Angeli's Salt-Dependent Generation of Hydroxyl Radical: Possible Cancer Treatment?

Detcho A. Stoyanovsky[1], Guy Salama[2], Robert M. Clancy[3], Nina F. Schor[4], Karen D. Nylander[4], and Hal Wrigley[5]

[1]Dept. of Surgery, MUH-NW654, University of Pittsburgh, 3459 Fifth Ave, Pittsburgh, PA 15213
[2]Cell Biology and Physiology, School of Medicine University of Pittsburgh A115 Scaife Hall 3550 Terrace St. Pittsburgh, PA 15261
[3]Department of Rheumatology, NYU School of Medicine, 301 East 17th Street, New York, NY 10016
[4]Departments of Pediatrics, Neurology, and Pharmacology, University of Pittsburgh, and Pediatric Center for Neuroscience, Children's Hospital of Pittsburgh, Pittsburgh, PA 15213
[5]pHroCure, LLC, 100 Rudolph Lane, Wexford, PA 15090

Structural studies at the molecular level have focused on the design of new anticancer drugs that do not have the limitations found with conventional drugs, such as the lack of selectivity for cancer cells and resistance phenomena. An ideal cancer prodrug would be completely inactive until metabolized by a molecular event unique to neoplasm. The intense metabolism of glucose to lactic acid, as well as the hydrolysis of ATP in the neighborhood of hypoxic tumors, lead to acidification in the microenvironment of these neoplasms. In actively glycolyzing tumors, the extracellular pH is in the range of 6.0 to 7.0, whereas the extra- and intra-cellular milieu of normal tissues has a pH of 7.4. These tumor pH gradients might be used for targeting of cancer tissue, inasmuch as a preferential metabolic activation of anti-cancer drugs to toxic species may be envisaged in the more acidic extracellular environment of cancer tissues. In this study, we present experimental evidence that the H^+-dependent, nitroxyl anion (NO^-)-induced production of •OH may prove to be selectively toxic to tumor cells. We have found that the NO^--dependent production of •OH was 40 times higher at pH 6.0 than at pH 7.4. In weakly acidified solutions, NO^- exhibited strong toxicity to cancer cells that was inhibited by •OH-scavengers; no toxicity was observed at pH 7.4. The treatment of tumor-bearing mice with nitroxyl anion donors resulted in a pronounced inhibition of the tumor growth (up to 90 %), suggesting that the H^+-amplified, nitroxyl anion-dependent production of •OH could be a selective mechanism for destruction of tumor tissue.