MRI of tumor-associated macrophages with clinically applicable iron oxide nanoparticles.

The presence of tumor-associated macrophages (TAM) in breast cancer correlates strongly with poor outcome. The purpose of this study was to develop a clinically applicable, noninvasive diagnostic assay for selective targeting and visualization of TAMs in breast cancer, based on magnetic resonance and clinically applicable iron oxide nanoparticles. F4/80-negative mammary carcinoma cells and F4/80-positive TAMs were incubated with iron oxide nanoparticles and were compared with respect to magnetic resonance signal changes and iron uptake. MMTV-PyMT transgenic mice harboring mammary carcinomas underwent nanoparticle-enhanced magnetic resonance imaging (MRI) up to 1 hour and 24 hours after injection. The tumor enhancement on MRIs was correlated with the presence and location of TAMs and nanoparticles by confocal microscopy. In vitro studies revealed that iron oxide nanoparticles are preferentially phagocytosed by TAMs but not by malignant tumor cells. In vivo, all tumors showed an initial contrast agent perfusion on immediate postcontrast MRIs with gradual transendothelial leakage into the tumor interstitium. Twenty-four hours after injection, all tumors showed a persistent signal decline on MRIs. TAM depletion via CSF1 monoclonal antibodies led to significant inhibition of tumor growth.
nanoparticle enhancement. Detection of iron using 3,3'-diaminobenzidine-enhanced Prussian Blue staining, combined with immunodetection of CD68, localized iron oxide nanoparticles to TAMs, showing that the signal effects on delayed MRIs were largely due to TAM-mediated uptake of contrast agent. These data indicate that tumor enhancement with clinically applicable iron oxide nanoparticles may serve as a new biomarker for long-term prognosis, related treatment decisions, and the evaluation of new immune-targeted therapies.