In vivo evaluation of device-associated inflammation using Positron Emission Tomography Imaging

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Introduction: Medical implants often trigger a varying extent of inflammatory responses, accompanied by the accumulation of macrophages (MΦ) and neutrophils (PMN). These implant-mediated inflammatory responses may cause the failure of many devices. Unfortunately, non-invasive methods to assess foreign body reactions in patients are not available. To monitor biomaterial-mediated inflammatory responses *in vivo*, we have recently developed a series of optical imaging probes for non-invasive and real-time assessment of MΦ and PMN responses to biomaterial implants.[1,2] However, due to limited penetration depth of light, as well as attenuation and scattering of light by tissues, these optical imaging probes are not suitable for clinical applications on human patients. To address these issues, the MΦ imaging probe was modified for Positron Emission Tomography (PET) imaging. PET imaging was chosen since it is a quantitative, highly sensitive, tomographic clinical imaging modality without limitation of penetration depth. The effectiveness of this probe in detecting biomaterial implants-associated inflammatory responses was evaluated using both subcutaneous and intramuscular implantation model.

Methods: Since activated MΦ possess a large number of folic acid (FA) receptors, macrophage-specific PET probes were made in which FA, polyethylene glycol (PEG) and 1,4,7,10-Tetraazacyclododecane-1,4,7,10-tetraacetic acid 1-(2,5-dioxo-1-pyrrolidinyl) ester (DOTA) were used as the targeting ligand, carrier, and radioisotope chelator, respectively. We first prepared DOTA-PEG-FA by conjugating FA and radioisotope chelator DOTA to the end of PEG diamine (M_w: 5k) using 1-Ethyl-3-(3-dimethylaminopropyl) carbodiimide coupling chemistry. Chemical structure and mass weight of the conjugate was analyzed using FTIR and MALDI-TOF MS, respectively. The macrophage-specific PET probe ^{68}Ga-DOTA-PEG-FA was obtained by radio-labeling the conjugate with freshly eluted $^{68}GaCl_3$. The purification of the probe was performed by a pre-activated Sep-Pak C-18 plus cartridge. The radiochemical yield and purity were determined by radio-HPLC. The validation of the PET probe was assessed in an intramuscular implantation model. Imaging was performed 3hrs after injection using a Siemens Inveon Multimodality PET/CT system (Siemens Medical Solutions Inc.).

Results: The PET probe prepared in this study is composed of three structural components: MΦ-specific FA; PEG carrier (increase of probes' water solubility and circulation time in blood); and radioisotope ^{68}Ga. FTIR spectrum of DOTA-PEG-FA shows characteristic IR absorption peaks of FA at 1600, 1695, and 1498 cm^{-1}, indicating conjugation of FA moieties into PEGs. MALDI-TOF MS analysis shows that the average molecular weight of the conjugate is around 6,000. After radio-labeling the conjugate with ^{68}Ga, the radiochemical yield is 78% as determined by radio-HPLC. The radiochemical purity is higher than 99%. The ^{68}Ga-DOTA-PEG-FA has the same retention time as its respective conjugate at 20.5 minutes. The validation of the PET probe in detecting implant-associated inflammation was assessed using a silicon dioxide (SiO_2, 10 nm diameter) intramuscular implantation model. SiO_2 nanopaticles were implanted for 24 hours to prompt acute implant-mediated inflammatory responses. The PET probe was then administered intravenously (3.7 MBq/animal). PET/CT images were taken three hours after PET probe administration (Fig. 1a). It may be observed that SiO_2 implant induces more radiotracer accumulation compared to the control (Fig.1 (a)). Quantitative analysis shows the intensity of the SiO_2 implant site is higher than the control by a factor of 4 (Fig.1 (b)). In agreement with PET/CT imaging results, H&E staining reveals that increased inflammatory cells are recruited to SiO_2 implant site with respect to the control (Fig.1(c)).

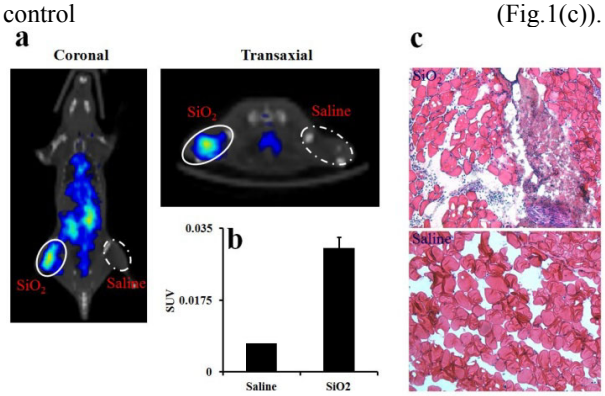

Fig. 1 (a) Fused transaxial and coronal PET-CT imaging for SiO_2 implant and saline. (b) The SUV values were calculated for SiO_2 implant and saline. (c) Optical imaging of H&E stained tissue slices of SiO_2- and saline implantation sites.

Conclusions: Our studies demonstrate that ^{68}Ga-DOTA-PEG-FA can effectively detect implant-associated MΦ and associated foreign body reactions, suggesting that the PET probe can potentially be translated for detecting immune responses to various medical implants, including surgical mesh, degradable implants/scaffold, and other joint implants.

References:

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2. Zhou, J. Biomaterials. 2011; 32 (35):9383-9390.