Vacuolar H+-ATPases in tumor angiogenesis

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Intracellular pH regulation plays a fundamental role in the regulation of most, if not all cellular processes. Several pH regulatory mechanisms control pH homeostasis: Na+/H+ exchanger, HCO3--based H+ regulatory systems and proton ATPases. V-H+-ATPases regulate pH in endocytic compartments. In some cells, V-H+-ATPases are located at the cell surface, and work to maintain pH homeostasis and to extrude acid needed for the activity of extracellular proteases. **Erro! Nenhuma sequência foi especificada.**Angiogenesis, i.e., new blood vessel formation, is required in physiological and pathological states. In cancer, angiogenesis is increased to allow for growth, invasion and metastasis. The tumor and angiogenic cells micro-environment is acidic and not permissive for growth. We have shown that to survive,highly metastatic and angiogenic cells employ V-H+-ATPases at their plasma membranes (pmV-ATPases) to maintain an alkaline pHcyt. However, in lowly metastatic and in non-angiogenicendothelial cells from larger vessels, the pmV-ATPase and the cell invasiveness are decreased. Therefore, overexpression of pmV-ATPase is important for cell invasion, and essential for tumor progression, angiogenesis and metastasis. Cancer isanheterogeneous disease that involve many different proteins and signaling pathways. Changes in pHcyt have been associated with the regulation of a myriad of proteinsandsignaling molecules affecting many if not all cellular functions. Since changes in pHcyt are pleiotropic, we hypothesize that alteration in a single protein, pmV-ATPase that can regulate pHcyt, may explain the dysfunction of many proteins and cellular pathways in cancer. Our long term goal is to determine the molecular mechanisms by which pmV-ATPase expression regulates tumor angiogenesis and metastasis.