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"Phosphatidylserine Externalization in the Tumor Microenvironment: The Role of Lipid Scramblase TMEM16F and the P2X7 Receptor in Immunosuppression and Cancer Progression"

By

Rachael Pulica
PhD Biomedical Sciences
Molecular Biology, Genetics, and Cancer Program
Bachelor of Science, Gettysburg College, 2020

Thesis Advisor: Dr. Raymond Birge
Professor and Vice Chair
Department of Microbiology, Biochemistry, and Molecular Genetics

Thursday, September 10th, 2026
11:00 AM
Cancer Center, G-1196

Join Zoom Meeting:
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Abstract

The anionic phospholipid phosphatidylserine (PS) is typically confined to the inner side of the plasma membrane in healthy cells. In the tumor microenvironment (TME) of solid cancers, PS becomes constitutively externalized on the outer surface of the cell membrane on cancer and stromal cells, leading to an immunosuppressive phenotype, immune escape, and tumor progression. While previous studies have interrogated the binding of externalized PS by immune inhibitory receptors such as TAM (Tyro3, Axl, MerTK) receptors, as well as the mechanisms of PS externalization in healthy cells, the molecular mechanisms and signals by which PS becomes externalized in the TME are still not well understood. Here, we analyzed PS externalization by two unique mechanisms: calcium-activated scramblase TMEM16F and ATP-induced P2X7R (purinergic receptor 7). Knockout of TMEM16F in E0771 cells, which inhibits PS externalization from increases in cytosolic calcium, suppressed PS externalization upon exposure of cells to calcium ionophore, or after cells were treated with cell-permeable proteasomal inhibitor MG132 or glucose deprivation. Knockout of P2X7R blocks extracellular ATP-mediated PS externalization in a TMEM16F-independent manner, suggesting that both intracellular and extracellular triggers can induce PS externalization in tumor cells. Loss of function of either TMEM16F or P2X7R suppressed tumor growth in an immunocompetent orthotopic E0771 breast cancer model. Analysis of the tumor microenvironment by flow cytometry revealed that TMEM16F knockout tumors had increased immune cell and macrophage infiltration, while single-cell sequencing and flow cytometry of P2X7R knockout tumors revealed increased macrophage infiltration and M1 macrophage polarization, promoting an inflammatory TME. This reveals the immunosuppression induced by tumor-externalized PS and the potential to polarize the TME back to an inflammatory state. The tumor-exposed PS was then targeted using a novel chimeric fusion interferon (IFN) wherein an IFNβ-IFNλ fusion protein was connected to Gas6 using a flexible linker, resulting in the molecule Gas6IFNβλ. These molecules enhanced MHC Class I and PDL1, implying they are better used as a combination therapy than a monotherapy. Collectively, this thesis reveals the mechanism of action of two unique pathways for PS externalization, TMEM16F and P2X7R. We reveal how TMEM16F and P2X7R expression promote EO771 tumor growth, and that P2X7R shifts the immune system towards immunosuppressive, particularly through macrophage polarization. Finally, we propose a novel strategy to treat solid cancers using PS-targeting interferons. In total, this dissertation highlights the importance of PS externalization in tumor growth and immune polarization, and insights into therapeutic approaches.