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Anti-tumor activity of a nanoliposomal anti-PCSK9 vaccine in BALB/c mice bearing 4T1 breast cancer.

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Topic(s):
Cardio-Oncology

Citation:
Background: Although suppression of proprotein convertase subtilisin/kexin 9 (PCSK9) has been known to be an effective lipid-lowering approach, the efficacy and safety of PCSK9 inhibitors in non-cardiovascular diseases, particularly cancer, are yet unknown.

Purpose: The present study aimed to evaluate effect of PCSK9 inhibition on cancer behavior and endpoints in mice model of breast tumor, using a nanoliposomal anti-PCSK9 vaccine.

Methods: The nanoliposomal anti-PCSK9 vaccine was formulated via conjugation of immunogenic PCSK9 peptide to the surface of nanoliposome particles by using DSPE-PEG-Maleimide lipid. The prepared vaccine was adsorbed to Alum adjuvant (L-IFPTA+) and immunized subcutaneously four times with a bi-weekly interval in BALB/c mice. Two weeks after the last immunization, the vaccinated and unvaccinated mice were subcutaneously inoculated with 4T1 breast carcinoma cells into the right flank. After tumor mass was palpable, the mice were randomly divided into four groups and subjected to different treatment protocols: (1) PBS (untreated control), (2) vaccine group, (3) the combination group which involved vaccinated tumor-bearing mice who received single tail vein injection of Doxil®, and (4) Doxil® (positive control) group which involved unvaccinated tumor-bearing mice who received Doxil®. To evaluate therapeutic efficacy, mouse body weight, tumor size, and survival were monitored every other day for 60 days.

Results: The vaccine was found to efficiently generate specific antibodies against PCSK9 in BALB/c mice, and thereby reduce concentration of plasma PCSK9 and impede its function. Evaluation of tumor size demonstrated that time to reach endpoint (TTE) of the vaccine, combination, Doxil, and control groups was 47±10, 57±4, 60±4, 39±9 days, respectively. Rate of tumor growth in vaccine, combination, and Doxil groups was decreased by 21, 48, 53%, respectively, when compared with the control group (Figure). In the vaccine group life span was increased by 4.2%, while the survival in the combination and Doxil group was significantly lower than the control group.

Conclusions: Our results reveal that PCSK9 inhibition not only exerts no harmful effects, but also can moderately improve breast cancer behavior in animal model.
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Figure. Anti-PCSK9 vaccine efficacy. (A) Anti-PCSK9 antibody titers (ODmax/2) over 14 weeks post prime immunization. (B) Plasma concentrations of PCSK9 in vaccine and control groups. (C) Direct detection of antibodies bound to plasma PCSK9 in blood samples from vaccinated and control mice. (D) In vitro PCSK9/LDLR binding assay.