Pre-Clinical MR of Cancer
MR in Cancer Cell Models

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Highlights

- Combination of MR with "omics" technologies allows novel insights on molecular mechanisms responsible for cancer hallmarks.
- Multivariate statistical analysis and metabolite quantification of MRS profiles provide tools to test and translate new proofs-of-concept from cell models to in vivo cancer lesions.
- An increasing interface of MR with other molecular and cellular imaging methods opens new perspectives to identify non invasive markers of tumor progression and therapy response.

Target audience: oncologists; cancer cell biologists; MR technologists
Who will benefit: users of multimodal molecular imaging approaches in cancer

Cancer is a heterogeneous disease characterized by dysregulation of multiple molecular events leading to a series of general features (cancer *hallmarks*) first introduced by Hanahan and Weinberg in 2000 and recently revised to include reprogramming of energy metabolism and specific characteristics of tumor microenvironment (*Cell* 2011). **Purpose of the talk**: to guide learners across a critical overview of recent applications of high resolution (HR) MRS approaches which, combined with other molecular and cellular imaging technologies, offer novel insights on links between metabolic profiles and oncogene-activated cell signaling pathways, and on their relationships with cancer hallmarks. **Methods:** frequently adopted cancer cell models include oncogene-transfected cells; leukaemia cells; stabilized cell lines and primary cell cultures derived from breast cancers of different phenotypic and genotypic subtypes; solid or ascite-derived ovarian cancers; primary and metastatic prostatic and colo-rectal carcinomas; osteosarcomas; gliomas. The metabolic profiles of human cancer cells cultured under controlled conditions of nutrients, growth factors and oxygenation are frequently compared with those of the same cells xenografted in experimental rodents. Analyses of cell and tissue extracts allow improved spectral resolution and detection of a larger number of metabolites. Applied technologies include 1D and 2D MRS analyses; HR magic angle spinning (MAS) ^{1}H MRS methods; conventional or hyperpolarized MRS detection of metabolic fluxes in intact cells using precursors enriched with stable isotopes possessing a nuclear spin. **Results:** Major metabolic features investigated by MRS in cancer cells are: **A)** *Redirection of mitochondrial-to-glycolytic bioenergetics* under normoxic conditions. While [^{18}F]-2-FDG PET detects increased glucose uptake and enhanced hexokinase activity, conventional and hyperpolarized MRS of ^{13}C-enriched substrates measures differential fluxes through reduced pyruvate dehydrogenase- and enhanced lactate dehydrogenase-mediated reactions and acidification of the tumor microenvironment [**1**]. **B)** *Aberrant choline phospholipid metabolism*. Among over thirty MRS-detected metabolites, the ^{1}H MRS profile of choline-containing compounds (tCho, 3.2 ppm) reflects the links between oncogene-driven cell signaling and activities of phosphatidylcholine (PtdCho)-cycle enzymes such as choline kinase (ChoK), specific phospholipases (PLC and PLD) and phosphodiesterases; inactivation of ChoK and PLC could significantly affect tCho profile, cell proliferation, differentiation and migration [**2,3**]; notably, recent evidence showed physical binding of PLC to epidermal growth factor receptors, with striking effects on receptor overexpression [**3-5**]. This emerging scenario suggests new ways to therapy targeting and monitoring. **C)** *Formation of cytoplasmic lipid bodies.* ^{1}H MRS provides a unique tool to quantify the production of triacylglycerol/cholesteryl ester aggregates in intact cells in response to inducers of environmental stress, mitochondrial dysfunction, differentiation and apoptosis [**6,7**]. **Conclusion:** The assessment of MRS-detected metabolic levels and fluxes in cancer cells and comparison of spectral profiles of cultured cells with those of surgical specimens and clinical lesions provide novel information on in vivo cancer cell biology, along with new perspectives for the design of targeted treatments and therapy response monitoring. **References**: **[1]** Gallagher FA et al. *Prog NMR Spectr* 2009; 55:285-295; **[2]** Glunde K et al. *Nat Rev Cancer* 2011;11:835-848; **[3]** Podo F et al. *NMR Biomed* 2011; 24:648-672; **[4]** Paris L et al. *Breast Cancer Res* 2010; 12: 12:R27; **[5]** Abalsamo L et al. *Breast Cancer Res* 2012; 14/2/R50; [**6**] Delikatny EJ et al. *NMR Biomed* 2011;24:592-611; **[7]** Iorio E et al. *Biochim Biophys Acta* 2003;1634:1-14.