Heterogeneity of tumor perfusion and pH measured by MRI/MRS.

Dynamic contrast enhanced MRI monitors the time course of signal enhancement following a bolus injection of contrast agent, usually Gd-DTPA (Magnevist®). The time-dependent signal enhancement kinetics can be analyzed on a pixel-by-pixel basis using a variety of algorithms to yield values for vascular density and the capillary permeability-surface area product. These analyses illustrate that virtually all solid tumors, in animal models as well as human patients, are heterogeneously perfused. Regions of high perfusion co-exist with regions with virtually no perfusion.

The poorly perfused volumes are important both therapeutically and biologically. Because they are hypoxic and aciditic, they are resistant to radio- and chemotherapies. Under controlled, in vitro, conditions hypoxia and acidity also lead to development of more aggressive tumorigenic phenotypes.

Poorly perfused regions likely correspond to the hypoxic volumes that can be visualized with PET, SPECT or MRI. Hypoxic regions are resistant to ionizing radiotherapy due to the generation of longer lived reactive species. Cells under hypoxic conditions must derive their energy from glycolysis, the end-product of which is lactic acid. The combination of poor perfusion and high glycolysis is the likely major cause for the acidic extracellular pH seen in tumors.

Acidic extracellular pH (pHe) in tumors can be measured non-invasively using 31-P MRS. This approach also allows the pH distribution across tumors to be measured, which shows that some tumor cells exist under very acidic pHe conditions (e.g. 6.2). More recently, regional pHe distributions have been measured using 1-H spectroscopic imaging, which allows spectra from multiple voxels to be obtained simultaneously. These measurements show large regional variations in tumor pHe, which are likely due to perfusion heterogeneity.

Acid pHe in tumors leads to a “physiological” resistance to weakly basic chemotherapeutics, such as anthracyclines. This occurs via a mechanism of “ion trapping” wherein weakly basic molecules are sequestered in relatively acidic compartments. In the case of tumors, ion trapping favors drugs to be retained in the interstitium, and not enter the cells. The extracellular space can be alkalinized with bicarbonate, and this leads to increased sensitivity of tumors to anthracyclines, such as doxorubicin or mitoxantrone. The acidic pHe of tumors can also affect the process of tumorigenesis itself since, in vitro, acid pHe causes transformation, mutation and chromosomal rearrangements.