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PET imaging of DNA damage response following 225Ac-radioimmunotherapy in a pancreatic ductal adenocarcinoma mouse model.

Objective: When the integrity of the DNA is impaired, a series of DNA damage responses lead to the recruitment, upregulation or activation of specific protein within the nucleus. When present in sufficient copies, these proteins can represent attractive targets for molecular imaging. This presentation will present our recent efforts to image DNA damage repair proteins via PET imaging following α-radioimmunotherapy(αRIT). Such non-invasive approach will be a precious tool for the monitoring of treatment response as well as the determination of optimal therapeutic dose. Two DNA damage repair proteins will be evaluated as potential target for the evaluation of DNA damage following αRIT. First, the poly(ADP-ribose) polymerase 1 (PARP-1) enzyme, involved in the DNA repair of single strand breaks, will be targeted using a PARP inhibitor radiolabeled with fluorine-18 ([18F]F-PARPi). Then, the γH2AX protein, most commonly probed biomarker for DNA double strand breaks, will be targeted using an anti-γH2AX antibody radiolabeled with zirconium-89 ([89Zr]Zr-DFO-anti-γH2AX-TAT).

Methods: Pancreatic ductal adenocarcinoma αRIT was previously developed in our laboratory using a fully-human antibody targeting the carbohydrate antigen CA19.9 (5B1) radiolabelled with actinium-225. Mice bearing CA19.9 positive PDAC tumors (n=5/cohort) were administered a single injection of [225Ac]Ac-DOTA-5B1 with an injected activity of 37 kBq, known to result in significant prolonged survival as compared to control mice. DNA damage imaging was performed using [18F]F-PARPi (11-15 MBq, 1 nmol) and [89Zr]Zr-anti-γH2AX-TAT (500 kBq, 5μg) following the αRIT. As positive and negative controls, mice were either irradiated with 10 Gy or mock-treated (0 Gy). Mice were sacrificed following the PET imaging. Volume of interest analysis of the PET images were performed and correlated to the biodistribution data.

Results: PET imaging with [18F]F-PARPi shows accumulation of the radiotracer at the tumor site. Transverse representative images are shown in Figure 1. Tumor uptake at 4h, 24h and 72h (0.98±0.20, 1.08±0.39 and 1.01±0.24 %ID/g) post-αRIT was greater as compared to the negative control mice (0.62±0.23 %ID/g) even though no significant difference was observed. Imaging with [89Zr]Zr-anti-γH2AX-TAT results in tumor uptake of 7.6±2.2 %ID/g 72h post-αRIT with [225Ac]Ac-DOTA-5B1 This uptake was significantly higher than mock-treated control group (5.1±0.9 %ID/g, $P<0.05$). Mice irradiated with 10 Gy demonstrated tumor uptake of 6.8±1.2 %ID/g. Transverse representative images are shown in Figure 1.

Conclusion: DNA damage response proteins PARP1 and γH2AX were targeted and imaged via PET using 18F- and 89Zr-radiolabeled conjugates after PDAC targeted αRIT. Both proteins seems like promising targets for the monitoring of α-radiotherapy response.

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