TSPO PET IMAGING IN PRE-CLINICAL MODELS OF HUMAN GLIOMAS

Pigeon Hayet[1], Peres Elodie[2], Boisgard Raphael[1], Boumezbeur Fawzi[2], Caillé Fabien[1], Jego Benoit[1], Jacobs Andreas H.[3], Winkeler Alexandra[1]

[1]Inserm / CEA / Université Paris Sud, UMR 1023 – ERL 9218 CNRS, IMIV, Orsay, France
[2]CEA / I[2]BM / Neurospin / UNIRS, Saclay, France
[3]European Institute for Molecular Imaging, Westfälische Wilhelms University - Münster, Germany

Introduction

The 18 kDa translocator protein (TSPO) is a protein of the outer mitochondrial membrane widely expressed in peripheral organs. TSPO expression in the brain is low but its expression is dramatically increased after glial cell activation and has become a well-characterized marker for neuroinflammation. Moreover, TSPO expression has also been shown in some cancers including gliomas. TSPO imaging can be performed using positron emission tomography (PET) with the specific radioligand [^{18}F]DPA-714. As demonstrated in a rat glioma model, TSPO imaging in glioma monitors TSPO-positive neoplastic and to a lesser amount TSPO-positive inflammatory cells. To study a) the use of [^{18}F]DPA-714 PET imaging in human gliomas and b) the impact of the tumor microenvironment, in particular glioma-associated inflammation, we have started to characterize an angiogenic and an invasive human glioma model for in vivo imaging using [^{18}F]DPA-714 PET as well as immunohistochemistry (IHC).

Methods

2x10^5 human glioma cells (U87dEGFR angiogenic or P3 invasive) were stereotactically implanted in the striatum of nude mice (n=8 or n=7, respectively). To monitor tumor growth [^{18}F]DPA-714 PET scans were acquired 10 days (U87dEGFR), angogenic model or 1, 3, 5, 7 and 9 weeks (P3), post-inoculation. For the invasive tumor model T2w MRI have been acquired at 5, 7, 9 weeks 24hours prior PET scans. The PET images were manually co-registered to corresponding MRIs. PET findings were validated using *ex vivo* autoradiography and immunohistochemistry (IHC) using specific human and murine TSPO antibodies.

Results

Ten days after cell implantation significantly higher uptake of [^{18}F]DPA-714 has been demonstrated in human U87dEGFR tumors as compared to the contralateral brain (%ID/cc: 1.4±0.7 and 0.7±0.3, $p<0.01$) with a tumor-to-brain ratio of 2.1±0.3. Furthermore, IHC confirmed TSPO expression within the tumor. IHC using human and mouse specific TSPO antibodies allowed distinction between tumoral and stromal TSPO, indicating the presence of TSPO-positive stromal cells within the glioma. In contrast tumor-to-contralateral-brain ratios in the invasive model ranged from 1.2 to 2.0, with a significantly higher uptake in the tumor after 7 and 9 weeks post implantation ($p<0.01$), which was confirmed by *ex-vivo* autoradiography ($p< 0.001$). T2w-anatomical MR images showed hyperintense areas at tumor location only 9 weeks after P3 implantation but the precise boundaries of the tumor were difficult to observe.

Conclusions

First results demonstrate that imaging of TSPO expression *in vivo* using [^{18}F]DPA-714 PET is feasible in the human U87dEGFR glioma mouse model. Distinction between tumoral and stromal TSPO could be achieved by *ex vivo* IHC, which will be of use in studying changes of tumoral and stromal TSPO expression during tumor progression and therapy. We found significantly higher tumor-to-contralateral [^{18}F]DPA-714 uptake ratios starting 7 weeks after P3 glioma cell implantation and could visualize glioma infiltration into the contralateral hemisphere. However, MRI T2W does not detect any anatomical change in that early time point. These results suggest that advanced PET imaging

methods, such as [^{18}F]DPA-714, may be suitable to visualize glioma and tumor infiltration at an early stage.