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Gold Nanoparticle (AuNP) as a Therapeutic Enhancer for Radio – And Immunotherapy Therapy Combination in Triple Negative Breast Cancer

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Imaging of Primary and Metastatic Tumors Treated with Radiotherapy-Directed Antigen-Capturing Nanoparticles, Reducing Metastasis-Seeding and Colonization, under PDL-1 Blockade

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Purpose/Objective(s): We tested a treatment combining radiotherapy with antigen-capturing nanoparticles (AC-NPs; 112 ± 73 nm) containing digitoxin and anti-STAT-3 inhibitor (HJC0152) encapsulated in nanocapsules (545 ± 24 nm), which release their contents upon radiation exposure. We conducted two radiotherapy sessions: 1) treatment of primary tumor and metastases by immuno-radiotherapy and abscopal effect with PDL-1 blockade, respectively, and 2) reduction of new metastasis seeding and colonization by dissociation of circulating tumor cell (CTC)-clusters using digitoxin, and by impairing premetastatic niche (PMN) formation using a STAT-3 inhibitor (HJC0152), respectively.

Materials/Methods: In session one, nanocapsules were generated by mixing iopamiron, 400 mg of an anti-PD-L1 antibody (Ab), and 10 μg/mL HJC0152 with a 1.0 mL solution containing 4.0% alginate, 3.0% hyaluronate, and 1 μg/mL P-selectin. This mixture was sprayed into 0.5 mmol/l $FeCl_2$ supplemented with 1 μg/mL anti-VEGFR-1/2 Ab. In session two, 400 nM digitoxin was encapsulated in poly lactic-co-glycolic acid (PLGA) AC-NPs using the nanoprecipitation method. The particles were mixed with the above cocktail and sprayed into 0.5 mmol/L $FeCl_2$ with 1 μg/mL anti-P-selectin Ab. This yielded encapsulated PLGA AC-NPs containing digitoxin. In session one, 1×10^{10} nanocapsules were intravenously injected into BALB/c mice exhibiting a primary 4TI mammary carcinoma in the left hind leg and lung metastases. Tumor accumulation was monitored by computed tomography (CT). Subsequently, 10 or 20 Gy ^{60}Co γ-radiation was locally administered to primary tumors and lung metastasis. In session two, 1×10^{10} nanocapsules were injected i.v. and allowed to interact with P-selectin for 9 h; additionally, 10 or 20 Gy ^{60}Co γ-radiation was administered solely to the primary tumor.

Results: In session one, CT imaging of the accumulation of anti-VEGFR-1/2 nanocapsules around the primary and metastatic tumors improved their diagnosis. The nanocapsules released P-selectin, anti-PD-L1 Ab, and HJC0152 in response to the initial radiation dose. After session two, the nanocapsules accumulated around the primary tumor via a P-selectin Ag-Ab reaction. PLGA AC-NPs captured tumor-derived protein antigens released by the second radiation dose and intensified DC-mediated $CD8^+$ T-cell priming. The primed $CD8^+$ T-cells attacked PD-L1-suppressed primary and metastatic tumors. PLGA AC-NPs also released digitoxin, which dissociated CTC-clusters and reduced new metastasis seeding; the colonization of seeded tumor cells was subsequently inhibited through impaired PMN formation by HJC0152. Additionally, HJC0152 intensified DC-mediated $CD8^+$ T-cell priming. These treatments significantly increased the antitumor effect (EF 1.7) and reduced metastasis by 88.8%.

Conclusion: Our CT-detectable nanocapsules will lead to better diagnosis and tumor treatment.

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Gold Nanoparticle (AuNP) as a Therapeutic Enhancer for Radio − And Immunotherapy Therapy Combination in Triple Negative Breast Cancer

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Purpose/Objective(s): Triple negative breast cancer (TNBC) is the most aggressive breast cancer (BC) form, with a high metastases rate and a very low survival. The aggressiveness of TNBC coupled with a significant toxicity and suboptimal chemotherapy outcomes underscores the urgency for new TNBC treatments. In recent years, immunotherapy has emerged as a promising option. In particular, immune checkpoint blockers (ICB) targeting PD-L1/PD1 inhibitory T cell check point pathway showed clinical responses and have been explored for TNBC. Unfortunately, the response rates to standalone ICB therapy are low (15-20%), indicating the presence of inhibitory immune mechanisms. Radiation therapy (RT) has been widely used in BC therapies. In addition to antitumor (antiproliferative) effects, RT has been evidenced to stimulate immune tumor rejection through immunomodulation of the tumor microenvironment (TME) that has been shown to enhance the response to immunotherapy in mouse BC models. Antitumor RT effects, including TME immunomodulation, can be improved by using radiosensitizers, such as gold nanoparticles (AuNPs). We hypothesize that AuNP potentiates RT-induced immunomodulatory effects, leading to a more efficient response to ICB in TNBC. To test this hypothesis, we used AuNP as an enhancer of RT-induced immunological TME changes, to improve ICB therapy response in murine orthotopic syngeneic 4T1Luc TNBC model.

Materials/Methods: Female Balb/c mice bearing 4T1Luc tumors received intratumoral injections of 14 nm AuNPs. After 24h mice were irradiated with fractionated regimen of 3 × 6 Gy dose using 225 kV photons. After the 3rd RT dose, mice received 3 doses of anti-PD-L1 antibody that were 4 days apart. Therapeutic efficiency was determined by assessing the tumor growth and animal survival. Tumor tissue immunohistochemistry determined the expression of TME immunological markers and immune cell tumor infiltration.

Results: AuNPs improved response to anti PD-L1 treatment in mice receiving RT, shown by significant delay in tumor growth and increase in survival compared to the animals receiving RT+ AuNP ($p<0.01$) and to the animals receiving RT+ anti PD-L1 or RT alone ($p<0.05$). These results were accompanied with changes in the expression of TME immunological markers and T cell and macrophage infiltration.

Conclusion: In TNBC patients, induction of antitumor immune response may play a critical role in improving clinical outcomes. Here we show that AuNP enhanced the effect of a fractionated RT regimen that has significantly improved the response to anti PD-L1 treatment in 4T1Luc TNBC mouse model. This effect was measured by a delay in tumor growth and an increase in animal survival. These findings support the role of immunological mechanisms in TNBC and provide a platform for designing multimodal TNBC RT formulations with novel radiosensitizers or immunotherapy.

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Preclinical Evaluation of Tumor Treating Fields Combined with Personalized Ultra-Fractionated Stereotactic Adaptive Radiotherapy (PULSAR)

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