JAMES MADISON UNIVERSITY

SEMINAR

Friday, April 5

Dr. Joseph J. Provost

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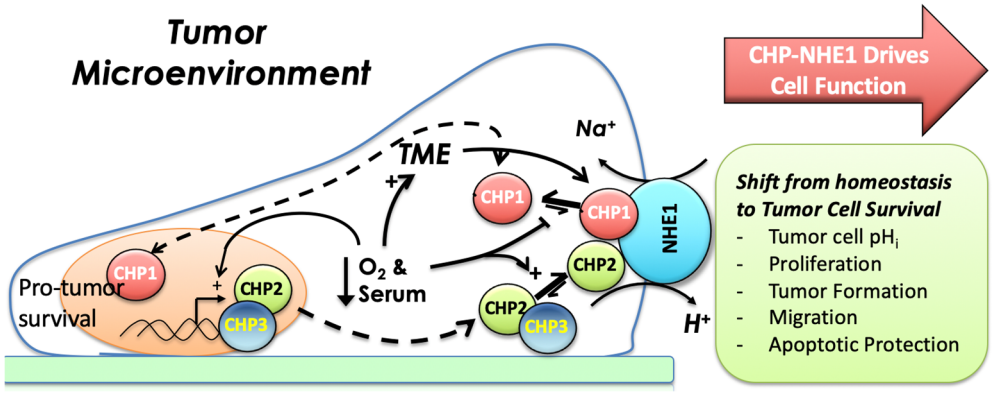
San Diego, CA

How the sodium hydrogen exchanger shapes the fate of lungs in cancer and fibrosis



The sodium-hydrogen exchanger (NHE) is a critical regulator of intracellular pH, playing a significant role in various physiological and pathological processes, including cell proliferation, migration, and survival. NHE's function has garnered attention due to its contribution to the altered cellular behaviors that of lung cancer and fibrosis. Nascent cancer cells develop a unique tumor microenvironment (TME) which influences cells to shift into a survival and growth mode. One of these inputs results in a move to a high anaerobic glycolysis rate resulting in increased acid production which is deleterious for the cancer cell. To survive, tumor cells are forced to compensate for the resulting increase in intracellular acidity, avoid apoptosis and continue to grow and migrate. In lung cancer, the overexpression of NHE1, a prominent isoform of the exchanger, has been linked to increased tumor growth, metastasis, and resistance to apoptosis. NHE1 facilitates an alkaline intracellular environment conducive to cancer cell proliferation and survival, while also promoting extracellular acidification, which can lead to tissue invasion and metastasis. The modulation of NHE activity affects various signaling pathways involved in cell cycle regulation, apoptosis, and epithelial-mesenchymal transition (EMT), crucial for cancer progression. Conversely, in lung fibrosis, NHE plays a role in fibroblast activation and the excessive deposition of extracellular matrix components, leading to tissue scarring and impaired lung function. The aberrant activation of NHE in lung fibroblasts contributes to the alkalization of intracellular pH, which is necessary for fibroblast proliferation and the synthesis of collagen and other fibrotic markers. We have studied the dual role of NHE in lung cancer and fibrosis, as a molecular switch in the regulation of cellular behaviors that contribute to disease pathogenesis. Targeting NHE and its downstream signaling pathways offers a promising avenue for the development of novel therapeutic strategies aimed at inhibiting cancer progression and fibrotic remodeling in the lung.

Seminar 3:30pm, King 159