Functional Apparent Diffusion Coefficient Mapping the Uptake of Tumor-Targeting Bombesin Probes in Human Breast and Prostate Cancer Xenografts

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Introduction

Cancer receptor-targeting molecular imaging probes and radiopharmaceuticals provide a means to early detection and targeted therapeutic interventions of malignancies by recognition of receptors uniquely over-expressed on human cancer cells. Bombesin is a 14-amino acid peptide that shows high affinity and specificity for gastrin releasing peptide receptor (GRPr). The GRPr is over-expressed on many human cancer cell lines including breast, prostate, colon, and small cell lung cancers. We and others have recently developed a series of BBN conjugates for fluorescent, SPECT and PET imaging of human breast and prostate cancer cells[1,2]. In this current study we applied magnetic resonance imaging (MRI) to investigate the relationship of apparent diffusion coefficient (ADC) map and the uptake distribution of florescent or radio-labeled bombesin conjugates in breast and prostate tumor xenografts.

Methods

Fusion MRI/SPECT/PET/CT/optical Imaging Studies were performed using severely compromised immunodeficient (SCID) mice bearing human PC-3 prostate tumor or human T-47D breast tumor xenografts. Radiolabeled or fluorescent BBN conjugates were administered intravenously when mice were awake. Mice were placed in a home-built cradle. The cradle was mounted with thin glass tubes that served as reference points for fusion of the multimodality images. Mice were imaged and data was collected using established scan protocols.

MRI and ADC Mapping: Water diffusion-sensitive images were acquired on a 7 T/210 mm horizontal small animal MRI system using birdcage RF coil with the inner diameter of 3.8 cm. Images were collected as 256x256x1mm or 256x512x1mm resolution. All MRI images were obtained immediately post Micro-PET, Micro-SPECT or florescent data acquisition. The diffusion weighted imaging (DWI) was performed with data collection synchronized with the respiration of the animal. The diffusion spin-echo sequence (TR/TE≅2000/37 msec) was used to collect a set of diffusion-weighted images at high diffusion sensitivity (b2=1,037 sec/mm2) and low sensitivity b1 =0 (i.e. T2-weighted) along all diffuse directions. ADC maps were calculated according to:

$$ADC = 1/(b_2 - b_1)\ln(S_{b1}/S_{b2})$$

Where the S_{b1} and S_{b2} are the signal intensities at low and high-diffusion weighting, respectively.

Results

We applied multimodality fusion imaging of micro-MRI, micro-PET, micro-SPECT and fluorescence imaging to evaluate the tumor uptake of the bombesin agents in severe combined immunodeficient mice bearing human prostate and breast cancer xenografts. Diffusion weighted and T_2 weighted MRI were performed to assess the tumor ADC values. Functional ADC maps were derived by quantitative measurements of ADC values of each imaging pixels over the entire tumor. Concurrent regions of interest (ROIs) were drawn on the ADC map and co-registered on the PET or SPECT imaging slice. ADC values and PET intensity distributions were measured on tumor tissues. For example in Figure 1, the regions 3 and 5 show low water diffusion and high SPECT intensity of In111-BBN uptake. The region 2 shows relatively high water diffusion and relatively low SPECT intensity. The regions 1 and 4 appear very high water diffusion and very low SPECT intensity possibly due to lack of proton or cell densities.

Discussion and Future Work

The purpose of this study is to regionally compare the relationship of the tumor apparent diffusion coefficient map and the uptake distribution of florescent or radio-labeled bombesin imaging probes in breast and prostate cancer xenografts *in vivo*. We found correlations between the tumor ADC and the tumor cellularity and the uptake distribution of radio-labeled or florescent bombesin imaging probes in breast and prostate cancer xenografts. ADC mapping approach is sensitive and quantitative as an imaging biomarker to evaluate imaging or therapeutic efficacy.

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Literature Citations

1. Ma, L.; Yu, P.; Veerendra, B.; Rold, T.L.; Retzloff, L.; Prasanphanich, A.; Sieckman, G.; Hoffman, T.J.; Volkert, W.A.; and Smith, C.J., Molecular Imaging, 2007, 6(3) 171-80.
2. Prasanphanich, A.; Nanda, P.K.; Rold, T.L.; Ma, L.; Lewis, M.R.; Hoffman, T.J.; Sieckman, G.L.; Figueroa, S.D.; and Smith, C.J., PNAS, 2007, 104,12462-7.

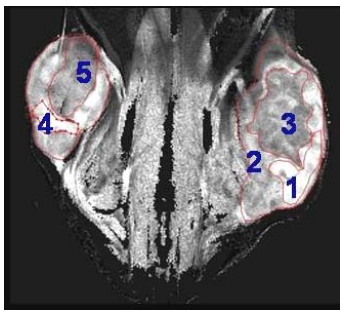

Figure 1 –Functional ADC map of SCID mouse bearing human PC-3 cancer xenografts.