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# **Is the information provided by amino-acid PET radiopharmaceuticals clinically equivalent in gliomas?**

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## **Letter to the Editor**

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Over the past few years, brain tumors imaging has been evaluated with several radiolabeled amino-acid radiopharmaceuticals whose the increased uptake is classically associated with the metabolic reprogramming necessary to meet growth requirements. In this line, the Response Assessment in Neuro-Oncology (RANO) working group has recently recommended the use of amino-acid PET as an additional tool for evaluating gliomas [1]. With a low tracer uptake in normal grey matter, amino-acid PET radiopharmaceuticals have actually a higher sensitivity compared to  $^{18}\text{F}$ -FDG [1]. Parallel to these developments, several studies have led to an increased understanding of tumor biology such as the identification of *IDH1* and *IDH2* (isocitrate dehydrogenase enzyme isoforms) mutations in gliomas. These mutations have an impact in individualized treatment decisions, and in this line the World Health Organization (WHO) has recently updated Central Nervous System (CNS) classification by integrating these molecular parameters for diagnostic and prognostic assessment of gliomas [2]. Beyond its localization value, nuclear imaging provides unique opportunities for better characterization of tumors at the molecular level. Consequently, the relationship between amino-acid imaging phenotype and *IDH* mutation status has become an emerging area of clinical interest.

The first and most validated radiolabeled amino-acid is  $^{11}\text{C}$ -methionine ( $^{11}\text{C}$ -MET).  $^{11}\text{C}$ -MET is a natural amino-acid avidly taken up by gliomas. MET is used for protein synthesis, or converted to S-adenosylmethionine which is the primary methyl donor for transmethylation reactions and a precursor of polyamide synthesis. A smaller part of MET is also metabolized by decarboxylation [3].  $^{11}\text{C}$ -MET uptake is mainly mediated by the L-type amino-acid transporter family, especially member 1 (LAT1)[4], but also by A-amino-acid transporters [5]. In an effort to overcome disadvantages of its short half-life and complex metabolism, and despite a modified amino-acid structure, several iodo- and fluoro-amino-acids have been developed for SPECT and PET imaging [6]. These agents include  $^{123}\text{I}$ -iodo- $\alpha$ -methyl-L-tyrosine (IMT) for SPECT, and  $^{18}\text{F}$ -fluoro-ethyl-tyrosine ( $^{18}\text{F}$ -FET PET) and  $^{18}\text{F}$ -fluoro-L-

dopamine ( $^{18}\text{F}$ -FDOPA) for PET, which are transported by the same specific amino-acid transport system L as MET, but unlike MET are not incorporated into proteins biosynthesis [6]. The use of amino-acid PET for prognostication of gliomas at diagnosis is still subject to controversies [7–10], and relationship between *IDH* mutation status and imaging metabotype remains to be confirmed [11–13].

Recently, Lopci et al.' reported a study of 109 gliomas, aiming to determine relationship between  $^{11}\text{C}$ -MET PET uptake and *IDH* mutation status in glioma [12]. Higher  $^{11}\text{C}$ -MET uptake was associated with *IDH* wild-type tumors, even when the analysis was restricted to diffuse grade I, II and III [12]. On the other hand, our group have thereafter assessed the relationship between *IDH* mutation and  $^{18}\text{F}$ -FDOPA PET uptake in 43 diffuse grade II and III gliomas [13]. This last study reveals that  $^{18}\text{F}$ -FDOPA uptake was higher in *IDH*-mutated gliomas compared to their sporadic counterparts [13], a finding which is in apparent contradiction with the previous amino-acid tracer PET study on  $^{11}\text{C}$ -MET [12]. It is noteworthy that differences in proportion of oligodendroglial component inside sub-groups of *IDH*-mutated gliomas among these two studies are observed and could influence results. Indeed, this component may positively affect the substrate metabolism of gliomas particularly the  $^{11}\text{C}$ -MET PET uptake [14]. However, this latest correlation was not found in our study's group [13]. These results suggest that, despite similar indications, these radiopharmaceuticals exhibit different pharmacokinetics potentially linked to the presence of driver mutations [6,15].

From a molecular genetic standpoint, *IDH1* and *IDH2* belong the  $\text{NADP}^+$ -dependent *IDH* isoforms which are found in the mitochondria for *IDH2* and cytosol for *IDH1*. *IDH1* and *IDH2* produced NADPH which plays a substantial role in cellular control of oxidative damage. Loss of enzyme activity due to dominant negative effect of *IDH* mutants leads to accumulation of 2-hydroxyglutarate (2-HG), which may act as an oncometabolite with alternative molecular pathways [16] that may influence the imaging metabotype. On one hand, accumulation of 2-

HG inhibits histone and DNA hydroxymethylases, leading to an hypermethylated phenotype [17,18]. It could be hypothesized that decreased  $^{11}\text{C}$ -MET uptake in *IDH* mutant gliomas could be related to the enhancement of transmethylation pathway [17,19]. On the other hand, IDH mutation status is associated with an elevation of intracellular free amino-acids including tyrosine [19,20], which could potentially facilitate the uptake of  $^{18}\text{F}$ -FDOPA via amino-acid transporters which act as exchangers.  $^{18}\text{F}$ -FDOPA uptake in *IDH*-mutated gliomas could also be influenced by an impairment in dopamine catabolism due to a mitochondrial dysfunction [18]. Finally, the impact of *IDH* mutation on cell metabolism remains widely dependent on oxygen supply, a finding which could partially explain some differences observed between amino-acid PET findings between low-grade and high-grade gliomas.

In conclusion, the apparent discrepancy between the uptake patterns of  $^{11}\text{C}$ -MET and  $^{18}\text{F}$ -FDOPA in diffuse gliomas may be linked to the metabolomic profile of *IDH*-mutated tumors. Further studies are needed to better investigate the relation between genetic-imaging phenotype in glioma and the potential role of using multi-tracer imaging for tumor characterization.

## **Compliance with Ethical Standards**

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