

Next-generation metabolic imaging in pancreatic cancer

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In pancreatic ductal adenocarcinoma (PDAC), the lack of specific symptoms or diagnostic markers, the highly aggressive nature of the disease and high intrinsic and acquired therapy resistance all result in a virtually unchanged overall 5-year survival rate of around 5%.¹ Thus, early detection of PDAC is a major task for improvement of prognosis and management of this fatal disease as surgery currently presents the only option for long-term survival.² Conventional imaging techniques, including CT, proton-based MRI and endoscopic ultrasound, differentiate tumour tissue based

on morphological and physiological (eg, reduced perfusion) changes, often not present in precursor lesions and early-stage tumours. Consequently, emerging innovative imaging technologies include molecular and metabolic approaches that allow the assessment of tumour biology.

Cancer phenotypes result from a host of mutational events, including signalling pathways that adapt tumour cell metabolism to support growth. One of these metabolic phenotypes observed in tumour cells is the Warburg effect, that is, ATP generation from glycolysis even under normal oxygen condition, converting most incoming glucose to lactate. Key pathways involved include phosphoinositide 3-kinase, hypoxia-inducible factor, p53, MYC and AMP-activated protein kinase. These alterations in glucose metabolism have been used in positron emission tomography (PET) imaging, in which the glucose analogue ¹⁸F-labelled fluorodeoxyglucose (¹⁸F-FDG) has been extensively applied in many cancer entities including PDAC. However, reported sensitivities and specificities of 90% and 80%, respectively,³ and false-positive results due

to inflammation have so far limited clinical implementation of PET for diagnosis of PDAC.

Promising alternative metabolic imaging approaches include imaging of hyperpolarised compounds and their metabolites upon conversion using magnetic resonance spectroscopy imaging (MRSI). With the advent of dissolution dynamic nuclear polarisation,⁴ a technique that dramatically increases the sensitivity of MRSI, *in vivo* imaging of hyperpolarised isotope labelled tissue metabolites for the first time became feasible. A major advantage of MRSI is the ability to detect labelled substrate and metabolites dynamically upon intravenous injection instead of a momentary glimpse at the distribution of a particular tracer such as with ¹⁸F-FDG PET imaging. In addition, hyperpolarised MRI can provide both anatomical and physiological information, whereas PET only allows functional imaging, requiring a hybrid approach (ie, PET-CT or PET-MRI). An important limitation of this new technique is the relatively short half-life of the polarisation. Therefore, substrates employed have to fulfil certain physicochemical premises and must be subject to fast transport and metabolism.⁵ Hyperpolarised [^{1-¹³C}]pyruvate MRSI has been applied in several preclinical animal tumour models to visualise substrate circulation and uptake via monocarboxylate transporters as well as label flux (ie, label exchange and net conversion) to

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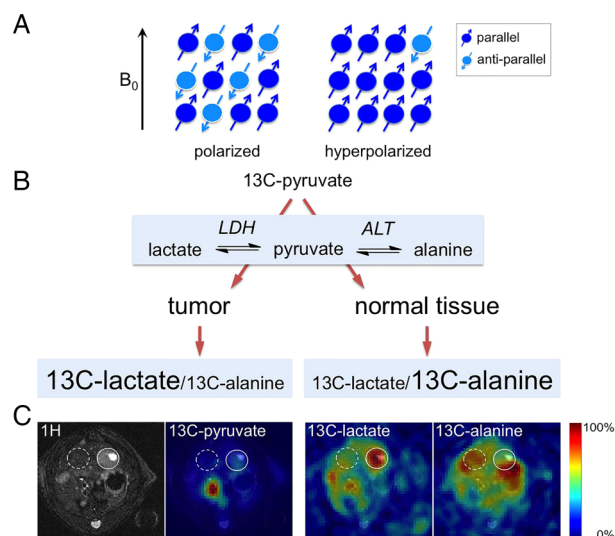


Figure 1 Hyperpolarised ^{13}C magnetic resonance spectroscopic imaging. Spin orientation in the magnetic field B_0 . Hyperpolarisation results in up to 10 000-fold increase in parallel orientation, which translates into higher MR-signal intensity (A). Increased aerobic glycolysis (ie, Warburg effect) is reflected by an increased lactate dehydrogenase (LDH) activity and lactate production in tumour compared with normal tissue (B). Proton (^1H) and hyperpolarised ^{13}C images of a hepatic tumour (circle) and normal liver tissue (dashed circle) exhibit differential lactate/alanine signal behaviour (C). ALT, alanine aminotransferase.

$[1-^{13}\text{C}]$ alanine and $[1-^{13}\text{C}]$ lactate metabolites via the alanine aminotransferase (ALT) and lactate dehydrogenase (LDH) (figure 1).

In this issue of *Gut*, Serrao and colleagues performed metabolic imaging with hyperpolarised $[1-^{13}\text{C}]$ pyruvate in mouse models of PDAC to test its feasibility for early disease detection and progression.⁶ They used a genetically engineered mouse model system harbouring preneoplastic lesions and complex microenvironmental alterations that faithfully recapitulate the human disease. The authors report decreased alanine/lactate concentration and ALT/LDH activity ratios in tissue extracts and correspondingly decreased $[1-^{13}\text{C}]$ alanine/ $[1-^{13}\text{C}]$ lactate signal ratios with disease progression following the injection of hyperpolarised $[1-^{13}\text{C}]$ pyruvate in vivo. Importantly, these imaging data are reproduced in ex vivo cell-free extracts, demonstrating that the in vivo imaging data accurately measure isotope exchange. With a high prevalence of activating mutations in the KRAS oncogene in >90% of PDAC, hyperpolarised $[1-^{13}\text{C}]$ pyruvate MRSI seems a particularly promising imaging strategy, as previous work established a pivotal role for oncogenic RAS in tumour metabolism with an increase in aerobic glycolysis, fuelling both anabolic and catabolic downstream pathways, leading to increased lactate production.⁷

What are the hurdles that need to be overcome for clinical translation? An

important technical issue regarding the clinical application of hyperpolarised substrate MRSI remains the measurement of rate constants rather than absolute concentrations, which complicates interindividual comparison. However, as the authors point out, longitudinal measurements may suffice to identify therapy response or disease progression of individuals. Further limitations present the low sensitivity with resultant low spatial resolution (ie, 7 mm^3) that has been reported for the first human trial of hyperpolarised $[1-^{13}\text{C}]$ pyruvate MRSI in human prostate cancer⁸ related to the short half-life of the polarisation state. Partial volume effects may, therefore, present an issue with regard to motion artefacts and the large tissue heterogeneity found in PDAC.

How can one envision the application of this new imaging technique in clinical patient care? Individuals with familial PDAC exhibit an increased rate of precursor lesions. This high-risk patient population would benefit from better surveillance screens to detect disease progression. In addition, hyperpolarised $[1-^{13}\text{C}]$ pyruvate MRSI may enable the differentiation of mass forming pancreatitis and pancreatic cancer, as indicated by the lack of change in alanine/lactate concentration ratio observed in an experimental pancreatitis model compared with normal pancreas in the study by Serrao *et al.*⁶ Furthermore, hyperpolarised $[1-^{13}\text{C}]$ pyruvate MRSI could enable early detection of metabolic tumour response to approaches that

interfere with increased glucose metabolism, for example, LDH-A inhibitors.⁹

In summary, this exciting study presents MRSI with hyperpolarised $[1-^{13}\text{C}]$ pyruvate as a novel and promising non-invasive, radiation-free method for early detection of disease progression in developing pancreatic cancer, for example, in high-risk patients. Furthermore, it may provide an opportunity for patient stratification and early therapy response monitoring in the highly heterogeneous group of pancreas tumours. While several technical issues remain to be resolved regarding the clinical translation, this study describes an exciting avenue to metabolic imaging of PDAC: the spotlight is on for early detection of this frightening disease.

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