**Extracellular Vesicle-Based Nano-Immunotherapy for Reprogramming Tumor Microenvironment**

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**Background and Aim.** Most solid tumors exhibit immunologically “cold” characteristics due to an immunosuppressive tumor microenvironment (TME) and limited T cell infiltration, resulting in poor response to immune checkpoint therapies (ICT). Tumor-associated macrophages (TAMs), particularly the M2-like subtype, are key contributors to this immunosuppression. This study aims to develop extracellular vesicle (EV)-based drug delivery systems to reprogram the TME, activate immune responses, and enhance antitumor efficacy (Figure 1).

**Methods.** We designed two complementary nanoplatforms using engineered extracellular vesicles. The first involves co-delivery of a photothermal agent (AXCB6, with AIE properties) and IDO inhibitor (NLG919) using M1 macrophage-derived exosomes (M1-Exos) decorated with RGD peptide and hollow mesoporous silica nanoparticles (HMSN). The second uses apoptotic body membrane-coated nanobiohybrids (PARM) containing R848 and Mn²⁺, with a pH-sensitive PEG corona that detaches in the acidic TME to enable targeted TAM uptake.

**Results.** M1-Exos@HMSN enabled targeted delivery to tumor cells, inducing hyperthermia via near-infrared (NIR) light to trigger immunogenic cell death (ICD) and activate in situ vaccination. Simultaneously, M1-Exos retained their ability to reprogram M2-TAMs into M1 phenotype, enhancing immunogenicity and T cell infiltration. PARM nanoparticles specifically targeted TAMs, where Mn²⁺ activated the cGAS-STING pathway, reducing SIRPα expression and enhancing macrophage phagocytosis. R848 further polarized TAMs to a pro-inflammatory state. In vivo, both platforms significantly suppressed tumor growth and metastasis while enhancing CD8⁺ T cell infiltration.

**Conclusions.** These EV-based strategies demonstrate a "one-stone-two-birds" approach: simultaneously modulating TAMs and inducing tumor immunogenicity. The dual function of photothermal activation and innate immune stimulation reshapes the TME, converting “cold” tumors into “hot” ones. This study highlights the potential of extracellular vesicles as intelligent drug delivery vectors and immune adjuvants, providing new avenues for enhancing cancer immunotherapy.

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**References:**

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