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"Targeting Externalized Phosphatidylserine on Cancer Cells: From Mechanisms to Therapeutic Opportunities"

By
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Molecular Biology, Genetics, and Cancer Program

B.E. Biotechnology, 2018, PES University, India

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Professor and Vice Chair
Department of Microbiology, Biochemistry and Molecular Genetics

Thursday, January 30th, 2025
10:00 AM
Cancer Center, G1196

Join Zoom Presentation:

https://rutgers.zoom.us/j/95437120365?pwd=vu1UNiXQwyza0RCgX6ikR7iT9X3fOV.1

Meeting ID : 954 3712 0365
Password : 296257

ABSTRACT

Phosphatidylserine (PS) is an anionic phospholipid that is predominantly localized to the inner leaflet of the plasma membrane under homeostatic conditions. When cells undergo apoptosis, PS is externalized to the outer leaflet, and acts as an "eat me signal" for PS receptors (Tyro3, Axl and Mertk) on macrophages to initiate clearance through a highly tolerogenic process known as efferocytosis. Blockade of efferocytosis and the PS-PS receptor signaling axis (using monoclonal antibodies against PS or monoclonal antibodies against Mertk) has been shown to have beneficial outcomes in pre-clinical models of cancer such as reduced tumor growth and infiltration of T cells. However, the role of PS externalized by viable, stressed cancer cells on cancer outcomes, and the mechanisms of PS signaling and externalization in the tumor micro-environment (TME) are not completely understood. In this thesis, I interrogate several aspects of PS biology in the contect of cancer that includes: (i) Targeted degradation of PS receptors to reduce efferocytosis and oncogenic signaling (ii) Blockade of scramblases TMEM16F or Xkr8 to evaluate anti-tumor effects (iii) Usage of modified PS ligands to localize immunomodulatory domains or chemotherapy to the TME. Using an E0771 breast cancer model, we show that PS targeting monoclonal antibodies Bavituximab and 11.31 localize to the tumor microenvironmen indicating that this tumor model harbor a microenvironment of exposed PS. We observed that ablation of Xkr8 or TMEM16F on cancer cells reduced tumor progression in C57BL/6 WT mice, indicating that PS externalized on apoptotic cells and live tumor cells contribute to tumor growth. This anti-tumor phenotype was rescued in immune-deficient mouse models. Further analysis using gene expression profiling revealed that Xkr8 and TMEM16F mediated PS externalization influence the TME by unique mechanisms. Novel PS targeting therapeutics, consisting of modified PS ligands, ProS1 or Gas6, were characterized for their ability to preferentially bind to viable PS+ cells in vitro. Vitamin K dependent γ-carboxylation of the Gla domain was shown to be essential for PS binding. ProS1 (G+E) derivatives recognized live PS+ cells and blocked Mertk signaling in vitro. Gas6-IFN-β-λ fusion proteins bound preferentially to PS+ cells in a clustered pattern and showed anti-tumor effect by upregulating MHC I and PD-L1. In addition, the targeted degradation of PS receptors, Tyro3, Axl and Mertk (TAM) receptor kinases was achieved using three generations of heterobifunctional degraders specific to Mertk only, Axl and Mertk or all three TAMs. In conclusion, this thesis provides insight into the role of scramblases in the tumor and proof of concept to leverage novel strategies to target the PS-PS receptor signaling axis in cancer and virus infections.