Does DCE-MRI Have a Metabolic Dimension?

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Introduction: Malignant tumor metabolism is currently receiving intense scrutiny (1,2). Biomedical imaging assesses this mainly via PET (3) and, more recently, hyperpolarized 13C-MRSI (4). Although [Dynamic-Contrast-Enhanced] DCE-MRI is increasingly used for cancer (5), it is widely thought restricted to microvascular property and extracellular space determinations. However, it has been recently discovered that the mean intracellular water lifetime [τi] is an inverse measure of ongoing cellular metabolic fluxes (6). Though the τi biomarker is artificially held effectively zero when DCE-MRI data are analyzed with the tracer pharmacokinetic paradigm, it is determined when equilibrium trans-cytolumenal water exchange kinetics are included (7). This suggests that DCE-MRI can have a heretofore unrecognized metabolic dimension. We have studied a genetically modified murine spontaneous breast cancer model. This is RFS-Myc:NeuNt:Blg-Cre; a cross of a mouse expressing a Cre-inducible homozygous c-Myc knock-in gene [ROSA26 locus] with an individual carrying a heterozygous Cre knock-in at its endogeneous oncogene, and with a Blg-Cre transgenic mouse for mammary specific Cre expression to drive c-Myc and NeuNT. Four to twelve weeks after their first pregnancy lactation to stimulate Blg-Cre, parous females develop mammary tumors morphologically and histologically similar to human breast cancer. The malignancy is driven by activated Her2 signaling and de-regulated c-Myc expression, with the c-Myc protein near human tumor levels (8,9).

Methods: An approximately seven month old 35 g female with a right gland tumor was anesthetized [ketamine/xylazine; maintained with isoflurane] and cradled supine in an 11.74T/31 cm MRI instrument (Bruker). Body temperature was maintained and respiration monitored. A spoiled GE-FLASH DCE-MRI acquisition [TR/FA; 40 ms/27 o] used a 7.2 cm body RF transmit coil and a 2 cm surface receive coil over the tumor. The slice thickness was 750 μm, the nominal in-plane spatial resolution (195 μm)2, and the temporal resolution 5 s. Just over one minute into the 13 minute acquisition, a dose [0.15 mmol/kg] of ProHance [75 μL of 71 mM contrast reagent (CR) was delivered in 4.5 s through a tail vein cannula, with a 12 s 200 μL saline chase. The arterial input function was determined by blind estimation (10) from the brain tumor tissue response to an identical injection in another mouse. For the breast tumor tissue response, the Fast-Exchange-Regime-allowed form of the Shutter-Speed pharmacokinetic analysis was used. This assumes the 1H2O T1 remains single-valued: i.e., there is one tissue 1H2O signal (7).

Results: Two DCE-MRI biomarkers are analyzed, τi and Kτi∗, primarily a tumor capillary CR extravasation rate constant (7). Figure 1 shows axial tumor parametric maps superimposed on gray scale T1-weighted whole body image slices. The view is from the inferior perspective [the right gland tumor is image left]: anterior is up. The image slice shown is the most superior of four contiguous planes passing through the tumor, which was ~5 mm in diameter. The left and right panels show Kτi∗ and τi maps, respectively, the color scales are given. The upper panels show the heterogeneity of the spontaneously developed tumor. The values of Kτi∗ and τi, each vary by a factor of five or more across the lesion. Comparison of the Kτi∗ and τi maps shows aspects of the negative spatial correlation often reported (11-14): in many regions where Kτi∗ is relatively large [e.g., anterior periphery] τi is relatively small, and vice-versa. This is thought not a parameter interdependence numerical correlation (7). Where capillaries are more permeable, metabolism (specifically trans-membrane ion and osmolyte cycling) is faster. The lower panels show analogous maps of the same tumor after 10 days of o.d. injection [IP] of 5 mg/kg OP449, a therapeutic peptide mimetic that re-activates the crucial tumor suppressor enzyme protein phosphatase 2A [PP2A] by inhibiting its SET oncoprotein inhibitor (15). Though the tumor volume increased 1.3 fold here, this is much less than mice with no therapy [5.4 fold; n = 12] and the pharmacokinetic parameters show pronounced changes suggestive of therapeutic efficacy. Kτi∗ decreases significantly with therapy, while τi increases. Thus, they are negatively correlated in this way also.

Since we have two responsive biomarkers, we can inspect DCE-MRI in a two dimensional fashion (16). Figure 2 shows pixel-by-pixel 2D scatter plots [Kτi∗ ordinate, τi abscissa] of the Fig. 1 image slices. The upper panel depicts the situation before therapy. The accumulation of some points at Kτi∗ = 3 min−1 is simply the upper bound of the analytical Kτi∗ iteration. The eye discerns instances of spatial parameter correlation [Fig. 1 upper] when simple numerical correlation is not evident [Fig. 2 upper]. The lower Fig. 2 panel shows the situation after therapy. Large changes are obvious. The cluster center of mass coordinates [Kτi∗, τi] go from approximately [0.7 min−1, 0.4 s] to approximately [0.2 min−1, 0.8 s] post-therapy; each coordinate changes by a factor of two or more. Kτi∗ has been found to decrease with approximately every anti-cancer drug tested (5). The τi magnitudes seen here are very reasonable (7).

Discussion: The c-Myc gene product is a transcription factor heavily involved in metabolic signaling (17). This tumor model has a human-like level of c-Myc activity, and the OP449 peptide is designed to counteract this through re-activation of PP2A, a direct negative regulator of c-Myc phosphorylation and activity (18,19). So, it is sensible that we see a τi change upon OP449 therapy consistent with a significant metabolic flux decrease. This is encouraging that DCE-MRI does have a useful metabolic dimension; τi is the parameter most directly pertinent to cancer. It can arise directly from the tumor cells.

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