Breast Cancer Cell Membrane Coated Nanoparticles Induce Anti-inflammatory Macrophage Response

Rohini Kumar, Jessica Widman, Chelsea Kraynak, Laura Suggs
Department of Biomedical Engineering, University of Texas at Austin, Austin, TX.

Introduction: The tumor microenvironment (TME) comprises various cell types and signaling molecules that interact with and support tumor cells. Macrophages (MP) are the most abundant immune cell type in the TME, and tumor associated macrophages (TAMs) are known to promote tumor growth.[1] MP phenotype ranges on a spectrum between classically activated (M1) and alternatively activated (M2), depending on the MP environment. The M1 phenotype is inflammatory, while the M2 phenotype is anti-inflammatory and pro-tumor. Tumor-derived factors affect MP polarization in the TME. For example, tumor cells produce lactic acid which induces an M2-like phenotype.[2] Breast cancer has multiple subtypes which vary in expression pattern and prognosis, and accordingly, each subtype may behave differently in the TME. This study focuses on how two breast cancer cell lines (MDA-MB-231 and MCF-10a) interact with MPs derived from the human monocytic cell line THP-1 (THP-1-MPs). We explore how the TME affects MP phenotype by stimulating THP-1-MPs with cancer cell membrane coated nanoparticles (CCNPs), composed of poly(lactic-co-glycolic) acid (PLGA). Since PLGA releases lactic acid when degraded, we predict CCNPs will cause a shift to an M2-like phenotype. Additionally, the cancer cell membrane coating may amplify this effect by providing another component of the TME.

Materials and Methods: THP-1 cells were treated with PMA (100 nM) to induce differentiation into THP-1-MPs. Cancer cell membranes were isolated through differential centrifugation. Membranes were coextruded with PLGA nanoparticles to form cancer cell membrane coated nanoparticles, which were characterized through dynamic light scattering (not shown) and TEM. THP-1-MPs were incubated with CCNPs for 48 hours (150-200 ug/mL). Gene expression was analyzed through qPCR.

Results and Discussion: TEM images confirmed successful coating of PLGA to form CCNPs. Confocal microscopy confirmed uptake of CCNPs by cancer cells and THP-1-MPs (not shown). THP-1-MP phenotype changed following incubation with CCNPs or bare PLGA NPs. Expression of M2 marker VEGF increased, while expression of M1 markers TNFα and CXCL10 decreased. Additionally, CXCL10 expression was further reduced by CCNPs as compared to bare PLGA, indicating the potential of membrane coating to diminish the MP inflammatory response.

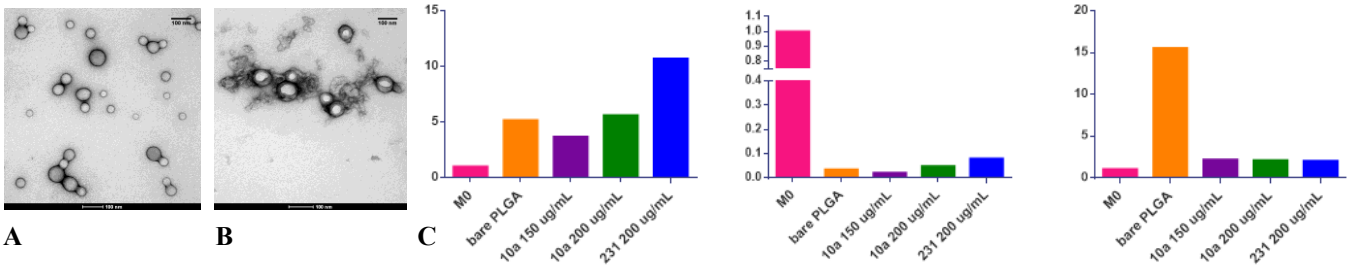

Figure 1. (A) TEM image of bare PLGA (B) TEM image of MCF-10a cell membrane coated PLGA (C) THP-1-MP gene expression in fold change after 48 h incubation with CCNPs at 150-200 ug/mL. Shows an increased expression of anti-inflammatory marker VEGF and decreased expression of anti-inflammatory markers TNF-α and CXCL10

Conclusions: We formed CCNPs from the combination of two TME components, cancer cell membrane and lactic acid, in order to determine their effects on MP polarization. MPs upregulate anti-inflammatory markers and downregulate inflammatory markers when incubated with CCNPs derived from aggressive breast cancer cell lines. In vivo, these results suggest that both factors, lactic acid and cancer cell membrane, may influence the shift to an M2-like phenotype. Since CCNPs have the potential to alter MP phenotype, future studies will attempt to make CCNPs induce an anti-tumor response in TAMs, creating an avenue for therapeutic potential.

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References: [1]Noy, Roy; *Immunity*, 2014, 41.1: 49–61. [2]Romero-Garcia, Susana, et al. *Front Immunol*, 2016, 7:52.