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LETTER TO THE EDITOR

^{18}F-FDG uptake of brown fat and cancer: casualty or causality?

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Dear Sir,

Brown adipose tissue (BAT) is an extremely annoying issue for most nuclear medicine physicians, being a potential confounder in the interpretation of ^{18}F-FDG PET images. Indeed, either typical or atypical localization of BAT can mask pathological findings and thus lead to misdiagnosis.

As a consequence, during the last two decades the nuclear medicine community has assisted in several preliminary investigations aiming both at unraveling BAT biology and understanding its possible meanings in imaging findings. In the light of this research, potential unexpected correlations of BAT activation with oncologic and dysmetabolic disorders have emerged [1].

Recently, we have read with great interest more papers about this topic. In particular, pilot studies conducted by *Cao* and *Huang* have advocated neoplastic status to be a critical determinant of BAT activity, which might represent a biomarker for tumor development and progression [2, 3]. An even more recent paper published by *Bos* and colleagues has reintroduced the prospects of an intriguing role of BAT in cancer activity [4].

If these hypotheses were confirmed, they would represent an amazing breakthrough for ^{18}F-FDG PET imaging. Our nuclear medicine community assesses thousands of oncological patients yearly; it would be really impressive to discover that a direct correlation between BAT SUV_{max} and tumor activity does exist, and we have never realized it before. Confirmation of BAT implication in cancer would turn BAT into a formidable tool to be harnessed in the complicated but fascinating struggle to encode cancer activity. It could also bring considerable credit to the contentious role of quantitative assessment in PET imaging, currently well-established only in some types of lymphoma.

Nonetheless, evidence highlighting a significant association, especially in breast cancer and sarcoma, between ^{18}F-FDG PET uptake and active disease is rather weak if we consider the enormous amount of internal and external factors that may influence the FDG uptake of BAT (seasonal photoperiods, outdoor or indoor temperatures, sex, age, BMI, nicotine exposure, anxiety, renal function, benzodiazepine or beta-blockers administration, to name a few) [5].

Bos and colleagues probably designed the best retrospective analysis to date regarding BAT activation in oncologic patients. They identified a group of 142 BAT-positive patients assessed with PET/CT with history of malignant neoplasm. Patients were divided into two groups according to the presence of active cancer. The two populations were comparable in number, patient characteristics and environmental factors. Results showed that patients with active cancer on PET/CT had higher BAT volume and SUV_{max} compared to individuals without it [4].

To date, there is neither prospective nor retrospective ^{18}F-FDG PET investigation considering all these factors simultaneously; this might also explain discrepancies in the results [6]. Moreover, even if all these variables were taken into consideration, it would be unlikely that a relevant clinical tool would result from the analysis of BAT uptake, given the very low specificity of its activation. By trying to explain the possible implication of BAT in cancer biology through PET imaging, we have been shaping clinical studies with stricter and stricter inclusion criteria to meet the requisites for statistical significance. Still, we should wonder whether this approach constitutes a trump card to unravel this possible correlation. Molecular imaging provides information to clinicians in a smart, practical way due to our in-depth knowledge of its underlying biological mechanisms. Much remains unknown about BAT biology and function. This notwithstanding, new research paths are on the horizon.

Hard evidence exists about a pro-inflammatory status in patients with active cancer. In patients affected by cancer, high

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levels of IL6 are present, which may stimulate UCP1, and thus BAT metabolism. In fact, cancer-associated cachexia has been linked to transformation of white tissue into hypertrophic and hyperplastic BAT (so-called "browning" phenomenon), with a consequent increased ^{18}F-FDG uptake. It has been postulated that browning inhibition might even represent an approach to ameliorate the severity of cachexia in cancer patients [1].

We know ^{18}F-FDG PET sensitivity for cancer-related brown adipocyte recruitment could be boosted by using a β3-adrenergic stimulation, but this would not improve specificity [6]. The introduction of pharmacological agents that augment BAT activity advocates the use of specific preclinical imaging methodologies that correlate well with specific gene expression in BAT. Indeed, specific genes like UCP1, PGC1α or PECAM 1 seem to be upregulated in animal in vivo models with active cancer [7, 8].

Specific gene activation can be imaged. *Wang* et al. expressed near infrared fluorescence protein iRFP720 driven under a UCP1 promoter in mice, and used multispectral optoacoustic imaging technology with ultrasound tomography (MSOT-US) to assess adipocyte activity during adrenergic stimulation. PET/MR had the fundamental role in validating this imaging modality [9]. This mouse model suggests how hybrid PET imaging may be used not only for metabolic identification, but also as a validating modality of other, more specific, imaging modalities in the preclinical setting [9, 10]. Furthermore, downstream effectors of specific genes may be suitable for pharmacological targeting. The identification in brown adipocytes of such targets for potential labeled radiotracers might provide potential imaging biomarkers to track cancer activity.

With a different grade of evidence, these studies deserve credit for having raised awareness about the likelihood of a brown fat involvement in the systemic cytokine-mediated response to cancer. However, as acknowledged by *Bos* and colleagues, after more than two decades of preliminary studies, ^{18}F-FDG PET alone is still "an imperfect standard of reference," [4] and no other type of imaging can be considered specific enough to identify a specific BAT activation secondary to cancer.

More data about molecular implications of BAT in patients affected by cancer are needed to refine the role of ^{18}F-FDG PET imaging in such an assessment. Until then, even if well-designed prospective studies are performed, it is our opinion that a direct correlation at imaging between BAT activation and cancer activity will remain a confusing mix of hype and hope.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest related to this paper.

This article does not contain any studies with human or animals participants performed by any of the authors.

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