High field MR imaging of pre-invasive pancreatic carcinoma in a transgenic mouse model

P. N. Venkatasubramanian[1], P. Grippo[2], R. Knop[3], A. Wyrwicz[1]

[1]Center for Basic M.R. Research, ENH Research Institute, Evanston, IL, United States, [2]Dept of Surgery, Robert H Lurie Comprehensive Cancer Center, Northwestern University School of Medicine, Chicago, IL, United States, [3]Dept. of Medicine, Evanston Northwestern Healthcare, Evanston, IL, United States

INTRODUCTION

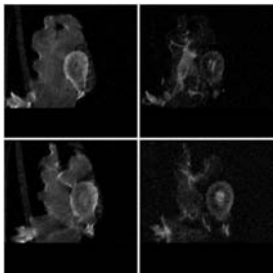
The development of pancreatic cancer is considered to be a stepwise progression of intraepithelial cellular changes, which are categorized into three histologically premalignant lesions termed pancreatic intraepithelial neoplasia or PanIN [1]. The EL-Kras FVB6 F1 transgenic mouse is an ideal model for evaluating these neoplastic lesions since all mice develop several PanINs within 6 months of age [2]. We have used high field MR imaging to investigate early morphological changes in the EL-Kras mouse model of pancreatic cancer progression. We report results from MR imaging in which we could differentiate transgenic mouse pancreas from normal mouse pancreas, based only on classical endogenous contrast. Ability to detect PanINs using MR imaging may translate to earlier detection of pancreatic cancer by bridging the gap between structural tissue correlates (or the stages of PanINs) and the molecular correlates associated with those stages.

EXPERIMENTAL

Pancreas was surgically removed from male EL-Kras FVB6 F1 mice and normal control B6 mice (n=6). Excised tissue was fixed by immersion in 10% formalin. High resolution MR images of fixed tissue were acquired either at 9.4T or at 4.7T. Multi-slice T1- and T2-weighted spin-echo images were acquired using TR/TE 500msec/10msec and 2000msec/40msec, respectively.

RESULTS AND DISCUSSION

Images of a normal mouse pancreas (Figure 1) reveal that high field MR imaging is capable of spatial resolution that is high enough to visualize acinar cell architecture. Different regions of this architecture have distinct appearances in T1- and T2-weighted images. In T1-weighted images, the basal region of acinar cell showing basophilia appears bright relative to the secretory product, centroacinar cells and the duct. In T2-weighted images, the centroacinar cells appear brighter than basophilia.



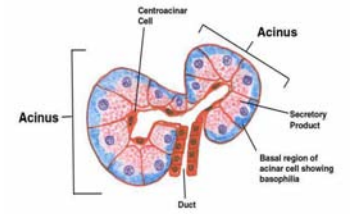
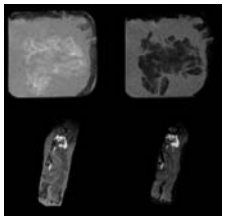


Figure 1. T1-weighted (left panels) and T2-weighted (right panels) images of a normal pancreas from a control mouse. Multislice images were acquired on a 400MHz imager using slice thickness 250 μm and pixel size 77μm x 77μm from which two adjacent slices are shown. The schematic of acinar cell architecture is shown in the diagram.

T1- and T2-weighted images of pancreas from a 1.5-month old EL-Kras mouse and an age-matched normal control show striking contrast differences (Figure 2). T1-weighted image of the normal pancreas appears isointense over the entire tissue,



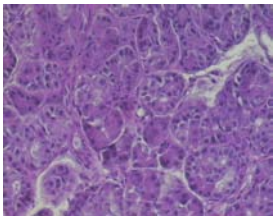
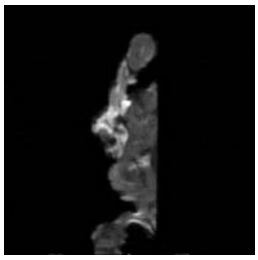


Figure 2. T1-weighted (left panels) and T2-weighted (right panels) images of pancreas from a control mouse (top row) and an EL-Kras mouse (bottom row) acquired on a 400MHz imager. Slice thickness= 250 μm, in-plane resolution= 125 μm for the control mouse image; slice thickness= 500 μm, in-plane resolution= 62 μm for the transgenic mouse image. H&E stain of the transgenic mouse pancreas shows abnormal acinar parenchyma including dysplasia and hyperplasia.

namely, duodenal, gastric and splenic lobes, indicating uniform T1 in all the lobes. The T2-weighted images the normal pancreas also appears isointense in all the lobes, although with reduced intensity relative to the T1-weighted image as expected. On the contrary, T1-weighted image of the EL-Kras mouse pancreas shows a markedly hyper-intense region in the duodenal lobe, indicating a lesion with short T1 in the transgenic mouse pancreas. The same duodenal lobe region appears hyper-intense in the T2-weighted image also, signifying longer T2. Thus the pancreas from1.5 month old EL-Kras mouse has a lesion with shorter T1 and longer T2 compared to normal pancreas, which appears hyper-intense in both T1-weighted and T2-weighted images acquired at high field strength. Lesions with similar hyper-intense MR appearance were also found in other EL-Kras mice. Representative images from a 3-month old transgenic mouse acquired at 4.7T are presented in Figure 3 to illustrate this phenomenon.



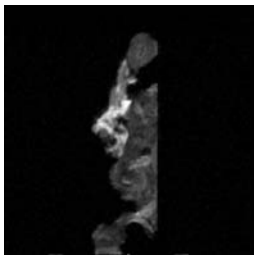


Figure 3. T1-weighted (left) and T2- weighted (right) images of a representative slice from a 3-month old EL-Kras mouse pancreas acquired at 4.7T. Note that the hyperintense lesion in T1-weighted image remains hyperintense in T2-weighted image also.

In clinical MRI, tumors appear hyper-intense in T2-weighted and hypo-intense in T1-weighted images as a result of longer T2 and T1 relaxation times for water in the tumor. In contrast to this well-known MR appearance of tumors, lesions in the EL-Kras mouse pancreas appear hyper-intense in both T1- and T2-weighted images, characteristic of short T1 and long T2. This novel T1-shortening and T2-elongation seen in EL-Kras pancreas may be related to one of the molecular events that have been correlated to each PanIN stage: mutation in the Kras gene and increased expression of mucins in PanIN1, loss of the p16 tumor suppressor gene in PanIN2, and loss of DPC4 and p53 tumor suppressor gene in PanIN3 [3-5]. In clinical imaging, to delineate tumors more accurately in T1-weighted images, contrast is enhanced by the use of T1-shortening agents that make the tumor appear hyper-intense. No such external contrast enhancing agent might be required for imaging PanINs as the inherent relaxation times of water in this pre-neoplastic tissue provides adequate endogenous contrast in MR images.

References

1. R.H. Hruben, M. Goggins, J. Parsons, and S.E. Kern. Clin. Cancer Res. 6: 2969-2972 (2000).
2. P.J. Grippo, P.S. Nowlin, M.J. Demeure, D.S. Longnecker, and E.P. Sandgren. Cancer Res. 63: 2016-2019 (2003).
3. C.M. Barton, S.L. Staddon, C.M. Hughes, et al. Br. J. Cancer 64: 1076-1082 (1991).
4. C. Caldas, S.A. Hahn, L.T. da Costa, et al. Nat. Genet. 8: 27-32 (1994).
5. S.A. Hahn, M. Schutte, A.T. Hoque, et al. Science 271: 350-353 (1996).