Introduction
Magnetic resonance spectroscopy (MRS) allows detection of abnormal profiles of aqueous phospholipid derivatives and mobile neutral lipids in cancer cells and tissues at preclinical and clinical level. Progressive elucidation of the molecular mechanisms underlying these spectral features gives access to novel insights on molecular cancer biology and allows the identification of noninvasive biomarkers of in vivo tumor progression and therapy response [1-11]. In particular, integration of molecular imaging with genomic, proteomic and metabolomic approaches point to an aberrant choline phospholipid metabolism as an emerging hallmark of cancer, beyond its large phenotypic variability. The altered profiles of MRS-detected choline-containing compounds (MRS-Cho) in cancer result from multiple links with oncogenic signalling pathways and interaction with molecular mechanisms of tumor adaptation to its microenvironment. Quantification of the aberrant phospholipid and neutral lipid profiles in cancer cells and tissues is relevant to a better understanding of the relationships between MR spectral features and the modifications of gene expression associated with tumor progression and response to therapy.

The MRS-Cho profile of cancer cells in vitro and in vivo
Phosphocholine (PCho), glycerophosphocholine (GPCho) and free choline (Cho) are the major constituents of the $^1$H MRS-Cho profile of cancer cells and tissues. These metabolites play the dual role of precursors and products of biosynthetic and catabolic reactions taking place in the phosphatidylcholine (PtdCho) cycle [2,12]. An elevated peak due to the trimethylammonium headgroup of these compounds (collectively called tCho, centered at 3.2 ppm) is usually detected by single-voxel $^1$H MRS and MRSI examinations of a variety of cancers, including epithelial carcinomas in breast, colon, prostate, ovary, lung, bladder and other organs, neuroepithelial tumors in brain, hepatomas, sarcomas, lymphomas and others. An average global tCho concentration of 2.2 mM (range 0.0-8.5 mM) has for instance been measured at 4.0 T in breast cancers, compared with an average concentration of 0.2 mM (range 0.0-1.1 mM) in benign lesions [13]. PCho and GPCho signals can also be detected, together with those or their ethanolamine analogues, in phosphomonoester (PME) and phosphodiester (PDE) spectral regions of on vitro and in vivo $^{31}$P MR spectra of cancer cells and tissues [2,14]. Choline-based discrimination of malignant from benign lesions has been reported in eight pilot studies performed at 1.5 T in the years 1998-2006 (reviewed in [15]) with ranges of sensitivity 70-100% (average 89%) and specificity 67-100% (average 87%). Measurement of the ratio of the tCho peak area to the area of other signals, of the signal-to-noise ratio of tCho in the spectrum or determination of the tCho integral in arbitrary units could allow tumor diagnosis with sensitivities and specificities up to about 90%, reaching an
area under the curve (AUC) of over 0.92 in receiver operating characteristics (ROC) analyses performed in clinical settings ([16] and references therein).

Identification and quantification of the individual tCho molecular components in appropriate preclinical settings are relevant to the elucidation of molecular mechanisms responsible for tCho detection in different cancer types and to the possible improvement of protocols for non invasively monitoring tumor response to molecularly targeted therapies in the clinical setting.

Absolute quantification of the individual tCho components requires in vitro high resolution (HR) MRS analysis of cancer cell or tissue extracts or the use of HR Magic Angle Spinning (MAS) MRS approaches to analyse intact biotrial or surgical specimens [17]. A mean tCho concentration of 15.0 ± 0.7 fmol/cell (range 5-35 fmol/cell) has for instance been measured in aqueous extracts of human ovarian cancer cells compared with a value of 5.0 ± 2.4 fmol/cell in non tumoral counterparts (EONT, consisting of primary cultures of cells from the ovary surface epithelium (OSE) and/or their non tumoral immortalized cell variants) [8,18]. Phosphocholine represents the major tCho constituent in these cancer cells (PCho/tCho = 0.80 ± 0.14 (±SD)). A similar result has been reported for xenografts obtained by subcutaneous or intrapelvic implantation of these cells in severe combined immunodeficiency (SCID) mice, in which a PCho/tCho ratio of 0.99 ± 0.01 was measured in vivo at 4.7 T (tCho range 2.9-4.5 mM) and confirmed by ex vivo analyses on excised tissues and their extracts at 9.4 T [19]. These results were in good agreement with those obtained in our laboratory for colon cancer cells (tCho 18.6 ± 5.5 fmol/cell, PCho/tCho 0.73 ± 0.07) [8], or reported in the literature for breast cancer lines (tCho 15.1 ± 4.0 fmol/cell,mean PCho/tCho ratio 0.80 ± 0.03) [20] and for a cell line isolated from primary prostate cancer (tCho 15.4 fmol/cell; PCho/tCho 0.70) [21]. Metabolic maps constructed from [tCho, PCho/tCho] pairs allowed a highly significant discrimination of these epithelial cancer cells from their respective nontumoral counterparts [8]. Furthermore, decreased values of the GPCho/PCho ratio have been reported using 1H and 31P NMR analyses of breast, prostate and ovarian cancer cells compared with the respective nontumoral counterparts (reviewed in [8]). A comparative evaluation of these features in metastatic vs. primary tumors would be worth of future efforts.

The changes reported in the intracellular contents of choline metabolites in breast cancer cells characterized by different molecular subtypes and in ovarian cancer cells derived from either primary or ascitic tumors did not correlate with cell doubling time [20,22,23]. This finding suggested that the increased tCho peak area is not a simple indicator of the rate of cancer cell proliferation, but likely represents the metabolic outcome of the network of signalling pathways activated during malignant transformation and tumor progression.

Changes in the intracellular contents of choline derivatives have been reported in mammalian cells following oncogene transformation or transfection with genes characteristic of cancer cells. Examples are the increase in PCho and decrease in the GPCho/PCho ratio reported in ras-transformed rat Schwann cells [24]; the about 3-fold increase in PCho in ras-transformed NIH-3T3 fibroblasts [25]; the about 10-fold increase in PCho in mammary epithelial cells transfected with the human epidermal factor receptor 2 (HER2) gene [20]; the about 2.2-fold increase in PCho in the ovarian cancer cells SKOV3 following in vivo passage in the peritoneum of SCID mice, a procedure which allowed selection of a cell variant characterized by a 1.7-fold amplification of HER2 overexpression [19]; the over 2-fold increase in PCho in the p53-/- cell variant of a colon cancer cell line [26]; and the decrease in PCho and increase in GPCho in the highly metastatic breast carcinoma cell line MDA-MB-435 following stable transfection with the metastatic suppressor gene nm53 [27].
Multivariate analysis of HR MAS \(^1\)H MR spectra showed that higher PCho and lower GPCho levels contributed to the discrimination of estrogen receptor (ER)-negative from ER-positive breast cancer surgical specimens [17]. Furthermore, different MRS-Cho profiles were detected in human luminal-like and basal-like human breast cancer xenografts grown in immunodeficient mice [28], in agreement with the different spectral patterns shown by surgical breast cancer specimens respectively classified as triple-negative or estrogen- and progesterone-positive by histopathological examination.

**Molecular mechanisms responsible for altered MRS-Cho profiles in cancer cells**

The molecular mechanisms responsible for altered MRS-Cho profiles have been investigated in a variety of cancer cells compared with the respective non tumoral counterparts [reviewed in 8,10,11].

**Choline transport**

Choline transport can be mediated by different types of molecular transporter systems, such as the high-affinity choline transporter CHT1 and the choline transporter-like (CTL1-CTL5) and organic cation transporter (OCT1-OCT3) proteins. Differential expression of members of these families of transporters may differently affect the uptake of choline in different cancer cells, with expected implications on both the MRS-Cho profile and the standardized uptake value (SUV) of radiolabelled choline in PET examinations. For instance, upregulation of OCT2 and CHT1 has been reported in a set of different breast cancer cells irrespective of their different molecular subtype classification. This evidence was in agreement with an enhanced maximum velocity (Vmax) of choline transport in these cells compared with non tumoral human mammary epithelial cells (HMEC) [22]. A high CTL1 overexpression has been reported in lung adenocarcinoma cells [29]. Upregulation of CTL3 was instead accompanied by downregulation of OCT3 in ovarian cancer cells, in which all other transporters were practically unmodified compared with OSE cells [18].

**The Kennedy pathway**

Once entered in the cancer cell, free choline is efficiently converted into PtdCho (the most abundant phospholipid of eukaryotic cells) by the Kennedy pathway (Fig. 1). This biosynthetic reaction cascade consists of three consecutive steps respectively catalysed by choline kinase (ChoK), CTP:phosphocholine cytidylyltransferase and diacylglycerol (DAG) choline phosphotransferase.

ChoK, a cytosolic enzyme consisting of three known isoforms, ChoK\(\alpha\)1 and ChoK\(\alpha\)2 (formed by alternative splicing of the CHKA gene transcript) and ChoK\(\beta\) (encoded by CHKB gene), is a regulatory enzyme of the de novo PtdCho biosynthesis. Choline kinase activity depends upon the relative abundance of ChoK\(\alpha\) and ChoK\(\beta\) homo- and heterodimers. In mammalian cells ChoK is activated by hormones, mitogens, and growth factors. Its activation is involved in both Ras-dependent and Ras-independent carcinogenesis, with bi-directional regulatory links with different oncogenic pathways, including the MAPK and PI3K/AKT kinomic axes [30,31]. Recent evidence showed that ChoK expression can be regulated by the hypoxia inducible factor HIF-1, whose \(\alpha\)-subunit showed the capability to bind in vitro to a CHKA promoter region [32]. ChoK overexpression/activation has been reported to correlate with high histological grade and negative estrogen receptor status in breast carcinoma [33] and act as potential prognostic factor in non-small cell lung cancer [34] and in bladder cancer [35]. The activity of ChoK measured by Eliyahu et al [22] in breast cancer cells ranged 2 to 5 nmol/mg protein/h in cell lines belonging to different molecular subgroups, compared with a value of about 1 nmol/mg protein/h in HMEC. Microarray and RT qPCR analyses of these
cells showed 5- to 8-fold increases in mRNA expression of CHKA, without major changes in CHKB expression [22]. Mean ChoK activity rates ranging 7.4 to 12.0 nmol/10^6 cells/h (corresponding to about 30-50 nmol/mg protein/h) were measured by Iorio et al [18] in ovarian cancer cells, compared with a value of 0.6 ± 0.2 nmol/10^6 cells/h (corresponding to about 3 nmol/mg protein/h) measured in the non-tumoral hTERT cells. These 12- to 20-fold increases in the mean ChoK activity rates measured in cancer cells were associated with a lower and rather uniform (3-4-fold) increase in ChoK protein expression and in a 3.8 ± 0.4 relative (2^-ΔΔCt) increase in CHKA mRNA expression, while CHKB mRNA expression was practically unaltered. These results suggest that additional factors, besides gene and protein expression, can contribute to ChoK activation in cancer cells, likely due to the effects of with post-translational mechanisms and deregulated cell signaling pathways.

The mRNA expression levels of genes encoding for the enzymes of the next two steps of PtCho biosynthesis, CTP:phosphocholine cytidylyltransferase (PCYT1A and PCYT1B) and diacylglycerol (DAG) choline phosphotransferase (CHPT1), were not significantly different in ovarian cancer cells from those of OSE cells, indicating that the build-up of a PCho pool in the Kennedy pathway was mainly due to ChoK overexpression and activation [18]. Similar conclusions were reported by Eliyahu et al [22] for breast cancer cells compared with HMEC cells. However, in both breast and ovary cancer cells the PCho levels did not significantly correlate with the ChoK activity rates, suggesting that additional molecular mechanisms, likely linked to PtdCho degradation pathways, should also contribute to the intracellular accumulation of this metabolite.

**Phosphatidylcholine catabolism**

PtdCho hydrolysis can occur along three major catabolic pathways, respectively mediated by phospholipase D (PLD), phospholipase C (PtdCho-PLC, here abbreviated as PC-PLC) and by a combination of phospholipase A2 (PLA2), phospholipase A1 (PLA1) and lysophospholipases (LPL) acting in the PtdCho deacylation pathway, followed by GPCho phosphodiesterase-mediated GPCho hydrolysis. All catabolic pathways may contribute to the MRS-Cho profile by either fueling free choline into the Kennedy pathway and/or producing PCho and GPCho (Fig 1).

**Phospholipase D**, responsible for PtdCho hydrolysis into Cho and phosphatidate (PA), is a regulator of cell physiology, proliferation and survival, cell transformation and tumor progression, under the control of oncogene-driven pathways such as those triggered by Raf-1, Ral-GDS and AKT. Furthermore, PLD is activated in response to stimulators of vesicle transport, endocytosis, exocytosis, mitosis and cell migration and is abnormally expressed and activated in a number of human cancer types. Two major isoforms have been isolated and sequenced, PLD1 (mainly localized in perinuclear and Golgi regions) and PLD2 (located in raft domains of the plasma membrane) [36]. Phosphatidate is a pleiotropic second messenger, acting as precursor for the phosphohydrolase (PAP)-mediated formation of another second messenger, DAG [37], and production of lysophosphatidate (LPA), a potent regulator of ovarian cancer cell growth [38]. Furthermore, PA is an antagonist of rapamycin and its analogs for binding to mTOR at the mTORC-1 complex binding site [39]. In combination with the action of ChoK, PLD activation could in principle contribute to an increase of the PCho pool in cancer cells. However only a moderate, if any, increase in mRNA expression of PLD2 and unaltered PLD1 expression level were measured in ovarian cancer cells compared with OSE cells [18]. Furthermore a 2-4-fold PLD activation was observed in only two of four examined ovarian cancer cell lines, although the PCho level increased in all of them. Similar results were reported for breast cancer cells [22], in which a 2- to 3.5-fold PLD activation...
was detected in only three of five cell lines. Notably the PLD activity was maintained unaltered in the highly metastatic triple-negative MDA-MB-231 as well as in the luminal-like MCF-7 cells.

*Phosphatidylcholine-specific PLC* is responsible for PtdCho hydrolysis into PCho and DAG. This enzyme, already sequenced from prokaryotic cells, has been isolated but not yet cloned from mammalian sources. Accruing evidence supports a functional role of this enzyme in mitogenesis, cell differentiation, apoptosis, and immune cell activation [40-47]. There is an increasing interest in assessing the role of PC-PLC in oncogene-transformed and cancer cells and tissues [18,23,48-52]. A 5- to 19-fold PC-PLC activation has been measured, using NMR-based assays, in total lysates of ovarian cancer cells compared with a nontumoral counterpart (HTERT) [18]. Using cross-reactive antibodies raised in rabbit against bacterial (*B. cereus*) PC-PLC [48,53] we were able to detect PC-PLC overexpression in ovarian cancer cells, in which the enzyme accumulated on the plasma membrane, although it was also present in inner cell compartments including cytoplasm and nucleus [50]. A PC-PLC accumulation was also detected on membrane of HER2-overexpressing breast cancer cells, where the enzyme was found to co-localize and physically associate with HER2 in raft domains [51]. Moreover, PC-PLC inhibition by the xanthate D609 resulted in a strong downmodulation of both PC-PLC and HER2 from the plasma membrane, as well as in a striking, long-lasting reduction of the overall HER2 protein expression in these cells [*ibidem*].

In the *PtdCho deacylation pathway*, PLA2, PLA1 and LPLs produce lysophospholipids and fatty acids involved in the regulation of normal cell and organ function, cell differentiation, proliferation, apoptosis, senescence and cancer progression. Group IIA-PLA2 is for instance held as a potential marker of malignancy in colorectal, prostatic and gastric carcinoma [54-59].

The level of GPCho produced by the deacylation pathway can be modulated by the downhill formation of free choline and glycerophosphate (Gro3P) under the action of GroPCho-phosphodiesterase (PD). This enzyme has been reported to be involved in leukaemia cell differentiation and in the response of these cancer cells to cytokines [60,61].

The contribution of the deacylation pathway to the MRS-Cho profile in cancer cells may depend on the cancer type and molecular subtypes. A lower PLA2 expression has been for instance reported for the calcium-dependent PLA2 group IV in malignant MDA-MB-231 compared with non tumoral cells [62]. The mRNA expression level of GDPD5, candidate gene for GPCho-PD, was found to be higher in MDA-MB-231 compared with MCF-7 breast cancer cells and to a non tumoral counterpart (MCF-12A), while GDPD5 inhibition or silencing by RNA interference (RNAi) resulted in increase of GPCho and decrease of PCho [63]. Non significant differences were on the other hand reported for the overall mRNA expression levels of 19 PLA2 isoforms in ovarian cancer cells and a 40-50% decrease in the formation of 2-Lyso-PtdCho was measured in total lysates of these cells using a short-chain PtdCho as substrate [18].

Table 1 summarizes the quantitative alterations measured in the levels of MRS-Cho components and in the activity rates of PtdCho enzymes in total lysates of ovarian cancer cell lines, compared with non tumoral counterparts [18]. These data show that there is not a single enzyme capable to explain the altered MRS-Cho profile of these cancer cells. However, the relationships between these activity rates of these enzymes and MRS-detected choline derivatives are not linear nor simply additive, as expected from reactions taking place in different cell compartments.
Table 1. Intracellular levels of tCho, PCho and GPCho (nmol/10^6 cells) and the activity rates of PtdCho-cycle enzymes (nmol/10^6 cells/h) measured in total lysates of ovarian cancer cells compared with non tumoral counterparts [18].

<table>
<thead>
<tr>
<th>Cancer cell</th>
<th>tCho</th>
<th>PCho</th>
<th>GPCho</th>
<th>ChoK</th>
<th>PLD*</th>
<th>PLC</th>
<th>GPCho-PD</th>
</tr>
</thead>
<tbody>
<tr>
<td>EONT</td>
<td>5.4±0.7a</td>
<td>2.6±0.3a</td>
<td>1.9±0.4a</td>
<td>0.6±0.2b</td>
<td>6.7±1.2b</td>
<td>0.5±0.3</td>
<td>3.8±0.4</td>
</tr>
<tr>
<td>CABA-1</td>
<td>17.0±2.1</td>
<td>14.4±1.9</td>
<td>1.1±0.4</td>
<td>10.2±1.7</td>
<td>6.1±0.9</td>
<td>2.4±1.3</td>
<td>10.9±3.5</td>
</tr>
<tr>
<td>IGROV-1</td>
<td>14.5±2.1</td>
<td>11.2±1.7</td>
<td>1.7±0.4</td>
<td>7.9±2.3</td>
<td>14.1±1.3</td>
<td>7.6±2.1</td>
<td>12.5±3.1</td>
</tr>
<tr>
<td>OVCAR-3</td>
<td>12.6±1.5</td>
<td>10.2±1.9</td>
<td>1.9±0.4</td>
<td>12.0±3.0</td>
<td>23.2±2.2</td>
<td>9.6±1.3</td>
<td>17.6±3.2</td>
</tr>
<tr>
<td>SKOV-3</td>
<td>10.3±1.2</td>
<td>8.1±1.0</td>
<td>1.5±0.4</td>
<td>7.4±1.6</td>
<td>4.9±1.4</td>
<td>4.6±2.0</td>
<td>3.5±1.1</td>
</tr>
</tbody>
</table>

* EONT, epithelial ovarian non tumoral cells (ovary surface epithelial (OSE) cells and their stably immortalized nontumoral variants IOSE and hTERT); b hTERT cells.

The MRS-Cho profile as a marker of PtdCho cycle activation

As summarized in the previous sections, the aberrant MRS-Cho profile in cancer cells reflects anomalous rates of production, utilization and fluxes of water-soluble choline-containing compounds in the different pathways of the PtdCho cycle. While the standard uptake value (SUV) of radiolabeled choline in PET examinations mainly depends upon choline transport and phosphorylation in the Kennedy pathway, the altered MRS-Cho profile in cancer cells may result from changes in the activity rates of multiple enzymes acting in both the biosynthetic and catabolic pathways of the PtdCho cycle. Activation of this cycle under the effect of oncogene-driven genomic and post-translational modifications, results into the production of second messengers and mitogens such as diacylglycerols (DAG), phosphatidate (PA), lysophosphatidate (LPA) and PCho (reputed to act as both endogenous and exogenous mitogenic factor [64]. In addition, activation of the PtdCho deacylation pathway also produces mediators of inflammation such as arachidonic acid (AA, precursor of eicosanoids and prostaglandins) and general precursors of glycerolipid biosynthesis such as glycerophosphate (Gro3P), free fatty acids and DAG (Fig 1). Besides contributing to the biosynthesis of membranes, an overproduction of the latter compounds may also result into the intracellular accumulation of MRS-detectable lipid bodies, whose formation has been alternatively related to arrest of cell proliferation [65-67].

Choline metabolism as potential target for anticancer therapy

PtdCho-cycle enzymes can play a role as targets for cancer treatment, whose effectiveness can be monitored by the concomitant changes induced in MRS-Cho profiles of cancer preclinical models. RNAi–mediated ChoK knockdown reduced cell proliferation, promoted cell differentiation ad induced a substantial decrease in the PCho signal in breast cancer cell lines [68]. Furthermore, lentiviral vectors used to target ChoK induced a decrease of in vivo tumor growth and reduced the PCho level in human breast xenografts in SCID mice [69]. A ChoK inhibitor (MN58b) induced reversible arrest of normal cells at the G0/G1 phase, but promoted non reversible cytotoxic effects on tumoral cells [70]. The in vivo administration of this inhibitor induced antitumor activity against human breast cancer xenografts in nude mice along with a decrease in the 31P MRS PME resonance [71].

Inhibition of PC-PLC by exposure of ovarian cancer cells to the xanthate D609 resulted in a long-standing (up to at least 72h) arrest of cell proliferation in ovarian cancer cells (an effect which was very close to that induced by serum deprivation), associated with a 30-40% decrease in PCho at 24 h [18]. A substantial decrease in cell proliferation was also detected in HER2-overexpressing cancer cells exposed to the same PC-PLC inhibitor [51].
Figure 1. The aberrant MRS-Cho profile in cancer cells reflect anomalous rates of production, utilization and fluxes of choline-containing compounds (PCho, GPCho and Cho) in the PtdCho cycle. This cycle simultaneously produces second messengers, mitogens and mediators of inflammation such as diacylglycerols (DAG), phosphatidate (PA), PCho, lysophosphatidate (LPA), and arachidonic acids (AA precursors of eicosanoids and prostaglandins) as well as precursors of lipid biosynthesis (glycerophosphate (Gro3P), free fatty acids and DAGs. The scheme shows some of the major links between oncogenic pathways and PtdCho cycle activation.

MRS-Cho profile as possible biomarker of tumor response to targeted therapies
Increasing evidence shows that changes in the MRS-profile may reflect the effectiveness of therapies targeted against specific oncogenic signalling pathways and/or selected reaction steps of the cell kinome. The potential use of in vivo MRS signals for noninvasively detecting the effects of these treatments appears particularly relevant in view of the need to identify new pharmacodynamic markers capable to monitor functional parameters of the lesion in addition to those recommended by the Response Evaluation Criteria In Solid Tumors (RECIST) for imaging clinical trials.

In this frame, recent studies confirmed the potentiality of using the MRS-PCho profile to monitor the effectiveness of either agents designed to selectively inhibit phosphorylation reactions in the Raf/MEK1/2/ERK1/2 or PI3K/AKT/mTOR pathways activated by tyrosine kinase receptors; or enzymes such as fatty acid synthase (FASN) or histone deacetylase (HDAC); or molecular chaperones like HSP90, which affects the cell response to stress by regulating protein folding, cell signalling and tumor repression (reviewed in [7-11]). It is
interesting to note that, although inhibition of these mechanisms is commonly associated with reduced cancer cell proliferation, the PCho signal does not always decrease in response to all tested inhibitors. These evidences are not surprisingly in view of the discussed multiplicity of PtdCho pathways contributing to the PCho pool. The spectral response to different agents may therefore not only reflect different cancer phenotype and molecular histotypes, but also give in the future additional ways to improve patient stratification, better selection of tailored treatments and identification of the most suitable imaging modalities for monitoring the effectiveness of applied targeted therapies. An appropriate development and implementation of these approaches require quantification of the MRS signals and further understanding of their links with the tumor phenotype and genotype.

Conclusions and future directions
Quantification of anomalous MRS profiles of phospholipid and lipid derivatives in cancer cells and tissues gives access to new insights on molecular mechanisms responsible for oncogene-activated signalling pathways, and may allow a better understanding of the significance of the MRS signals as non invasive indicators of diagnosis, prognosis and predictors of tumor response to treatment. The role of Chok and its ChoKα isoform in controlling cell proliferation and PCho content in cancer cells, suggests the use of this enzyme as potential target for antitumor therapy, whose effectiveness could be non invasively monitored in preclinical and clinical settings. Furthermore, the recent detection of a physical association between PC-PLC and a specific membrane receptor such as HER2, together with the capability of PC-PLC inhibition to induce downmodulation of this receptor in HER2-overexpressing breast cancer cells, point to the existence of a previously unknown mechanism by which the activation/deactivation status of a phospholipase can regulate the oncogenic signalling, with potential future applications for the design of new therapeutic strategies.

Further evaluation of the MRS choline profile as indicator of cell proliferation, cell differentiation, survival and invasiveness may contribute to further developments of newly-designed molecularly targeted anticancer treatments and offer new means of detecting their effectiveness by MRS and choline-based PET approaches.

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