Time-Resolved Molecular Imaging of the "Angiogenic Switch" in Animal Models of Cancer

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Introduction

Tumor growth beyond 1-2 mm is limited in most cases until a switch to the angiogenic phenotype, dependent on a net balance of positive and negative growth factors, induces the formation of new capillaries which invade the surrounding tissue. Noninvasive high-resolution MR molecular imaging can provide a unique and powerful tool to characterize and quantify the "angiogenic switch" in tumor models, which has a promising role in personalized medical regimens, particularly with antiangiogenic treatments.

Materials and Methods

The temporal and spatial progression of angiogenesis was delineated in two animal models of adenocarcinoma (xenograft mouse and syngeneic rabbit) using αvβ3–targeted paramagnetic nanoparticles incorporating 30 % Gd-DOTA-PE, and 0.1 mole% $\alpha_v\beta_3$–integrin antagonist[1,2]. Nude mice implanted with human MDA435 cells were administered nontargeted paramagnetic control (n=6) or αvβ3-targeted nanoparticles (n=8) i.v. and were imaged by MRI (Philips Achieva) at baseline and 120 min postinjection on days 14 and 21. Rabbits implanted with Vx2 tumors received either nontargeted paramagnetic control (n=4) or αvβ3-targeted paramagnetic nanoparticles (n=4) on 8, 14, and 16 days post implantation. 3D T1w fat suppressed FFE images were collected using a 6 cm surface coil for mice (0.2x0.2x0.5 mm res., 1.5T) or an 8-element knee coil for rabbits (0.25x0.25x0.5mm res., 3T). Baseline images were obtained to establish mean signal intensity and variation. The threshold for postcontrast enhancing MRI pixels was set as 3 standard deviations above the baseline mean. The number of signal-enhanced voxels was calculated, and 3D neovasculature maps were reconstructed to spatially characterize the distribution of angiogenesis.

Results and Discussion

In the Vx2 tumor model, $\alpha_v\beta_3$–targeted paramagnetic nanoparticles delineated angiogenesis in 2D slices[3], which allowed the tumor volume and distribution of neovasculature to be quantified within a slice. 3D reconstruction of enhancing voxels provided a unique visualization of the spatial distribution of angiogenesis and the primary growth front of the tumor. On day 8, MR signal enhancement was minimal and did not differ between the nontargeted and targeted treatments (Fig 1). At 14 days, $\alpha_v\beta_3$–targeted paramagnetic nanoparticles detected the expansion of the neovasculature (3.8±0.7% of periphery), reflecting the occurrence of the "angiogenic switch" in the implanted tumor. This increase in neovasculature was not detected with the nontargeted particles. MR molecular imaging with $\alpha_v\beta_3$–nanoparticles on day 16 detected the progression in angiogenesis between days 14 and 16 (7.9±1.7% of tumor periphery, $p<0.05$), whereas the signal from the nontargeted nanoparticles remained unchanged. Time-resolved 3D neovascular maps illustrated the "angiogenic switch" between days 8 and 14, and revealed the spatial organization of neovessels, which was confined to the tumor periphery and involved densely coalesced regions of neovasculature interspersed with a more sparse distribution of angiogenic positive voxels. In contradistinction, the nontargeted MR contrast pattern was less prominent and random. In the mouse MDA435 tumor model (Fig 2), angiogenesis was sparse at 14 days post implantation (0.4±0.2% of tumor periphery) and increased slightly over the next 7 days (1.0±0.5% of tumor periphery, $p>0.05$). Nontargeted tumors showed minimal enhancement. These data suggest that tumor growth of the MDA-435 tumor may be diminished due to T-cell depletion resulting in an impaired induction of the angiogenic switch.

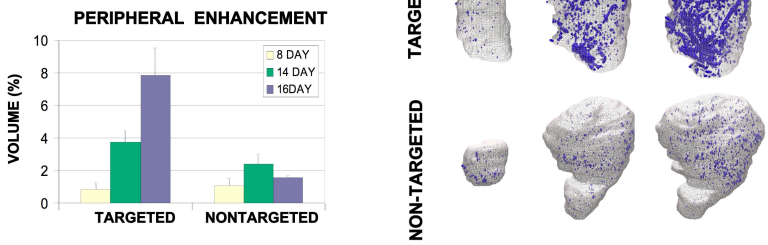

Fig 1. Left, percent volume of MR enhancement in the targeted and nontargeted Vx2 tumors with time. Right, 3D neovascular maps of Vx2 illustrating the angiogenic switch between days 8 and 14 and the spatial progression of angiogenesis over time.

Conclusion:

High-resolution MR molecular imaging using $\alpha_v\beta_3$–targeted paramagnetic nanoparticles can provide a unique and powerful tool to noninvasively interrogate tumors and characterize the "angiogenic switch". MR assessments of tumor neovasculature differentiated angiogenesis progression in the syngeneic Vx2 rabbit versus xenograft MDA-435 mouse model. Characterization of tumor neovasculature could support individualized stratification of patients into anti-angiogenic based treatment regimens and their longitudinal monitoring.

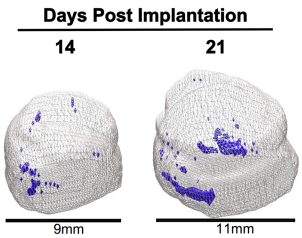

Fig 2. 3D neovascular maps from MDA 435 tumors illustrating minimal angiogenesis at 14 and 21 days post implantation.

References: (1) Schmieder et al. Magn Reson Med, 2005 (2)Flacke et al. Circulation, 2001 (3) Winter et al. Cancer Res, 2003.