A Dynamic Contrast-Enhanced MRI Comparison of the Perfusion of Spontaneous and Transplanted Pancreatic Ductal Adenocarcinoma in Genetically Engineered Mice

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Background and Aim

The genetically engineered KPC mouse conditionally expresses endogenous mutant Kras and p53 alleles under the control of a pancreas-specific Cre recombinase and as a result develops spontaneous pancreatic ductal adenocarcinoma (PDA) at 3.5 - 5 months old. These tumours have molecular and pathological features closely resembling those of human PDA, notably the low vascular density, high desmoplastic stromal content and poor sensitivity to gemcitabine, currently the standard-of-care drug clinically. Subcutaneous transplantation of cell lines derived from excised KPC tumours gives rise to tumours of the same genotype but with contrasting architecture with minimal desmoplastic stroma, higher vascular density and greater gemcitabine sensitivity. The aim of the study was to perform longitudinal studies to assess the relative perfusion in tumours of both types, to investigate the contribution of perfusion to gemcitabine sensitivity[1].

Methods

Animals were isoflurane anaesthetised and scanned in a 40mm Millipede coil in a 9.4T horizontal bore magnet. T2W FSE images were acquired from tumour and paraspinal muscle (TR=2000ms, TE_{eff}=25ms, ETL=4, 512x256 points, FOV 80x40mm, slice thickness/gap 1.0/1.0mm, 9 slices) with chemical shift-selective fat suppression and respiratory gating. All other images were matched to the slice positions and FOV of the anatomical images. Baseline T_1 maps were obtained from inversion recovery turbo-FLASH data (TE=1.52ms, TR=3ms, TI=0.2/0.5/1/2/5/10 seconds, 128x128 points). DCE-MRI time course data were acquired using T_1-weighted RF-spoiled gradient echo (TE=1.52ms, TR=50ms, 128x128 points, α=45°, slice thickness/gap 1.5/0.5mm). Scans were acquired with 6s time resolution, with 5 baseline points before an i/v bolus of 0.1 mMol/kg Gd-DTPA, and 100 points after injection. Flip angle mapping data were acquired to correct for coil radiofrequency inhomogeneity [2]. DCE-MRI data were analyzed in software custom-written in MATLAB 7.4 using the model of Tofts and Kermode [3-4] to evaluate the pharmacokinetic parameter K_{trans} (sec^{-1}), the Gd-DTPA volume transfer constant which is related to perfusion, blood flow and vessel surface area. Tumours imaged ranged from ~100mm^3 to 800mm^3. ROIs were drawn around tumour on T_2W images, and transferred to T_1 maps. Transplanted tumours frequently exhibited cystic and/or necrotic regions clearly visible on T2W images, which were excluded from the K_{trans} analysis; this was rare in spontaneous tumours. Mice with transplanted tumours were entered into the study 14-21 days after inoculation of bilateral tumours and those with spontaneous tumours were entered when the tumour reached ~100mm^3 (single tumour per mouse). Each mouse was imaged up to 5 times over the course of ~2 weeks. Tumour volumes were calculated by summing the tumour areas in each slice and extrapolating the volume of the gap.

Results

Transplanted tumours grow faster than spontaneous tumours (doubling times are 5.25 ± 0.71 days and 10.25 ± 3.02 days) respectively. Figure 1 shows K_{trans} colourmaps for single slices of a typical transplanted tumour 21 days (panel A) and 24 days (panel B) after inoculation and for two typical spontaneous tumours (panels C & D) in mice 95 and 142 days old. The maps show that spontaneous tumours have very poor perfusion, shown by their low $K_{trans,}$ values compared with transplanted tumours. This is consistent with the relatively poor vascularisation of the spontaneous tumour as shown by CD31 staining [1]. Figure 2 shows up to 4 median K_{trans} values for each of 8 transplanted and 6 spontaneous tumours plotted against tumour volume, and clearly shows that K_{trans} values fall with increasing tumour size. However in spontaneous tumours the values are consistently about half of that measured in transplanted tumours. Paraspinal muscle K_{trans} was also measured in all animals, and was essentially the same in both hosts: in transplant hosts median K_{trans} was 0.00136 ± 0.00013 sec^{-1} (mean ± 2SE) and in spontaneous hosts it was 0.00171 ± 0.00036 sec^{-1}.

Figure 1. Transplanted (A, B) and spontaneous (C,D) PDAs

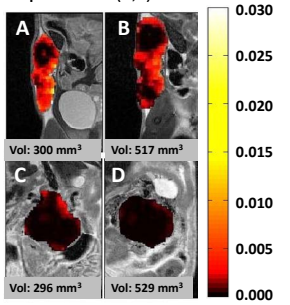
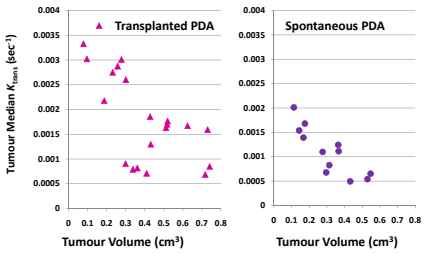


Figure 2. Median K_{trans} falls with increasing tumour size



Conclusions

The consistently lower median K_{trans} values in spontaneous tumours than in transplanted tumours of comparable size confirms the relatively poor status of the functional vasculature in the spontaneous tumours. It is likely that this contributes substantially to the reduced drug sensitivity of the spontaneous tumours, since the desmoplastic stroma intervenes between the blood vessels and tumour cells [1]. The present work confirms and extends preliminary studies which suggested this [1].

References

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