Diminished Aqueous Microviscosity of Tumors in Murine Models Measured with in Vivo Radiofrequency Electron Paramagnetic Resonance

Howard J. Halpern, G. V. R. Chandramouli, Eugene D. Barth, Cheng Yu, Miroslav Peric, David J. Grdina, and Beverly A. Teicher


ABSTRACT

Using very low frequency in vivo electron paramagnetic resonance (EPR), we have compared, for the first time, the average microviscosity of the total aqueous compartment of murine fibrosarcomas and that of normal leg tissue in a living animal. EPR spectra from dissolved nitrooxide spin probes report the solvent microviscosity. The tumor aqueous microviscosity, 1.8 ± 0.1 centipoise, was significantly lower than that of the corresponding normal tissue, 2.9 ± 0.3 centipoise, a difference of 38 ± 7%. These results confirm the commonly observed increase in the water proton transverse relaxation times (T2) in magnetic resonance imaging of hyperproliferative states, for example, malignancy. The specificity of the localization of the EPR signal indicates a substantial portion of the T2 increase seen in magnetic resonance imaging derives from decreased bulk-water viscosity. The effect of this microviscosity differences may be the basis of several physiological differences between tumors and normal tissues which could confer a growth rate advantage to tumor tissue.

INTRODUCTION

MRI is sensitive to alterations in tissue water induced by hyperproliferative tissue states, particularly malignancy (1–6). Regions of increased signal intensity in T2 weighted magnetic resonance images are commonly taken to define the spatial or anatomical extent of a malignant tumor determined by biopsy (3), the stage of uterine cervical malignancy (3, 4), and the tumor response to the antiproliferative effects of radiation therapy (5); malignancy and substantial increases in the T2 of tumor water protons are common spatial correlates in routine clinical magnetic resonance images. An extensive analysis of the literature of normal tissue and tumor relaxation measurements of water proton relaxation times (both T2 and T1) shows large increases in tumor relaxation times relative to normal tissue (7, 8). Diffusion weighted water proton MRIs confirms the increase in transverse relaxation time seen in malignant tissue relative to normal tissue (9).

What aspects of the malignant cell or tissue contributes to the change in the water relaxation times? It is commonly accepted that T2 depends principally on bulk-water viscosity, restricted diffusion, and protein/macromolecule hydration (8). In addition, local susceptibility heterogeneity due principally to iron in deoxyhemoglobin can affect T2 (T2*). Definition of the specific changes in architecture that gives heterogeneity due principally to iron in deoxyhemoglobin can affect T2 (T2*).

Part of the difficulty in correlating general tissue and cellular structural motifs with the water proton T1 and T2 lies in the large relaxation time magnitude: on the order of 0.1 s for T2 and 1 s for T1. During this time, the water molecule can diffuse through linear distances of as many as ten cell diameters. The relaxation time will reflect the average effect of rotational diffusional limitations from all of the potential contributions to T2 mentioned above. This duration-related averaging makes it difficult to distinguish the individual effects exerted by the varied environments (11).

Classically both NMR and EPR spectra have been used to characterize solvent viscosity. Water proton NMR and MRI directly interrogate water solvent molecules. EPR uses a paramagnetic substrate molecule with a stable unpaired electron spin to report solvent viscosity. The rotational hindrance encountered by the both the EPR substrate molecule and the water molecule depends on the solvent viscosity through the Brownian collisions with the solvent molecules. At higher viscosity, a higher collision rate or more effective collisions will slow the unhindered rotation of the EPR substrate molecule and increase its rotational autocorrelation time (12, 13). The autocorrelation time is measured in the spectral line width and is inversely proportional to T2. Many varieties of small EPR substrate molecules with the molecular weight approximately that of hexose sugars are available. Their solubility characteristics can be modified to target various tissue water compartments (the extracellular, the intravascular, and, potentially, the intracellular compartment). Measurements of water characteristics, particularly viscosity, using EPR are made using these substrates as molecular reporters.

The EPR relaxation times of dissolved nitroxides are roughly six orders of magnitude shorter than water proton NMR relaxation times. During the EPR excitation, the spin probe will diffuse only a few molecular diameters providing a very localized measure of tissue fluid viscosity (14). Because of the nanometer or subnanometer radius sampled in the EPR spectrum from a dissolved nitro oxide, we refer to the reported viscosity as microviscosity (15). Signals from nitroxides located in different environments such as the membrane either are easily separable (16) or are broadened so much that they are undetectable (17). The EPR spectra are, therefore, more specific in their sensitivity to the viscosity of tissue bulk water than water proton NMR-based measurements. They also measure a slightly different aspect of viscosity, that encountered by a molecule the size of hexose sugar as a model of small molecular solutes. Finally, the development of in vivo EPR imaging promises a new imaging modality, electron paramagnetic resonance imaging (EPRI) that will allow images of these tissue characteristics analogous to those provided by nuclear MRI (18–21). From the increased local specificity and the ability to target specific water compartments, EPRI viscosity images may provide important additional information to that available from nuclear MRI. To investigate the widely observed differences between tissue and tumor NMR T1 and T2, to probe aqueous compartment microviscosity differences between tumor and normal tissue, and to indicate the extent to which increases in NMR relaxation times may be due to decreases in aqueous microviscosity, EPR measurements were undertaken. Preliminary measurements presented elsewhere showed a lower microviscosity from tumor tissue than had been reported in mammalian cells (22).

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2 To whom requests for reprints should be addressed, at University of Chicago Medical Center, Department of Radiation and Cellular Oncology, 5841 South Maryland Avenue, MC 1105, Chicago, Illinois 60637.
3 The abbreviations used are: MRI, magnetic resonance imaging; T2, transverse relaxation time; T1, longitudinal relaxation time; NMR, nuclear magnetic resonance; EPR, electron paramagnetic resonance; EPRI, electron paramagnetic resonance imaging; PBS, fetal bovine serum; CTPO, 3-carbamoyl-(2,2,5,5)-tetramethyl-3-N-pyrrolin-1-yloxy; mHCTPO, 4-protio-3-carbamoyl-(2,2,5,5)-tetraperdeuteromethyl-3-15 N-pyrrolin-1-yloxy; cP, centipoise; IFN, interferon; TPA, 12-0-tetradecanoylphorbol.

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MATERIALS AND METHODS

EPR spectral line shapes from dissolved nitroxide spin probes report solvent viscosity (23, 24). The spectral readout is provided by a radiofrequency EPR spectrometer (19) capable of measurements in vivo deep in tissue.

Very-Low-Frequency EPR Spectrometer Conditions. A low-frequency EPR spectrometer described previously (19) was operated at approximately 260 MHz (g = 2 field of 93 G) for these measurements. The resonator volume, a cylinder 1.5 cm long and 1.6 cm in diameter, comfortably accommodated the tumor-bearing leg of the C3H mouse with high filling factor (22). With the mouse leg and tumor in the resonator, giving a loaded Q (quality factor) of approximately 150, a radiofrequency a power of 3 mW produced a magnetic field (B0) of 0.1 G. The modulation frequency was 5.12 kHz, with a modulation amplitude of 0.1 G. A microcomputer controlled the data acquisition. Spectra were obtained with 246 points per scan, 5 scans per spectrum, and a time constant and point acquisition time of 0.1 s, yielding a spectral acquisition time of approximately 2.5 min for each of the two nitrogen manifolds.

Injectable Spin Probe. mHCTPO, also called monohydrogenated CTPO (25), was used as the infusible spin probe. Fig. 1 shows its structure (bottom) with its spectrum (top and middle). The use of deuterium in the methyl groups diminishes inhomogeneous broadening due to the methyl hydrogens by a factor of four, thus narrowing the spectral lines (25). The individual manifold spectral profile is a doublet split by the lone ring hydrogen as shown in Fig. 1. The mHCTPO toxicity was extremely low.4 The octanol partition coefficient has been measured to be 2.6 (26), consistent with a distribution in both lipid and the total body water. No lipid signal is seen, which indicates that the spin probe is sufficiently broadened in lipid as to be undetectable. Using extracellular broadening agents, the partitioning of the spin probe was measured to be consistent with the total body water (26). By using the paramagnetic contrast agent character of the spin probe for MRI T1 images, we validated a macroscopic distribution uniformity (26). The half-life of the spin probe in tumors was approximately 25 min.

Spectral Analysis. A shape hypothesis dependent on a number of spectral parameters was fitted to the spectral data as described (27) to minimize x2. The shape hypothesis was a doublet sum function approximation to the Voigt (or Lorentzian-Gaussian convolution) shape. Each line of the doublet was fit to the function

\[ F_H(B(x)) = -\tau_{\text{po}} \left( \frac{8x}{(3 + x^2)} + (1 - \tau_{\text{lo}}) \frac{e^{4/2x}}{2} \exp \left( \frac{-x^2}{2} \right) \right) \]

where \( \tau_{\text{po}} \) = overall amplitude; \( \tau_{\text{lo}} \) = normalized, variable Lorentzian weight; \( x = 2(B - B_0)/\Delta B \); \( B_0 \) = line center; \( \Delta B \) = peak-to-peak line width common to both the Gaussian and the Lorentzian components; individual terms are normalized to unit \( V_{\text{pp}} \). To this, a linear baseline was added. Line widths \( \Delta B \) within each nitrogen doublet were considered to be equal. Each nitrogen manifold was fitted separately. A Levinberg-Marquardt nonlinear least-squares fitting algorithm was used to minimize \( x^2 \). The fit, indicated by the line in Fig. 1, demonstrates the adequacy of \( F_H \). The spectral parameters that are relevant to this discussion are the separate nitrogen manifold line widths \( \Delta B_1 \) and \( \Delta B_2 \).

Measurement Uncertainty. Uncertainty in spectral parameter estimates derived from the error matrix is due to random fluctuations and artifacts from animal motion. (27) Parameter uncertainties are propagated to estimate uncertainties in the viscosity measurements. Several measurements were made from each tumor. The nitrogen manifold line widths so obtained agreed to within the fluctuation-derived uncertainties, as did the differences in the line widths.

Microviscosity Measurement. We use the term microviscosity (15) to refer to the average viscosity of the multiple aqueous environments of the heterogeneous milieu of living tissue sampled by the spin probe. The EPR measurements of such averages in a heterogeneous milieu are meaningful because the spectral line-width differences vary linearly with microviscosity in the measured region. The linear response of EPR line-width differences to microviscosity is important to insure that two nondistinguished subvolumes with different microviscosities will report a microviscosity that is the true volume-weighted average of their microviscosities. This linear response of the line-width differences to microviscosity allows calibration with uniform solutions, as discussed previously (26). From elementary line-width theory, rotational diffusion constants can be related to the spectral line-width differences, \( \Delta B_2 - \Delta B_1 \) (23, 24). The Stokes-Einstein model relates solute rotational diffusion constants to solvent viscosity (24). From these, the following relationship between the differences between line widths in the two \( ^{15}N \) manifolds (Fig. 1) \( \Delta B_1 \) and \( \Delta B_2 \), denoted \( \Delta \Delta B \), and the viscosity \( \eta \) can be derived,

\[ \Delta \Delta B = \Delta B_2 - \Delta B_1 = \frac{4\pi \eta R^2}{3kT} \]

where \( R \) is the spin probe radius, \( T \) is the solution temperature, \( F \) is a model-dependent constant and \( k \) is Boltzmann’s constant. We previously showed linearity between \( \Delta \Delta B \) and the viscosity of uniform aqueous solutions; with solutes as disparate in average molecular weight (over two orders of

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4 E. D. Barth and H. J. Halpern, unpublished data.
mice i.p. 10 min after the anesthesia injection. The cellular milieu was modeled with uniform solutions of FBS (Life Technologies, Inc., Grand Island, NY) and glycerol (Fisher Scientific, Fair Lawn, NJ; Refs. 22, 28). FBS was desiccated to volumes once, one-half, one-third, and one-quarter that of native FBS. The viscosity of the FBS solutions was measured with a falling ball Viscosimeter (Gilmont Instruments, Barrington, IL) oriented 15 degrees from the vertical. Glycerol solutions were prepared to have viscosities equal to those of the four FBS solutions by using the CRC tables (29) and verifying them with the Viscosimeter. Viscosities of solutions of 0.9% weight sodium chloride (154 mM) makes any

magnitude (as the components of FBS (principally albumen by weight) and glycerol, the $\Delta B$ over the relevant viscosity interval is constant, and constants of proportionality are similar (22). Because $\Delta B$ is a difference between line widths, it will be insensitive to environmental effects that will similarly broaden both manifolds, like oxygen and other paramagnetic species in the environment.

**Calibration.** The cellular milieu was modeled with uniform solutions of FBS (Life Technologies, Inc., Grand Island, NY) and glycerol (Fisher Scientific, Fair Lawn, NJ; Refs. 22, 28). FBS was desiccated to volumes once, one-half, one-third, and one-quarter that of native FBS. The viscosity of the FBS solutions was measured with a falling ball Viscosimeter (Gilmont Instruments, Barrington, IL) oriented 15 degrees from the vertical. Glycerol solutions were prepared to have viscosities equal to those of the four FBS solutions by using the CRC tables (29) and verifying them with the Viscosimeter. Viscosities of solutions of 0.9% weight sodium chloride (154 mM) were also measured with the Viscosimeter. $\Delta B$ was measured with 100 $\mu$m spin probe in all solutions.

**Tumor and Murine Models.** The murine tumor models were 12 mm diameter FSa (30) and NFSa fibrosarcomas (31). Both tumor models exhibited minimal necrosis at the 12-mm size used. Fourth-generation cells were obtained through the generosity of Dr. L. Milas and K. Mason at M.D. Anderson. In the above solutions.

**RESULTS**

Maximum signal in the tumor appeared several minutes after the i.p. injection. The EPR spectra from the spin probe in a normal leg and a tumor are shown in Fig. 1. The nitrogen hyperfine splitting measured in these spectra is consistent with an aqueous distribution (22). Fig. 1 shows a difference between the two $^{14}$N manifold line widths, $\Delta B_1$ and $\Delta B_2$. This is reflected in the difference between the heights of the right (upfield) and left (downfield) spectral manifolds. The height and width difference is more pronounced in the normal leg spectrum than in the tumor. Thus, the distinction between tumor and normal tissue can be seen in the raw spectra.

The legs of the mice, consisting of 70% muscle by weight, were used as the normal tissue for comparison with the tumors. Spectra were obtained with a resonator whose sensitive volume encompassed the tumor and a portion of the adjacent leg. Line width differences $\Delta \Delta B = \Delta B_2 - \Delta B_1$ derived from spectra as in Fig. 1 and Eq. B based on a FBS calibration, gave quantitative measures of the aqueous microviscosity of 18 NFSa tumors and 20 FSa tumors. In addition, measurements were made in 10 normal legs and 4 normal legs of tumor-bearing animals. The latter group was included to determine whether there was a systemic effect from a distant tumor (32). The results are presented in Table 1 and Fig. 2. Because the correction for the normal tissue contribution to tumor measurements would only have increased the difference between the normal tissue and tumor measurements and because the correction is small and within the experimental errors, no attempt was made to make this correction. The difference between microviscosities of different tumor types and the difference between the microviscosities of normal legs of animals with and without tumors were statistically insignificant ($P = 0.24$ and $P = 0.12$, respectively).

The mean aqueous microviscosity of all of the tumors was $1.8 \pm 0.1$ cP. The mean aqueous microviscosity of the corresponding normal tissues was $2.9 \pm 0.3$ cP. This $38 \pm 7\%$ normal tissue/tumor microviscosity difference was statistically significant ($P < 0.001$). Fig. 2 shows the microviscosity for each tumor of both types ( ), plotted as a function of tumor mass. The microviscosity of each of the normal legs ( ) is also plotted against an arbitrarily assigned sample number. The populations separate visually. It is unlikely that these differences are due to a temperature difference between tumor and normal tissue because of (a) the size of the microviscosity difference; and (b) the close experimental regulation of normal tissue and tumor temperature. The difference between the viscosity of sodium chloride and distilled water, 0.024 cP (3.5%) at 37°C, makes any

### Table 1: Viscosities, in cP, of both tumor types and of non-tumor-bearing normal tissues from which the tumors originated.

<table>
<thead>
<tr>
<th>Tissue or tumor</th>
<th>Viscosity (mean in cP)</th>
<th>SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>FSa fibrosarcoma</td>
<td>1.66</td>
<td>0.13</td>
</tr>
<tr>
<td>NFSa fibrosarcoma</td>
<td>1.92</td>
<td>0.18</td>
</tr>
<tr>
<td>Normal leg, non-tumor-bearing mouse</td>
<td>2.65</td>
<td>0.33</td>
</tr>
<tr>
<td>Normal leg, tumor-bearing mouse</td>
<td>3.7</td>
<td>0.4</td>
</tr>
</tbody>
</table>

The significance of the differences between groups is described in the text.
electrolyte concentration differences between tumor and normal tissue an unlikely source of this microviscosity difference. As discussed in “Materials and Methods,” the measurement technique is insensitive to tissue and tumor oxygen status or to the presence of other paramagnetic species.

DISCUSSION

Relationship with NMR and MRI Data. The 38 ± 7% difference reported here between mouse fibrosarcoma and normal tissue microviscosity is, to our knowledge, the result of the first direct measurements using EPR comparing the microviscosity of a malignant tissue and its normal analogue in a living animal. The normal tissue viscosity of 2.9 ± 0.3 cP, obtained in this study, is consistent with the aqueous microviscosity measured previously with EPR in three types of isolated nonmalignant cells (16, 17, 33). The EPR microviscosity difference between tumor and normal tissue of 38 ± 7% is similar in magnitude and sign to the 45% difference in water hydrogen NMR 1/T2 and the 27 ± 3% difference in 1/T1 between tissue specimens of the Walker sarcoma and rat rectus muscle tissue (34). The microviscosity difference reported here is similar to the decrease of up to 48% in 1/T1 as HeLa cells pass into divisional cycle relative to the minimum in G1 phase (35). Both of these water proton NMR parameters depend linearly on microviscosity at these microviscosity values. The similarity of the fractional difference in NMR 1/T2 and 1/T1 in the Walker rat sarcoma/normal tissue and the microviscosity differences in the C3H mouse sarcomas/normal tissues described here suggests that the NMR differences may be due in large part to changes in water compartment microviscosity.

Many groups have noted the strong correlation between tumor water content and both T1 and T2 (36, 37). Bottomley et al. have examined an extensive NMR literature to identify the tissue factors that influence NMR 1/T2 and 1/T1 in various normal (7) and pathological states (8). A major factor in the increase in 1/T2 in tumors was the change in tumor water content. The mechanism of changes in 1/T1 seems to be more complex. These data are consistent with a major difference in bulk-water microviscosity differences between tumors and normal tissues. These measurements, like the EPR measurements, do not distinguish between intracellular and extracellular water compartments.

Speculation on the Origin of the Difference in Microviscosity between Normal and Tumor Tissue: Correlation with Other Data. In addition to T2 measurements (35), other sources suggest that intracellular water microviscosity is diminished during cellular proliferation. For low-viscosity solutions, the specific viscosity is proportional to the concentration of solute (38, 39). As bulk water is added to a solution, solute concentration diminishes, and the viscosity diminishes. Tumors provoke an inflammatory response that is accompanied by increased tumor vascular permeability. (40) Breast cancer may be distinguished from nonmalignant states on the basis of an increased tumor capillary permeability-area product (41). This leads to increased bulk-water extravasation. The facile exchange of water between extracellular and intracellular environments, in turn, may transfer this increase in bulk water to the intracellular compartment and decrease the microviscosity of intracellular water.

The swelling of cells as they are stimulated to divide from increased electrolyte and osmotically driven bulk-water intake has been widely reported (42–45). This will decrease the microviscosity of intracellular water. For example, an influx of K+ acting against the normal K+ concentration gradient, has been seen minutes after the exposure of NIH 3T3 cells to mitogenic stimulation (42). Glucocorticoid-inducible transforming Ha-ras, which induces growth-factor-independent mitosis, also stimulated the furosemide-sensitive, ouabain-independent K+ transport system with an increase in cell volume (44). Factors that inhibited the mitogenic stimulation by the transforming Ha-ras or the mitogen bombesin also inhibited uptake of K+ analogue. Furosemide blockage of K+ uptake inhibited mitogenesis. Thus cell division and increased cell volume are tightly coupled. Similar data (43) have led to the hypothesis of a cell volume trigger for mitosis (43, 45). The magnitude of the volume changes (44) is similar to the magnitude of the viscosity changes measured here in vivo. Our measurements indicate that the electrolytes themselves have a minimal effect on water viscosity. Thus, the water influx will increase the solvent volume and reduce the microviscosity.

Changes in the aqueous microviscosity may occur early in tumorgenesis. Interaction of an immune surveillance mechanism with abnormal tumor cell antigens early in tumor development can lead to an inflammatory reaction with increased local free water (46) and a decrease in microviscosity. Carcinogens often affect vascular permeability. For example, of the α-, β-, and γ-IFNs added to a TPA-skin carcinogenesis protocol in mice, only γ-IFN was reported to induce a dose-dependent increase in vascular permeability (47). Only γ-IFN demonstrated copromotion of skin cancers (48) whereas α and β IFN had no copromotional capability. Tumors have been observed to develop only at the site of a needle wound in chicks carefully injected at a different site with Rous sarcoma virus (49). Tumors developed at distant wound sites or at sites of injection of growth factors that generated an inflammatory reaction. Injection at distant sites of growth factors that did not produce inflammation and/or an increase in vascular permeability failed to generate tumors. Blockage of the vascular permeability change induced by the growth factor blocked tumor development (49).

A change in aqueous microviscosity may occur later in tumor development. As neoplastic cells proliferate, they cause collapse of thin-walled vessels that provide fluid efflux (50) while stimulating fluid influx by angiogenesis (51). Increased intravascular hydrostatic pressure develops. Bulk water will extravasate from the clogged vessels and reduce local microviscosity.

It has been recently demonstrated that the extracellular matrix has a profound effect on cellular differentiation and growth (both normal and abnormal; Refs. 52, 53). The microviscosity changes reported here may affect the extracellular fluid, accelerating the signaling by the extracellular matrix proteins (53) by increasing diffusion rates and allowing more facile cell migration. Thus, reduced microviscosity may facilitate local invasion.

Gordina et al. (54, 55) have investigated the relationship between cell density subpopulations and the proliferation kinetics of cells from these subpopulations using the FSA tumor cells used in this study. Subpopulations with lower density and larger cell volumes had an increased ability to form lung colonies, a model of lung metastases. The lower-density, larger cells seem to have a lower aqueous microviscosity. Thus, increased metastasis correlated with lowered microviscosity.

It is tempting to hypothesize that these variations in microviscosity may be related to the fundamental sensitivity of all chemical reaction rates to the viscosity of the solution in which these reactions take place (56). In the high damping limit—microviscosity greater than ~1 cP—chemical rate constants are inversely proportional to microviscosity for simple bimolecular reactions (k) (56, 57), enzymatically catalyzed chemical reactions (kcat) (58, 59), and membrane-bound enzymes with extramembrane domains (60). A 40% reduction in the microviscosity will increase chemical rate constants k and kcat by 60% (56, 58, 60). The effect on kcat is not simply due to increased diffusion of substrates to the active sites. Microviscosity affects the rate at which the catalytic protein can adapt its conformation to accommodate its substrates. The ease and frequency of these “breathing”
motions depend on the hindrance to random motion presented by the solvent. Lower viscosity solvent will give lower hindrance, more facile random motion, optimum adaptation to substrate, and higher $k_{\text{cat}}$ (58, 59).

Such increases in chemical reaction rates may be a part of the regulation of malignant and nonmalignant growth. Cellular volume increase, as in the trigger for mitosis, and lowered microviscosity would provide a means of generally accelerating protein synthesis in preparation for mitosis. Acceleration of chemical reactions, due possibly in part to microviscosity changes, is consistent with the observation that the temperature of breast cancer tissue is greater than that of normal breast parenchymal tissue, the basis of thermography, used in the diagnosis of breast cancer (61). Elevated tumor temperature in turn correlated with both a reduction of tumor doubling time and an increased probability of metastasis (62). Thus, we hypothesize an overall acceleration of chemical kinetics in tumors, a condition that could be generated by a reduction of tumor microviscosity in addition to other changes in the regulation of genes and gene products (63–65). This remains hypothetical until the testing with microviscosity measurements in simpler cellular systems and the development of microviscosity images and their correlation with histological measures of cell proliferation are complete.

In summary, we have presented novel measurements using very-low-frequency EPR to measure the water compartment microviscosity in tumors and in corresponding normal tissues. The results indicate that the total water compartment of tumors has a lower microviscosity than the corresponding normal tissue by an average of 38 ± 7%. This substantial microviscosity reduction is similar in magnitude and sign to the difference between transverse relaxation times of tumor and normal-tissue water hydrogen nuclei seen in both quantitative and daily imaging studies of human malignancies. It would argue that much of the increase in signal intensity seen in T2-weighted MRI is due to this effect. We speculate, on the basis of chemical kinetic arguments, the reports cited, and the above data, that the lowered microviscosity in the aqueous compartment of the tumors reported here may increase the rate constants of chemical reactions in these tumors relative to those of normal tissues. It would suggest that tumors have an accelerated “chemical clock.”

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REFERENCES

10. Halpern, H. J., Yu, C., Peric, M., Barth, E. Karcern, G. S., River, J. N., Grinza, D. J., and Teicher, B. A. Measurement of pO2 differences in response to perfluoro-carbon oxygenation in macrophage and normal-tissue water hydrogen nuclei seen in both quantitative and daily imaging studies of human malignancies. It would argue that much of the increase in signal intensity seen in T2-weighted MRI is due to this effect. We speculate, on the basis of chemical kinetic arguments, the reports cited, and the above data, that the lowered microviscosity in the aqueous compartment of the tumors reported here may increase the rate constants of chemical reactions in these tumors relative to those of normal tissues. It would suggest that tumors have an accelerated “chemical clock.”

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REFERENCES

47. Reiners, J. J., Jr, Cantu, A., Thai, G., and Pavone, A. Tumor copromoting
diminished aqueous microviscosity of tumors
49. Martins-Green, M., Boudreau, N., and Bissell, M. J. Inflammation is responsible for
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