COLLEGE OF PHARMACY
PHARMACEUTICAL SCIENCES
UNIVERSITY OF MICHIGAN

Pharmaceutical Sciences Seminar
Wednesday, February 14, 2018
Room 2548 C.C. Little Building
4:00 – 5:00 p.m.

"PEGylated tumor membrane nano-vesicles for eliciting adaptive immune responses against melanoma"

Presented by:

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Abstract: Current efforts in cancer immunotherapy focus on eliciting cytotoxic T lymphocyte (CTL) responses against tumor-associated antigens and neo-antigens. Our work has focused on tumor cell lysates, which contain antigen-rich membrane vesicles, which can serve as a potent vaccine delivery vehicle. We utilized freeze-thawing and sonication of B16F10 OVA murine melanoma to generate tumor cell lysates, containing transmembrane model antigen ovalbumin (OVA). The nanoparticles (PEG-NPs) were prepared by aggregating cell membranes using calcium, washing, and then modifying them with DSPE-PEG by post-synthesis insertion method allowing for effective dispersion. The surface PEG layer also played a role in stabilizing the formulation in vitro and enhancing trafficking to the draining lymph nodes, the vaccine site of action. Additionally, cholesterol-modified CpG, potent immunostimulatory agent, was also incorporated into the vesicles allowing co-delivery with membrane-associated antigens. Compared to soluble cytosolic proteins, membrane vesicles were taken up 3-fold more efficiently by DCs and led to cross-presentation and expansion of OVA-specific T cells in vitro. Mice immunized with PEG-NPs demonstrated superior CTL responses against OVA compared to standard lysates. In additional, mice immunized prophylactically (two doses with two-week interval) were challenged with B16F10 OVA subcutaneously resulting in 50% protection against tumor growth. In comparison, naïve mice succumbed to tumor burden within 20 days. In a therapeutic setting, mice were inoculated subcutaneously with melanoma and immunized on days 5 and 12 leading to decreased tumor growth and increased median survival from 23 to 55 days compared to untreated control. Immune checkpoint blockade has increasingly been used in the clinic in order to activate and enhance the endogenous immune responses against cancer. Dual therapy utilizing PEG-NPs vaccination and αPD-1 antibody treatment has resulted in complete tumor regression in 63% of mice, compared to 13% effectiveness for each monotherapy. The results of these studies demonstrate that PEGylated tumor membrane vesicles can effectively drain to lymph nodes and generate effective adoptive immune response against melanoma.

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