Mapping pH in the tumour extracellular region as new MRI biomarker in oncology

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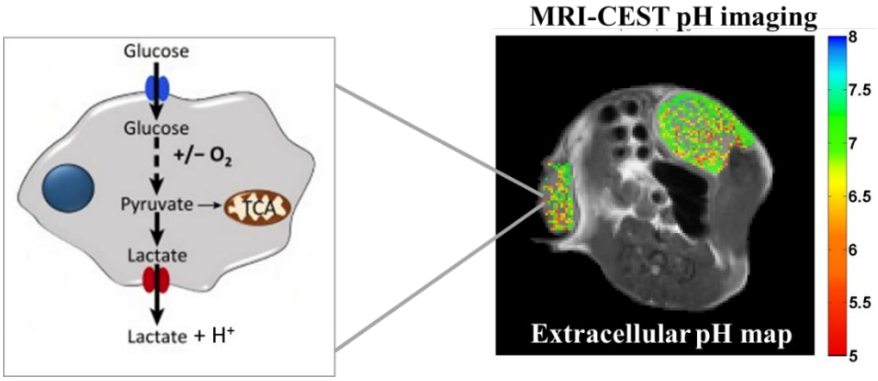
One of the main characteristics of solid tumours is their highly heterogeneous physical microenvironment. Cancer cells craving for energy much more glucose than normal cells and mainly process it through aerobic glycolysis, the so-called "Warburg effect" (1). Such an altered metabolic pattern associated to poor perfusion and regional hypoxia cause higher lactate production, higher proton extrusion and their consequent accumulation leads to an enhanced acidification of the extracellular pH (pHe), which is a salient feature within many solid tumours. The excessive protons are excreted into the extracellular matrix causing, not only the activation of some lysosomal enzymes with acidic optimal pH, but also the expression of some genes involved with pro-metastatic factors. Chronic exposure to acidic pHe has been reported to promote invasiveness and metastatic behaviour in several tumour types (2). Despite the excellent studies regarding tumour acidosis, an effective acid-based imaging protocol that allows extracellular tumour pH quantification and pHe related changes following therapeutic treatment is still needed. Recently, chemical exchange saturation transfer (CEST) imaging has been proposed as a novel MRI-based technique and several agents have been considered for assessing tumour metabolism and pHe. Among them, clinical approved radiographic contrast agents and heterocyclic compounds have been exploited for measuring pH and pathological-induced pH changes (3). The peculiar mechanism of action of these contrast agents is based on the selective saturation of exchangeable protons (that resonate at a chemical shift that is different from that of bulk water signal), followed by the transfer of the saturated protons to the bulk water, resulting in a decrease of the water signal intensity. CEST contrast agents have been reported and tested both *in vitro* and *in vivo* applications and the exchange rate of their mobile protons is pH-dependent. Among the CEST pH-responsive contrast agents developed so far, Iopamidol is a non-ionic clinical approved radiographic contrast agent used in many diagnostic applications. The chemical structure of Iopamidol contains mobile amidic protons that are exploited for the generation of the CEST contrast, which consequently confers its pH-responsiveness properties. In addition, MRI-CEST pH mapping was demonstrated to be an excellent tool to investigate the relationship between glycolysis and acidosis at clinical magnetic field (4).

In conclusion, this thesis is devoted to set up a novel diagnostic tool using MRI-CEST methodology for assessing tumour microenvironment changes (acidosis and vascularization) that can evaluate the therapeutic efficacy upon treatment.



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