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Selective Acidification and De-energization of Cancers with Lonidamine for Sensitization to Chemo and Radiation Therapy

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As a consequence of high levels of aerobic glycolysis, tumors exhibit an acidic extracellular pH (pHe) and a neutral to alkaline intracellular pH (pHi) leading to an acid-outside/neutral to mildly alkaline inside plasmalemmal pH gradient. This gradient also impacts tumor response to certain chemotherapeutic agents and to radiation therapy, hyperthermia, and photodynamic therapy. Manipulation of pHe and/or pHi of tumors have considerable impact on tumor growth and metastasis as well as response to therapy. Extracellular tumor acidification has been modified by administering sodium bicarbonate in order to increase the pHe and thereby reduce tumor invasiveness and facilitate uptake of weakly basic chemotherapeutic drugs. In contrast, our aim was to decrease the pHi in order to increase the intracellular activity of N-mustards and doxorubicin against varoius cancer xenografts. We accomplished this by administering lonidamine (LND, 100 mg/kg, intraperitoneal), an inhibitor of the monocarboxylate transporter (MCT), mitochondrial pyruvate carrier and complex II of electron transport chain that blocks cellular export of lactic acid and also inhibits transport of pyruvate into mitochondria, thereby inhibiting tumor energy production. LND sensitizes tumors to radiation therapy by increased tumor oxygenation and decreased ATP levels and decreased levels of glutathione. Other MCT inhibitors such as AZD3965, manufactured by AstraZeneca, alone or in combination with complex I inhibitors (metformin, phenformin) may exhibit similar properties to LND in modifying tumor pHi and bioenergetics. These agents may, therefore, play an important role in modifying the tumor microenvironment to make more susceptible to certain classes of chemotherapeutic agents and to radiation therapy.

Biography

Kavindra Nath is a Research Assistant Professor at the University of Pennsylvania, Perelman School of Medicine. He did PhD. in Magnetic Resonance Imaging and Spectroscopy (MRI/MRS) from premier medical institution in India. In PhD. he studied the role of MRI and MRS techniques in the differential diagnosis of cystic intracranial mass lesions in patients. His current research at University of Pennsylvania is utilizing multi-nuclear (^{1}H, ^{31}P, ^{13}C) MRS and other techniques *in vitro* and *in vivo* in order to delineate the mode of action of various monocarboxylate transports, mitochondrial pyruvate carrier and electron transport chain inhibitors, which distinguishes normal cells from malignant cells and potentiates the activities of various chemotherapeutic drugs, radiation therapy and hyperthermia in a variety of human cancers. He has published more than 30 papers in reputed journals and has been serving as an editorial board member of many reputed journals.

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