

Abstract

Innovative Strategies Using Immune-Derived Extracellular Vesicles and Epigenetic Drugs: A Nano-Scale/Organ-on-Chip Framework for Melanoma Therapy

Melanoma is a highly aggressive skin cancer with significant mortality rates, largely due to the limited efficacy of current therapeutic approaches in most patients. Treatment resistance is primarily driven by an immunosuppressive tumor microenvironment (TME) and the poor immunogenicity of melanoma cells. Within the TME, tumor progression is orchestrated by a complex interplay among tumor, stromal, and immune cells, in which extracellular vesicles (EVs) play a pivotal role. Acting as natural nano-scale mediators of intercellular communication, EVs shuttle functional biomolecules, including mRNAs and miRNAs, that reflect the physiological state of the donor cell and modulate signaling pathways in recipient cells, thereby shaping their phenotype and function.

Immune cell-derived EVs have emerged as key regulators of tumor progression and represent promising therapeutic tools. In our previous work, we demonstrated that EVs released by IL-33-activated eosinophils exert anti-tumor effects by transcriptionally reprogramming melanoma cells and suppressing their malignant phenotype, highlighting the therapeutic potential of immune-derived EVs in cancer treatment.

However, melanoma patients frequently develop resistance to conventional therapies, including the BRAF(V600E) inhibitor Vemurafenib, underscoring the need for innovative therapeutic strategies capable of simultaneously targeting multiple oncogenic and immune-regulatory pathways. In parallel, increasing evidence supports the use of nanoparticle-based therapeutics, including EVs, for targeted drug delivery, in vivo tracking, and treatment monitoring.

Epigenetic drugs, such as DNA hypomethylating agents (DHAs), have also shown the ability to reprogram melanoma cells by enhancing tumor immunogenicity and promoting immune recognition. These complementary mechanisms suggest that combining immune-derived EVs with epigenetic modulation may provide synergistic therapeutic benefits.

Based on these premises, we propose an integrated therapeutic strategy that combines immune-derived EVs with epigenetic drugs and conventional therapies to reprogram melanoma cells, enhance anti-tumor immune responses, and overcome treatment resistance. To faithfully recapitulate the complexity of the human TME and facilitate the translation of these nano-scale therapeutic approaches, we will exploit advanced organ-on-chip platforms that enable dynamic modeling of tumor-immune interactions within a physiologically relevant microenvironment. This integrated nano-scale/organ-on-chip framework is expected to provide a predictive platform for evaluating therapeutic efficacy and mechanisms of action, ultimately supporting the development of more effective and personalized treatments for melanoma.