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Manipulating tumor acidification as a cancer treatment strategy.

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Manipulation of the extracellular and/or intracellular pH of tumors may have considerable potential in cancer therapy. The extracellular space of most tumors is mildly acidic, owing to exuberant production of lactic acid. Aerobic glycolysis - attributable largely to chronic activation of hypoxia-inducible factor-1 (HIF-1) - as well as tumor hypoxia, are chiefly responsible for this phenomenon. Tumor acidity tends to correlate with cancer aggressiveness; in part, this reflects the ability of HIF-1 to promote invasiveness and angiogenesis. But there is growing evidence that extracellular acidity per se boosts the invasiveness and metastatic capacity of cancer cells; moreover, this acidity renders cancer cells relatively resistant to the high proportion of chemotherapeutic drugs that are mildly basic, and may impede immune rejection of tumors. Thus, practical strategies for raising the extracellular pH of tumors may have therapeutic utility. In rodents, oral administration of sodium bicarbonate can raise the extracellular pH of tumors, an effect associated with inhibition of metastasis and improved responsiveness to certain cytotoxic agents; clinical application of this strategy appears feasible. As an alternative approach, drugs that inhibit proton pumps in cancer cells may alleviate extracellular tumor acidity while lowering the intracellular pH of cancer cells; reduction of intracellular pH slows proliferation and promotes apoptosis in various cancer cell lines. Well-tolerated doses of the proton pump inhibitor esomeprazole have markedly impeded tumor growth and prolonged survival in nude mice implanted with a human melanoma. Finally, it may prove feasible to exploit the aerobic glycolysis of cancers in hyperacidification therapies; intense intracellular acidification of cancer cells achieved by induced hyperglycemia, concurrent administration of proton pump inhibitor drugs, and possibly dinitrophenol, may have the potential to kill cancer cells directly, or to potentiate their responsiveness to adjunctive measures. A similar strategy, but without proton pump inhibition, could be employed to maximize extracellular tumor acidity, enabling tumor-selective release of cytotoxic drugs encased in pH-sensitive nanoparticles.