treating patients with recurrent or chemoresistant ovarian cancer. Using Bola-amphiphilic dendrimer nanoparticles encapsulation, I found that dendrimer nanoparticles could effectively protect the imatinib, improve cell uptake and targeting performance, resulting in significantly higher anticancer efficacy comparing to naked imatinib. Dendrimer-based nanomicellar drug was effective and highly specific against ovarian CSCs, promoting apoptosis, decreasing self-renewal ability, suppressing stemness markers and c-Kit downstream effectors. Combined with conventional chemotherapy cisplatin and paclitaxel, dendrimer-based imatinib showed significantly improved treatment outcomes. Similar results were also obtained using c-Kit siRNA dendriplexes *in vitro* and *in vivo*.

Taken together, our findings provide new insights in the possible strategies of safe, effective, and affordable dendrimer nanoparticle-based cancer treatment.

--- ALL ARE WELCOME ---