Development of a Specific Tracer for Metabolic Imaging of Alveolar Echinococcosis: a Preclinical Study*

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Abstract— **Positron emission tomography (PET)-computed tomography (CT) using [18F]-fluorodeoxyglucose (FDG) (FDG-PET/CT) is a valuable method for initial staging and follow up of patients with alveolar echinococcosis (AE). However, the cells responsible for FDG uptake have not been clearly identified. The main goal of our study was to evaluate the uptake of PET tracers by the cells involved in the host-parasite reaction around AE lesions as the first step to develop a specific PET tracer that would allow direct assessment of parasite viability in AE.**

Candidate molecules ([18F]-fluorotyrosine (FET), [18F]-fluorothymidine (FLT), and [18F]-fluorometylcholine (FMC), were compared to FDG by *in vitro* studies on human leukocytes and parasite vesicles. Our results confirmed that FDG was mainly consumed by immune cells and showed that FLT was the best candidate tracer for parasite metabolism. Indeed, parasite cells exhibited high uptake of FLT.

We also performed PET/CT scans in mice infected intraperitoneally with *E. multilocularis* metacestodes. PET images showed no FDG or FLT uptake in parasitic lesions.

This preliminary study assessed the metabolic activity of human leukocytes and AE cells using radiolabeling. Future studies could develop a specific PET tracer for AE lesions to improve lesion detection and echinococcosis treatment in patients. Our results demonstrated that a new animal model is needed for preclinical PET imaging to better mimic human hepatic and/or periparasitic metabolism.

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I. Introduction

Alveolar echinococcosis (AE) is a severe chronic helminthic disease characterized by intrahepatic tumor-like growth of the metacestode of *Echinococcus multilocularis* [1]. Positron emission tomography (PET) using the radiopharmaceutical [18F]-2-fluoro-2-deoxy-D-glucose (FDG-PET) can detect inflammatory and infectious lesions [2],[3],[4]. Since FDG accumulates in cells that exhibit a high metabolic rate, FDG is readily taken up by macrophages and leukocytes of inflammatory infiltrates [5],[6],[7],[8]. Therefore, FDG-PET can be used to diagnose or follow infectious diseases, even if the PET images indirectly reflect the presence and/or proliferation of the infectious agent.

FDG-PET shows perilesional uptake of FDG near active lesions and has been used to follow AE patients since the 1990s [9],[10]. Similar to other infectious diseases, FDG is likely an indirect measure of AE progression [11]. An intense inflammatory reaction surrounds the parasitic tissue (*E. multilocularis* metacestode), and the activity of inflammatory cells can explain local FDG uptake [12]. However, the real target of FDG in AE lesions is unknown.

In AE, the parasitic tissue (germinal layer) is surrounded by an acellular laminated layer. The laminated layer has direct contact with immune response cells (macrophages, lymphocytes, eosinophils, and other effectors cells such as fibroblasts and myofibroblasts), which all constitute the periparasitic granuloma [13], [14], [15]. An intense inflammatory reaction thus surrounds the parasitic tissue, and the activity of inflammatory cells could also explain local FDG uptake, which suggests that inflammatory cells homing to the liver around the parasitic lesions might rather be best candidate to explain this uptake. Morover, negative FDG-PET findings despite the presence of viable parasite in immunodepressed patients, suggests that the periparasitic immune infiltrate (and not the parasite) is responsible of the uptake (signal) in AE [9],[16]. These observations have fueled interest to better understand the mechanism of FDG uptake by AE lesions and to develop a more specific tracer for AE imaging.

In previous studies, most of the inflammatory response cells (polymorphonuclear leukocytes, lymphocytes, monocytes) incorporated and phosphorylated FDG, and maintained the resulting FDG-6-phosphate for about 1 h after radiolabeling [17],[18],[19],[20]. On the basis of these data, we designed a radiolabeling protocol using fluorinated tracers to test the capacity of parasite vesicles and leukocytes to consume radioisotope tracers *in vitro*.

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In addition to FDG, we selected fluorinated tracers that were simple to produce: 1) O-(2-[18F]-fluoroethyl)-L-tyrosine (FET), an amino acid tracer that is highly taken up by tumors (lymphoma, lung, and breast cancer) and brain tumors [21],[22],[23],[24]; 2) [18F]-fluoromethylcholine (FMC), an analogue of choline (an important component of phospholipid synthesis), with high uptake in prostate, breast, and brain tumors [25],[26],[27],[28],[29]; 3) [18F]-fluoro-L-thymidine (FLT), a cell proliferation PET tracer used to detect and monitor tumor proliferation for tumor staging (lymphoma, melanoma, lung, and breast cancer) and to detect metastases [25],[30],[31],[32].

II. Materials and Methods

A. Cell preparation

"Whole" E. multilocularis vesicles: In vitro E. multilocularis metacestodes were cultivated at 37°C and 5% CO_2 with a co-culture of feeder cells (Rh- hepatocytes). The growth medium and feeder cells were changed weekly. All AE vesicles selected for the experiments were approximately 4 months old, and each experiment for each tracer was performed on three independent pools of AE vesicles.

"Broken" E. multilocularis vesicles: For these experiments, "whole" vesicles were washed five times with phosphate buffered saline (PBS) to remove the Rh-hepatocytes. The vesicles were then pipetted up and down with a 10-mL pipette, and subsequently passed through an 18-G needle to break up the vesicles. Each experiment for each tracer was performed on three independent pools of AE vesicles.

Human leukocytes: The five fluorinated tracers were studied in leukocytes obtained from whole blood samples. Healthy subjects provided blood, which was collected in 60-mL syringes containing 5 mL of acid-citrate-dextrose. Leukocytes were separated from platelets and red blood cells by sedimentation and centrifugation.

B. Cell radiolabeling

All cells were incubated at 37°C in 5% CO_2 under gentle rolling with 40 MBq of fluorinated tracer for 20 minutes. After radiolabeling, vesicles were suspended in 2 mL of PBS and leukocytes were suspended in 2 mL of platelet-devoid plasma (PPP). To remove unbound fluorinated tracer (free fraction), cells were centrifuged at 82 × g at 25°C for 15 minutes. Pelleted vesicles were washed again with 2 mL of PBS or PPP and then centrifuged (82 × g at 25°C for 15 minutes). Radioactivity was measured with a dose calibrator in the supernatant and in the cell pellet after each wash.

TABLE I. Average radiolabeling efficiency of the various cell types

Type of Cells	Tracers			
	FDG	***FLT***	***FET***	***FMC***
"Whole" vesicles	31.1%	92.9%	43.2%	49.2%
"Broken" vesicles	40.7%	70.9%	48.2%	59.3%
Leukocytes	59.1%	6.5%	5.6 %	56.0%

Radiolabeling efficiency (i.e., percentage of radioactivity incorporated into the cells) was determined as:

$$\frac{\text{Radioactivity in separated cells}}{\text{Radioactivity before separation}} \times 100$$

C. PET imaging

Wild-type mice were inoculated intraperitoneally (i.p.) with *E. multilocularis* metacestodes. Three months after inoculation, PET/computed tomography (CT) scans were performed using the Triumph PET/SPECT/CT system (Gamma Medica, Inc., CA, USA). The mice were fasted for 12 hours and blood glucose was measured before each scan. PET images were acquired over 1 h, 30 minutes after retro-orbital intravenous injection of 11.7 MBq of fluorinated tracer. Three FDG-PET/CT acquisitions and three FLT-PET acquisitions were performed in 6 pairs of animals: one i.p. infected mouse and one control mouse (not infected with AE). The mice were necropsied 1 day after PET imaging.

III. Results

The *in vitro* results are summarized in Table 1.

"Whole" E. multilocularis vesicles: Average radiolabeling efficiency was very high using FLT (92.9%), high using FMC (49.2%), and moderate using FET or FDG (43.2% and 31.1%, respectively).

"Broken" E. multilocularis vesicles: Average radiolabeling efficiency was high using FLT or FMC (70.86% and 59.30%, respectively) and moderate using FET or FDG (48.21% and 40.71%, respectively).

Human leukocytes: Radiolabeling efficiency was high using FDG or FMC (59.1% and 56.0%, respectively), and poor using FLT or FET (6.5% and 5.6%, respectively).

PET imaging: We observed no FDG or FLT uptake in AE lesions of infected mice (Fig. 1). However, macroscopic data showed widely developed lesions (Fig. 2).

IV. Discussion

AE is one of the most severe parasitic diseases worldwide [34]; therefore, it is important to improve AE diagnosis, follow up, and treatment monitoring [1]. FDG-PET is currently the gold standard for AE functional imaging in humans [13]. Nevertheless, FDG is not the ideal tracer for AE because its uptake reflects the homing and activation of leukocytes in the perilesional layer and the parasite viability [10], [11], [12], [13].

This study was a part of the IsotopEchino project, which aims to develop a specific radioisotope tracer to directly assess parasite activity. The ideal tracer should have a low affinity for leukocytes (and hepatocytes), but a high affinity for parasite cells, which will provide a high signal-to-noise ratio (parasite-to-healthy tissue) on PET images. As a first step of the project, we compared the radiolabeling efficiency *in vitro* which reflects tracer uptake *in vivo* [4],[5].

The comparison of data obtained by PET in humans and our *in vitro* results demonstrated that a radiolabeling technique used for human leukocytes can be applied to assess parasite metabolic activity *in vitro*.

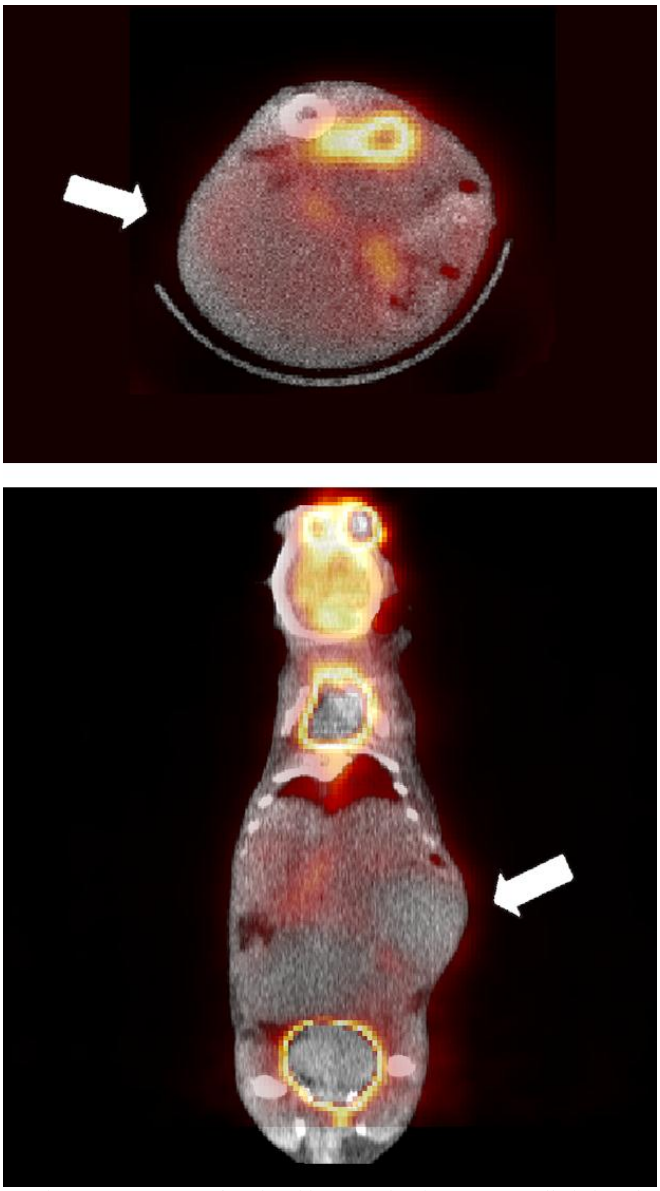

Figure 1. FDG-PET/CT fused images of an intraperetoneally infected mouse. Axial (top) and coronal (bottom) slices show no FDG uptake in a large AE lesion in the left flank (arrows). Physiological uptake in the brain, the heart and the kydneys was observed.

Indeed, as expected from previous studies [17],[18],[19],[20], we observed high radiolabeling efficiency of leukocytes using FDG. However, the radiolabeling efficiency of the vesicles was lower with this tracer (Table 1). This 2-times higher *in vitro* uptake of FDG is correlated to PET images observed in humans.

On the other hand, our results suggested that FLT was a good candidate tracer to assess parasite viability because both "whole" and "broken" *E. multilocularis* vesicles had higher uptake of FLT than of any other tested tracers. And, conversely, leukocytes showed much lower affinity for FLT than for FDG or FMC. Thus, in case of active AE, FLT-PET imaging should show high signal from the parasite with low or no signal from leukocytes.

Figure 2. Photograph (top) and necropsy (bottom) of an intraperitoneally infected mouse with a large, solid AE lesion in the left flank (arrows) and inflammatory multivesicular lesions (red circle).

FET seemed to be an interesting candidate also but its vesicles-to-leukocytes ratio of radiolabelling efficiency was lower for this tracer than for FLT. Moreover, radiochemical synthesis of FET is more difficult than that of FLT.

Concerning FMC, our study confirmed the results of Kubota *et al.* by demonstrating high radiolabelling efficiency of leukocytes [27]. However, the radiolabelling efficiency of vesicles was also high. Thus, FMC-PET could not differentiate the parasite activity from leukocytes activity.

In the second part of the study, we tried to correlate our *in vitro* results to PET imaging in AE mouse model. Previous *in vivo* experiments confirmed that the distribution of FDG in PET reflects inflammatory reactions in the periparasitic layer in humans [10],[13]. Furthermore, many studies reported the usefulness of FDG-PET imaging for tumors, infection, and inflammation models in rodents with high signal in PET [33],[34],[35]. However, in the current study, PET/CT scans showed no FDG or FLT uptake in infected mice with huge intraperitoneal lesions. To explain these findings, we hypothesized that physiological hepatic uptake may be more important in mice than in humans. On the other hand, the intensity of the immune response might be lower in i.p. infected mice than in orally or intra-hepatic infected ones. For the future studies, we will develop an imaging protocol with a mini-pig AE model also.

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