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Cancer Therapeutic Strategies to Rewire Tumor Microenvironment

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Abstract

The main objective of our research is to develop tumor-targeted therapies that modulate the tumor microenvironment (TME) to enhance therapeutic efficacy while minimizing side effects. Specifically, our focus lies in two key strategies: targeting tumor-associated macrophages (TAMs) to supress their protumor functions and utilizing extracellular vesicles (EVs) derived from dendritic cells to enhance intratumor drug delivery and immunotherapy.

We have previously explored the potential of statins, such as simvastatin (SIM), which exhibit antitumor effects at high doses. However, the systemic use of these high doses is limited due to severe side effects. To overcome this challenge, we incorporated SIM into long-circulating liposomes (LCLs) that have a natural tropism for the main key cell players in tumor microenvironment- tumor-associated macrophages (TAMs) [1]. In murine models of melanoma (B16.F10) and colon carcinoma (C26), our results demonstrated that LCL-SIM significantly enhanced antitumor activity compared to free SIM. Notably, LCL-SIM exerted its effects through a mechanism dependent on the tumor type. Thus, in melanoma-bearing mice, LCL-SIM inhibited TAM-driven oxidative stress and metastatic potential, primarily through the suppression of HIF-1α [1]. In contrast, in colon carcinoma-bearing mice, LCL-SIM reduced tumor growth via direct cytotoxic effects on tumor cells and by modulating the microenvironment, including anti-inflammatory and anti-angiogenic actions [2].

In parallel, our research has investigated EVs' ability to selectively deliver cytotoxic drugs that makes them ideal candidates for tumor-targeted drug delivery. In our recent studies, EVs derived from melanoma cells, when encapsulating DOX, demonstrated superior tumor growth inhibition compared to standard DOX liposomal formulations [3]. Furthermore, a combination of DOX-loaded EVs and SIM-loaded, IL-13-functionalized liposomes showed promising antitumor effects by disrupting the communication between TAMs and tumor cells [4].

Building on this, we are exploring EVs derived from activated dendritic cells as potential carriers for enhancing the efficacy of anti-PD-L1 immunotherapy in melanoma. This research aims to harness the natural properties of EVs to modulate the TME, enhance immune responses, and improve therapeutic outcomes in cancer treatment.

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