CONFERENCE

Institut d'Imagerie Biomédicale
Service Hospitalier Frédéric Joliot

30 mars 2015
à 11 heures

Salle de conférence
du Service Hospitalier Frédéric Joliot
(SHFJ)

Imaging of glioma and associated-inflammation using TSPO radioligands

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Résumé

Glioblastoma multiforme (GBM) is the most common and aggressive form of primary human brain tumors. Despite the use of multimodal treatment, most of patients relapse, in part due to the highly invasive nature of gliomas. Recently, the tumor microenvironment (TME), including associated-inflammation, has become an important factor in cancers correlated with the invasive capacities, angiogenesis and bad prognosis. Therefore, the study of glioma associated-inflammation may help us to better understand its role in tumor progression and response to treatment.

The 18 kDa translocator protein (TSPO) is a protein of the outer mitochondrial membrane expressed in peripheral organs and in activated microglia. Moreover, TSPO has become a well-characterised marker for neuro-inflammation and its overexpression has been shown in some cancers including glioblastoma. This up regulation has also been correlated with the stage of tumor progression and poor prognosis. Thus, TSPO has been proposed as a biomarker in oncology imaging. Furthermore, several radioligands for positron emission tomography (PET) have been evaluated as radiotracers for imaging glioma.

This thesis aims to characterize different types of gliomas and follow their associated-inflammation using non-invasive molecular imaging.

To achieve these objectives, we propose to create human glioma cells whose expression of TSPO is decreased. Using a RNA interference technique, glioma cells are transduced with a viral vector carrying a sequence inhibiting the expression of TSPO. To characterize the inflammatory component of glioma only, these new cells will be characterized *in vitro* by western blot and cell proliferation, *in vivo* by TSPO PET imaging, and validation of imaging findings will be done using immunohistochemistry.

Angiogenic and infiltrative glioma cell lines will be assessed for TSPO expression level and will be evaluated in animal models. The characterization of inflammatory aspect in these models will be estimated by PET imaging, and the *in vivo* findings will be correlated with *ex vivo* results.

In the first year, we established a mouse model of human U87dEGFR glioma. *In vivo* results obtained using PET have revealed higher uptake of [^{18}F]DPA-714 in human U87dEGFR tumors as compared to the contralateral brain. Furthermore, immunohistochemistry 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 an invasive glioma model demonstrated higher [^{18}F]DPA-714 uptake only after 9 weeks post implantation, which was confirmed by ex-vivo autoradiography.

Finally, new radiotracers for imaging of neuroinflammation (eg.CB2R) will be tested in the glioma model to analyze their specificity against activated microglial cells.