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EDITORIAL

PET imaging with ^{11}C-acetate in prostate cancer: a biochemical, radiochemical and clinical perspective

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Abstract
Purpose In the present study, the potential clinical role of ^{11}C-acetate PET mainly in the differential diagnosis, in the staging and in the follow-up of prostate cancer patients is reported.
Methods Each of the above points has been accurately investigated by studying the specific biochemical and radiobiochemical behaviour of this positron emitter compound.
Results and Conclusion The imaging quality of ^{11}C-acetate PET and its unique mechanisms of cellular uptake, make such radiotracer a powerful tool in evaluating all the steps of the prostatic cancer.

Keywords PET imaging · ^{11}C-acetate · Prostate cancer · Biochemical perspective · Radiochemical perspective · Clinical perspective

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Radiolabelled acetate is a simple metabolic probe used in the study of healthy and malignant tissues, organs and glands. The use of labelled acetate in biochemical research started decades ago, and involved studying glial metabolism in the brain by MRI and myocardial metabolism by PET. A new potential for the use of this molecule in conjunction with ^{11}C has been established for use in oncological PET investigations.

Clinical experience in some of our institutions in imaging prostate cancer by PET with ^{11}C-acetate appeals to the wider use of this tracer provided that the core questions underlying its biochemistry are solved. Preliminary studies performed at Castelfranco Veneto PET centre have allowed accurate "de novo" diagnosis of prostate cancer with a very low rate of false-positive cases (global accuracy approaching 90%), thus potentially playing an important role in early differential diagnosis between benign and malignant prostate lesions [1]. Moreover, the use of ^{11}C-acetate PET at Geneva University Hospital in the clinical setting of prostate cancer relapse after radical surgery allowed the detection of recurrences at a very early phase, i.e. in patients having only slightly increased PSA levels (lower than 0.8 ng/ml) [2]. This article deals on the early and current use of radiolabelled acetate with an attempt to understand the underlying biochemical and radiochemical principles that play a role in its applications.

Early research with ^{11}C-acetate

The use of ^{11}C-acetate on animals and humans started in the early 1980s to study myocardial metabolism [3] and proved useful in patients with coronary heart disease. In these studies, a correlation between radioactivity washout from

myocardium and the rate of myocardial oxygen consumption was observed. Moreover, the largest fraction of the radioactivity leaving the myocardium was attributable to ^{11}C-CO_2.

These early PET studies have provided evidence that ^{11}C-acetate traces the activity of the tricarboxylic acid cycle (TCA) in the myocardium [4]. Therefore, kinetic analysis of accumulation and washout curves of radiolabelled acetate reveals myocardial oxygen consumption and mitochondrial oxidative flux. Later on, most of clinical PET studies with ^{11}C-acetate were carried out in this direction [5].

After a number of improvements have been introduced to the radio-synthetic procedures of ^{11}C-acetate, this tracer became easily accessible for routine clinical studies. Many groups started to use this molecule to study different tumours, especially those that are difficult to detect with ^{18}F-FDG PET. The usefulness of ^{11}C-acetate and its complementary role to ^{18}F-FDG is well documented in hepatocellular carcinoma, astrocytoma, renal cell carcinoma, low-grade malignancies in lung cancer and prostate cancer [6, 7]. Moreover, indication exist that 2-[^{14}C]acetate might be incorporated into the amino acid pool of glial tumours, thus making ^{11}C-acetate labelled into its methyl position a potential imaging tracer for gliomas and meningiomas [8, 9].

Acetate metabolic routs

The fate of the acetyl group relevant to our discussion are summarised in Fig. 1.

Acetate is a physiologic metabolite normally present in the blood at 0.2–0.3 mM concentration, and a special active transport system exists for its uptake across the cellular membrane. Monocarboxylate transporter (MCT) was shown to be a reason for the preferential accumulation of ^{11}C-acetate in astrocytes with two different types (MCT1 and MCT2) found in astrocytes and neurons, respectively [10].

The acetate group serves as a source of fuel for the TCA or Kreb's cycle when activated to the acetyl-coenzyme A (acetyl-CoA) complex [11]. TCA cycle is a terminal end-point for energy-producing metabolic routes in all living cells. Complete oxidisation of acetate in the TCA cycle results in the release of two CO_2 molecules per one turn. To enter into the metabolic process, the acetate group must first be converted into acetyl-CoA by acetyl kinase.

It is interesting to follow the track of radioactive label attached to the acetate molecule. A radiolabel placed in the carboxyl group (one asterisk in Fig. 1) would need to complete one full turn and will leave the cycle as carbon dioxide at second evolution of Kreb's cycle. Radiolabel placed in the second position of the acetate molecule (on the methyl moiety, two asterisks in Fig. 1) will only have a 50% chance to leave the TCA cycle at the second round, and the radiolabel will continue to be released gradually with the half-life equal to the rate of TCA cycle evolution. Professor Långström and colleagues from Uppsala University PET centre [12] have measured the difference between the kinetic behaviour of acetate labelled with ^{11}C in different positions. The rate of TCA evolution can be appreciated from these studies in pig myocardium, showing at 15 min after injection that more than 90% of radioactivity taken up by the myocardium was released as [^{11}C]-CO_2 and the time lag between 1-[^{11}C] and 2-[^{11}C] labelled acetate washout was less than 5 min. Also to note that some 10% of radioactivity remained captured in the myocardium, pointing to the other important feature of the TCA cycle.

The TCA cycle also has a function of supplying important intermediates for many biosynthetic processes, including amino acid and fatty acid synthesis. These escape routes are represented on Fig. 1 by: ATP citrate lyase reaction, linking glucose oxidation to fatty acid synthesis by a citrate cleavage pathway [13], and by glutamate–pyruvate aminotransferase reaction, leading to amino acid synthesis [8].

The TCA cycle is not the only metabolic process where acetyl-CoA is a principal source of carbon. The other major acetyl-CoA consumer is the fatty acid synthase (FAS) reaction used by all cells as a principal route to build fatty acids, which then become incorporated into phospholipids and cellular membranes. In the process of lipogenesis, eight acetyl-CoA equivalents are used for the synthesis of one equivalent of palmitic acid [11].

Numerous PET measurements of ^{11}C-acetate kinetics have shown three distinct phases in its accumulation, which allow to delineate biochemical processes described above—rapid uptake reflects delivery and is used to measure regional blood flow, rapid washout reflects oxidation in TCA and is used to measure oxygen consumption [5] whilst plateau of retained activity is related to the accumulation of the tracer in the lipid pool and is used in oncological studies [7].

Mammal cells do not use acetate directly in normal conditions. They derive acetyl-CoA from numerous energy-generating metabolic pathways as glycolysis, fatty acid oxidation and amino acid metabolism. To make use of acetate, the cells must activate it into the acetyl-*S*-CoA complex; for this, there exist a special enzyme acetyl-CoA synthetase (AceCS), previously known mainly in yeasts and bacteria.

Recently, two distinctive forms of mammal AceCS were identified, cloned and characterised. It is interesting to note that they are differently localised in cells, have different functions and their expression in organs differs accordingly. One of these acetyl kinases is a cytosolic acetyl-CoA synthetase 1 (AceCS1). It produces acetyl-CoA, which is active only in fatty acid synthesis, is highly expressed in the liver and is regulated by the same factors and patterns as FAS [14]. The other (AceCS2) is an enzyme bound to the

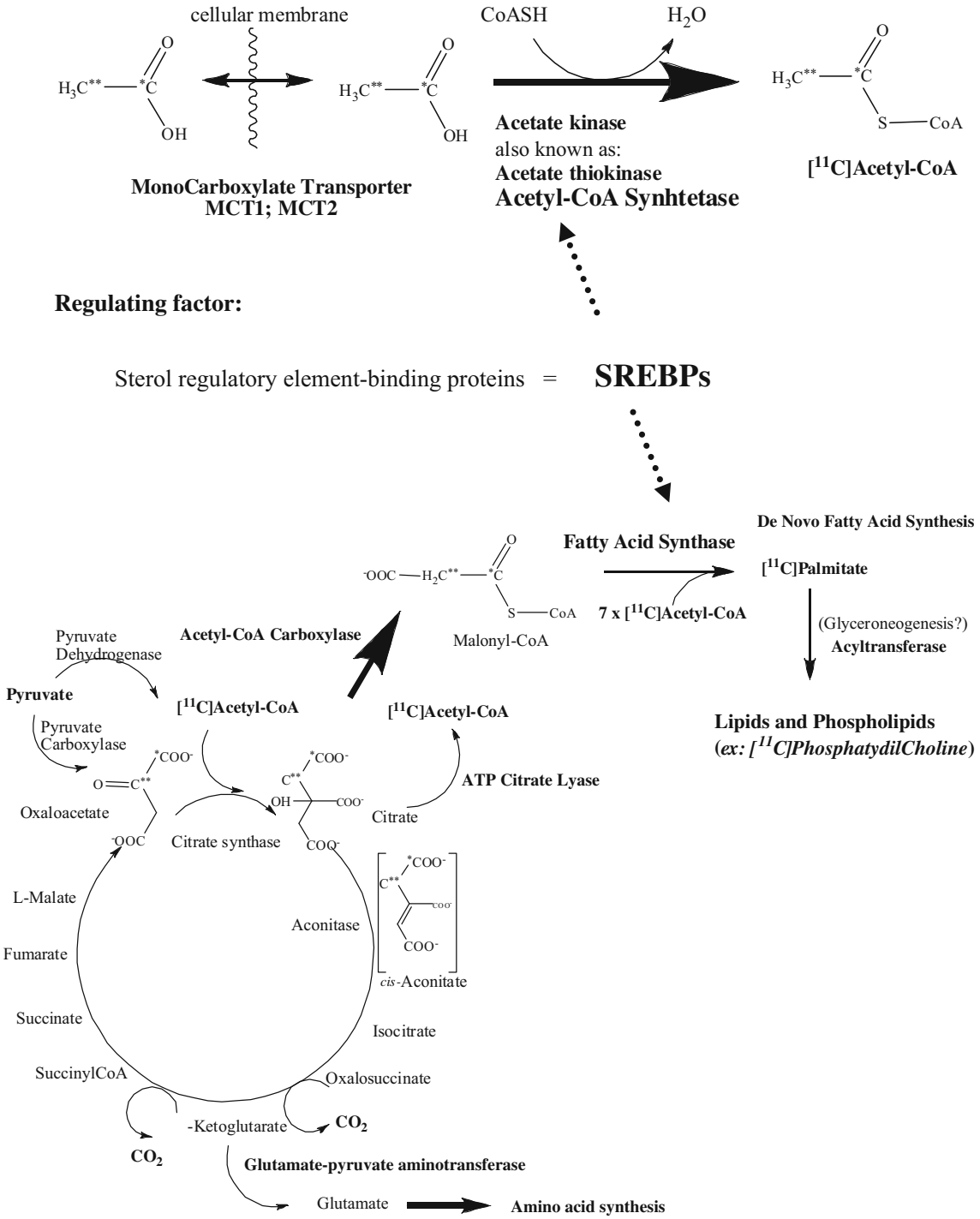

Fig. 1 Fate of radiolabelled acetate in tumour cells

mitochondrial matrix, found abundantly in hearts and kidneys, and synthesising acetyl-CoA active in the TCA cycle and producing $[^{14}C]CO_2$ from $[^{14}C]$acetate [15].

These enzymes were discovered recently and little is known about their expression and activity in normal and cancer cells. It is interesting to note that the authors who discovered human AceCS have found that from the screened 95 different cell lines AceCS1 was most abundant in human adenocarcinoma of the colon [14].

The growing body of evidence shows that most of the tumour cell lines activate the routes for the direct use of acetate in de novo fatty acid synthesis to cope with the lack of building blocks [16]. These newly synthesised fatty acids are further used for building cellular membranes.

A good illustration of this notion was provided by Yoshimoto et al. [17] who incubated different tumour cell lines with [^{14}C]acetate for 40 min. The distribution of radioactive label between different pools (lipids, phospholipids, amino acids, acetate, acetyl-CoA, carbon dioxide) was measured and compared to that of normal cells (fibroblasts) in growth and arrest. Predominant incorporation of [^{14}C]acetate activity into phosphatidylcholine and neutral lipids was observed in tumour cells, whilst in normal growing fibroblasts, the accumulation of [^{14}C] activity was slightly higher in the amino acid pool (Fig. 2). The authors took fibroblasts as a reference for normal cells.

From the distribution of activity between metabolic pools, one can notice a striking difference in the use of acetate by cells: cancer cells tend to use acetate predominantly for lipogenesis, dormant fibroblasts (in arrest) seem to accumulate amino acid building blocks for the following active phase, whilst growing normal cells use acetate almost equally for energy production, protein synthesis and lipogenesis.

Similar conclusions can be drawn from Shreve et al. [18] who used PET in human patients to measure the long retention of ^{11}C-acetate in renal carcinoma (presumably accumulated in the lipid pool) compared to the fast [^{11}C]CO_2 clearance from normal kidney. Dienel et al. [8] observed that 5 min after administration of 2-[^{14}C]acetate into rats bearing C6 glioma and human-derived glioblastoma/astrocytoma tumours, 98% of [^{14}C]acetate was already metabolised with 30–40% of metabolites in the acidic pool (presumably fatty acids) and 60–70% in amino acids. To the contrary, normal astrocytes utilise acetate predominantly in TCA for energy production, which can be measured by [^{14}C]CO_2 release [10].

Data accumulated to date do support the idea that lipogenesis plays an important role in tumourigenesis. It was convincingly proven that fatty acids and lipids are derived by tumour cells from “de novo” fatty acid synthesis [19]. FAS is up-regulated in many cancers and is a key enzyme for cancer cell survival [20]. It was shown that the accumulation of “de novo” synthesised fatty acids in lipid vesicles is characteristic for tumour cells undergoing apoptosis [21]. Co-ordinate activation of lipogenic enzymes is pronounced in hepatocellular carcinoma [22] and most likely is a common feature for majority of cancers [23]. Each of the key lipogenic enzymes—AceCS, ATP citrate lyase, acetyl-CoA carboxylase, FAS—is essential for cancer cell survival and malignant transformation. In fact, their inhibition can induce apoptosis in many types of cancers [13, 14, 20, 22, 24].

In a comprehensive review by Menendez et al. [16], the authors hypothesised that up-stream mechanisms controlling FAS expression in cancer cells are different from those in normal tissues and that in pre-neoplastic lesions, the early activation of fatty acid synthesis represents a survival strategy, which compensates for an insufficiency of oxygen and dietary fatty acid supply.

In this respect, it would be interesting to know more about the expression, activity and regulation of enzymes involved at each step leading from acetate to phospholipids in different cancers. The key steps in lipogenesis and respective literature references are summarised in Table 1. Although the authors do not pretend that this table is an exhaustive analysis of current literature, the relevant systematic study could not be identified.

As one can see from Table 1, all the steps implicated in lipogenesis are activated in different cancers [23]. It remains unclear whether this is a general feature of all

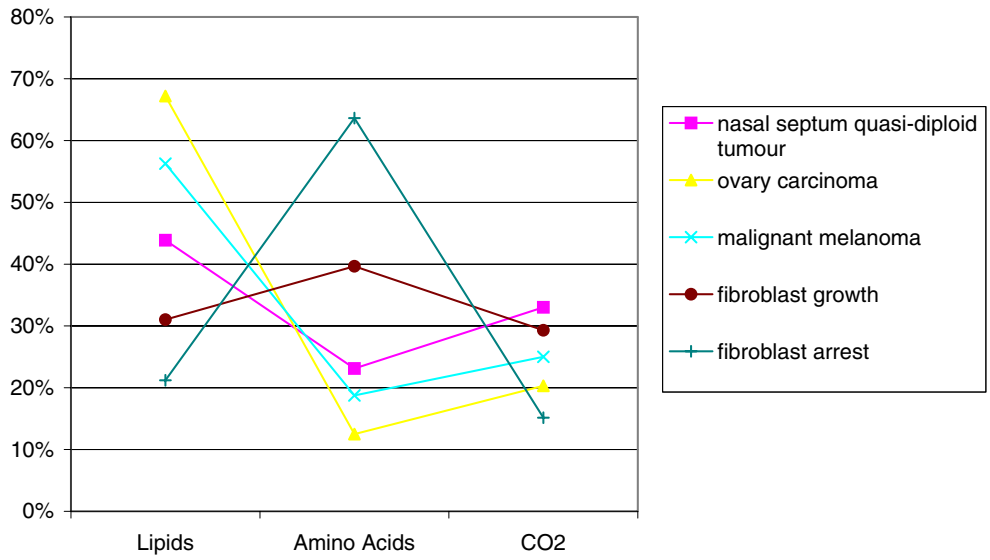

Fig. 2 Distribution of [^{14}C] acetate-derived radioactivity between different metabolic fractions. Data extracted and adapted from Yoshimoto et al. [17]

Table 1 Key biochemical processes involved in lipogenesis

Substrate	Enzyme	Product	Implication in cancer	Ref. #
Acetate in blood stream	Monocarboxylic acid transporters. MCT1, MCT2	Acetate in cytosol	Not studied.	[8, 10]
Acetate in cytosol	Acetyl-coenzyme A synthetase. AceCS1, AceCS2	Acetyl-CoA	Not studied, AceCS1 was reported to be over-expressed in colon adenocarcinoma.	[14, 15]
Acetyl-CoA	Citrate synthase	Citrate	First reaction in TCA cycle, linking glycolysis to lipogenesis. Higher activity in human pancreatic ductal carcinoma was reported.	[25]
Citrate	Aconitase	*cis*-aconitate	Is down-regulated in normal prostate epithelium cells by Zn. Its activity is restored in prostate carcinoma.	[26]
α-Ketoglutarate	Glutamate–pyruvate aminotransferase	Glutamate	Indication exist that this process is important in meningial and glial brain tumours.	[8]
Citrate	ATP citrate lyase (ACL)	Acetyl-CoA	Links the up-regulation of lipogenesis in cancer cells to the well known tumour-associated increase in glycolysis. ACL activity is elevated significantly in hepatocellular, breast and bladder carcinomas.	[13, 22, 23]
Acetyl-CoA	Acetyl-CoA carboxylase α	Malonyl-CoA	Rate determining enzyme in de novo FA synthesis. Its silencing induces apoptosis in breast and prostate cancer cells.	[24, 27]
Malonyl-CoA, acetyl-CoA (seven times)	Fatty acid synthase (FAS)	Palmitate	Is overexpressed in breast, prostate, colon, ovary, endometrium, thyroid cancers. Is up-regulated by SREBPs. Does not respond to PPAR-γ inhibition.	[16, 20]
Palmitate and other fatty acids	Fatty acid translocase (FAT), fatty acid transport protein (FATP), fatty acid binding protein (FABP)	Fatty acids available for lipogenesis	Are regulated by PPARs (superfamily of peroxisome proliferator-activated receptors). Their implication in tumourigenesis is poorly understood.	[28]
Gene expression in lipogenesis	Sterol regulatory element-binding protein (SREBP)	Intracellular cholesterol homeostasis	In prostate cancer cells androgens up-regulate expression of SREBP, which in turn stimulates AceCS1, FAS, ATP citrate lyase and cholesterol synthesis.	[29]

neo-plastic cells or only certain types of tumours triggering lipogenesis. It might easily happen that tumours with high oxidative glycolysis rate (^{18}F-FDG avid on PET) would activate the pyruvate carboxylase–ATP citrate lyase link to lipogenesis, whilst hypoxic tumours with low ^{18}F-FDG uptake would have AceCS1 activated for direct use of acetate.

Prostate metabolism in man

The human prostate gland is not homogeneous and consists of three distinctive zones of different functional activities. The peripheral zone is its major functional component, comprising about 70% of the total gland and, most importantly, is the major region of malignancy. This is the zone where specialised glandular peripheral epithelial cells are located that have evolved for the capability to accumulate and secrete citrate. The central zone accounts for 25% of the gland tissue and rarely develops carcinoma but harbours benign prostatic hyper-plastic tissue (BPH). The rest (5%) of the prostate is a transition zone. The principal function of the peripheral epithelial cells is to secrete high amounts of citrate and zinc into seminal fluids. Normal prostate contains ten times higher concentrations of citrate and zinc in comparison with other cells [26].

In the last 10 years, intensive research into citrate/iso-citrate relationships and the roles of zinc in the regulation of prostate metabolism has produced clear understanding that in normally functioning prostate cells high levels of Zn serve to inhibit the activity of mitochondrial aconitase. This inhibition results in that the second step in the TCA cycle,

when citrate is converted to iso-citrate by aconitase reaction, becomes a rate-limiting step and the evolution of Kreb's cycle is nearly truncated. Consequently, citrate is accumulated to the tissue levels of 10–15 mmol/g in the normal peripheral zone of the prostate, as contrasted with other tissues that generally contain 0.25–0.45 mmol/g [26].

This citrate–Zn relation is inverted in the prostate cancer where the peripheral area looses its ability to accumulate citrate and retain zinc. These reduced citrate and zinc concentrations are characteristic features of carcinoma and are not pronounced in BPH. Zinc depletion results in the restoration of *m*-aconitase activity and enhanced citrate oxidation rate. The inability of malignant prostate cells to accumulate citrate and zinc is accompanied by the down-regulation of the specific zinc transporter protein ZIPI [26]. Regulation factors for this transporter are not known yet and it is not clear whether the down-regulation of ZIPI is one of the causes of malignant transformation or is merely secondary to other carcinogenic factors.

Decrease in zinc and citrate concentration occurs early in malignant transformation, before any histopathological changes can be observed under the microscope. This is a very important aspect because the direct involvement of citrate and zinc in the pathogenesis and progression of prostate malignancy suggest that their detection might play a vital role in the diagnosis of prostate cancer [26].

In parallel with zinc and citrate depletion, prostate carcinoma cells activate "de novo" lipogenesis. A cascade of metabolic changes leading to enhanced fatty acid synthesis accompanies the malignant transformation of prostate cells. Androgens seem to orchestrate these changes. It was shown that in prostate cancer cells, the SREBP signalling pathway is up-regulated by androgens [29]. In addition to the direct stimulation of SREBP precursor levels, androgens induce a major increase in the expression of sterol regulatory element-binding protein cleavage-activating protein (SCAP). SREBP in turn is known to up-regulate the activity of AceCS and FAS. It has already been shown that FAS expression defines distinct molecular signatures in prostate cancer [30].

Androgen stimulation also stimulates the glucose–pyruvate–citrate lipogenesis via the ATP citrate lyase reaction [31]. It is interesting to note that as shown by small animal PET studies in rat prostate and prostate cancer models [32], androgen stimulation leads to increased ^{18}F-FDG uptake, indicating probable acceleration of the glucose–pyruvate–malate cycle, whilst ^{11}C-acetate uptake was not affected by androgen treatment.

We can hypothesise that prominent ^{11}C-acetate uptake in prostate cancer is not related to the activity of the TCA cycle but rather due to its direct activation to [^{11}C]acetyl-CoA by AceCS1 and further incorporation into [^{11}C]-palmitate by acetyl-CoA carboxylase and FAS reactions. If this is true, then androgens should not have direct action on ^{11}C-acetate uptake because the activity of the latter enzymes is up-regulated by the intra-cellular SREBP signalling pathway and seems to be an inherent feature of neo-plastic cells [16].

An alternative way of ^{11}C-acetate incorporation into the lipid pool of prostate cancer cells would be via [^{11}C]acetyl-CoA incorporation into TCA, its conversion to citrate and then, by ACL reaction transfer, to cytosolic [^{11}C]acetyl-CoA and further participation in fatty acid synthesis. Unfortunately, little is known about the activity and expression of corresponding enzymes in normal and neo-plastic prostate cells [26], and even less is known about the interrelation between these two alternative ways for acetate entry into lipogenesis.

However, there are indications from recent studies of the roles of ATP citrate lyase in cancer cell growth and transformation [13] that probably cancer cells utilise acetate by its direct activation to acetyl-CoA rather than via truncated Kreb's cycle. The authors studied the role of ACL activity in de novo lipogenesis in human lung adenocarcinoma cells by comparing the incorporation of [^{14}C] glucose and [^{14}C]acetate into lipids. They showed that silencing the ATP citrate lyase (Fig. 1) inhibited the incorporation of [^{14}C] carbon into lipids when it was administered as [^{14}C]glucose and had no influence on incorporation of [^{14}C]acetate into lipids.

In this respect, it would be interesting to know the activities and expression of ACL in benign and malignant prostate epithelial cells. If the pronounced ACL activity in neo-plastic cells is confirmed, then it might be one of the reasons why prostate carcinoma cells loose their ability to accumulate citrate (and concomitantly loose zinc as a counter-ion).

Considerations and conclusions

After the analysis of the available information, we can consider some aspects that are important for optimal PET imaging of the prostate cancer with ^{11}C-acetate:

– Why does ^{11}C-acetate produces clear images? From more than 300 clinical examinations in one of our institutions (Castelfranco Veneto), not a single scan was contaminated with bladder radioactivity. We can hypothesise that the main factor responsible for this would be AceCS, which could be differently expressed in normal and malignant cells. There is no other reported data in literature in this regard. On the other hand, this might be due to favourable renal kinetics. In spite the fact that kidneys accumulate most of the ^{11}C-acetate injected, no urinary activity is noticed

[18, 33] and radioactivity, which is not retained in the lipid pool, leaves the body as [^{11}C]CO_2 after oxidation in TCA and exhalation from lungs. Healthy renal cells are active in acetate oxidation.

– Radiolabelled acetate enters in both normal and malignant cells. Why can we detect a small area involved by adenocarcinoma but not the normal citrate-secreting cells of the rest of prostate (>70% of the gland) on ^{11}C-acetate PET images? This is probably due to the different pathways of acetate in normal and malignant cells. The entry point of acetate into the cell is the monocarboxylic transporter (MCT1 and MCT2). The cell, after up-take of acetate, must activate it to acetyl-CoA via acetyl thiokinase reaction (AceCS1 and AceCS2), to make use of it. Unfortunately, little is known about the expression and activity of these key enzymes in normal and neo-plastic prostate. If AceCS1 would be expressed in adenocarcinoma but not in normal epithelial cells, then this explains our observation. One large fraction (precise figure not known yet) of ^{11}C-acetate, which would have entered the malignant cell, would not be oxidised in TCA, but rather incorporated into [^{11}C] palmitate via FAS reaction (Fig. 1). It is probable that the direct use of acetate in healthy cells is not favoured due to the absence of AceCS1 and limited expression of AceCS2. Moreover, even though high Zn levels limit the activity of *m*-aconitase, acetyl-CoA will still be converted to carbon dioxide in the TCA cycle. In addition, biokinetic stoichiometry of palmitate synthesis can play its role in greater sensitivity. To build one palmitate, eight acetyl moieties need be used and two palmitates are built simultaneously by FAS, which would give a 16-fold amplification factor for fatty acid synthesis, respectively, for oxidation.
– Why is ^{11}C-acetate sensitive and specific in prostate cancer detection? Clinical experience shows that prostate cancer recurrences can be visualised very early, when PSA levels are well below 0.8 ng/ml. In the Castelfranco Veneto centre, ^{11}C-acetate PET has been performed in over 300 diagnostic scans with only few "false-positive" images and a global accuracy approaching 90% in differentiating malignant vs benign prostate lesions. Probably due to the early activation of "de novo" fatty acid synthesis in prostate cancer, ^{11}C-acetate is actively incorporated into newly synthesised lipids of malignant cells. Benign cells use acetate (if any acetyl-CoA can be formed by AceCS2 reaction) for energy production in TCA and radioactivity leaves the prostate as [^{11}C]CO_2.
– What is the optimal time to obtain a better separation between tumours and non-tumour tissue after injecting ^{11}C-acetate? Dynamic studies from Långström and colleagues show that activity taken by the cells into TCA will be washed out as [^{11}C]CO_2 after 15–20 min. Thus, delaying image acquisition to 30–40 min after injection (the longer—the better, but there is trade-off with the short half-life of ^{11}C) would increase the contrast between normal acetate-oxidising cells and malignant fatty acid-synthesising cells.
– Acetate can be labelled with ^{11}C in two positions. Which position is preferable and would give better contrast and sensitivity? From the biochemical analysis described above, it would appear that the commonly used 1-[^{11}C]acetate (labelled into the carboxyl moiety) is the tracer of choice. The position of the label would make no difference in the route where acetate is incorporated into the fatty acids. On the other hand, a large part of the injected tracer will be taken up by normal cells and organs. These will oxidise 1-[^{11}C]acetate to [^{11}C]CO_2 completely after one turn in Kreb's cycle, whilst the label in position 2 will continue to turn some 5–10 min longer. The use of 1-[^{11}C]acetate (the ^{11}C label is attached to carboxyl) will result in faster washout of activity non-specifically taken up by healthy cells.
– Last but not least, zinc serum levels detected by atomic absorption spectrophotometry might become a valid analytical support for the earlier detection of prostate malignancy.

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