mTOR complex activity and metabolic changes as potential targets in solid tumours
PhD theses

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1. Introduction

The regulation of cellular metabolic processes plays an important role in providing the bioenergetic background for biological changes. Metabolism is a set of complex processes that balance the building (anabolic) and depleting (catabolic) reactions to support energy and building blocks for the growth and maintenance of the living organism. In eukaryotic cells, citrate cycle and oxidative phosphorylation (OXPHOS) take place in the mitochondria, but a number of other processes (e.g. glycolysis, proteolysis and lipolysis, etc.) also facilitate to maintain bioenergetics equilibrium. The main pathways of glucose utilisation are well-known. Following the cytoplasmatic steps of glycolysis, the most efficient energy production is ensured by the mitochondrial processes (citric acid cycle and OXPHOS). In the absence of oxygen or even in pseudohypoxia, glycolysis can provide energy via lactate production (Warburg effect). The produced lactic acid is transported by monocarboxylate transporters (MCT) into the extracellular space where the acidic microenvironment also assists tumour growth. Glutamine can also be an important source of energy, its role in metabolic processes is diverse. Besides being involved in protein and nucleotide synthesis, N- and O-glycosylation, its degradation also produces bioenergetic (glutamate) and transaminase substrates. The glutamate-glutamine conversion is directed enzymatically by glutaminase (GLS). Glutamate could be utilised either after its incorporation into protein or nucleic acid or directly via α-ketoglutarate (α-KG). α-KG could participate in energy

production via mitochondrial oxidation or the conversing mechanism of isocitrate to citrate in fatty acid and lipid synthesis. The cell/organism may use saturated, unsaturated fatty acids and lipids in a wide variety of ways (e.g. energy extraction through β-oxidation or membrane construction) or storage. In tumours, increased production and activity of CPT1A are associated with lipolytic processes rather than lipid synthesis.

Cells that are unable to adapt to altered bioenergetic conditions die after a temporary proliferation inhibition via necrotic, apoptotic or other mechanisms. However, those cells that are able to rapid metabolic adaptation gain an advantage over other cells. Based on the former, the combination of metabolic inhibitors with conventional treatments (chemo-, radiation or targeted therapy) or the multiple administration of several metabolic inhibitors may help to break through tumour resistance.

Functional and inhibitor sensitivity differences between the two mTOR complexes (mTORC1 and C2) make more difficult to understand and examine mTOR kinase. The FKBP binding part of mTOR-kinase is located in the inner part of the mTORC2 protein complex, so FKBP12-rapamycin is unable to bind to the mTORC2 complex resulting rapamycin resistance.

As a central part of the signalling network, mTOR is also associated with several proteins and signalling pathways whose mutations (e.g. PI3K, TSC1/2, PTEN, etc.) and thus improper functions are frequent in tumours and other diseases. The target proteins of mTORC1 are involved in the regulation of catabolic and anabolic processes (protein, fatty acid, nucleotide and ATP synthesis, inhibition of autophagy).

The widely known function of mTORC1 is to support protein synthesis through the phosphorylation of eukaryotic translation initiation factor 4E-binding proteins (4E-BP) and p70 S6-kinase 1 (S6K1). mTORC1 is involved in both the synthesis of new membranes via fatty acid and lipid synthesis and glucose metabolism for instance increasing glycolytic enzyme production. In line with these, it has a role in regulating the enzyme expression of mitochondrial and pentose phosphate pathways. Additionally, in the abundance of biosynthetic building blocks and energy, it inhibits the autophagosome-realted proteins ULK1 and ATG13 and controls the steps of early and late autophagy formation (e.g. UVRAG). The knockout of the main elements of mTORC2 inhibits cytoskeleton reorganisation, chemotaxis and migration through lack of phosphorylation of PKCα. mTORC2-dependent phosphorylation processes also regulate PDK1, SGK1 and Akt kinase activities. By increasing the activity of GSK3b, it inhibits e.g. apoptosis; and controls glucose metabolism. Furthermore, it also plays an important/pivotal/essential role in protecting cells against stress factors.

Following its discovery, rapamycin, was registered as an immunosuppressant. After understanding the role of mTOR-kinase in cancer biology, the third-generation inhibitors are now being developed and tested. Rapamycin and its derivatives inhibit the activity of mTORC1 complex via binding to the FKBP12 protein of the kinase. Tumour indication areas of its derivatives: AML – temsirolimus; advanced renal carcinoma, neuroendocrine tumours, pancreatic, gastrointestinal tumours, and lung carcinomas – everolimus. Despite rapalogs are not always clinically successful. Rapalogs

have no or less effect on the mTORC2 complex, moreover, they may even increase the activity of mTORC2 due to the feedback mechanisms of signal transmission. Second-generation mTOR inhibitors are ATP-competitive inhibitors and target the effects of both mTOR complexes, and may also inhibit other signalling kinases (e.g. Akt). Nowadays, studies of third-generation inhibitors are ongoing as well. Current clinical results suggest that mTOR inhibitors alone are not effective enough, however, a better therapeutic outcome can be expected in combinations with other treatments. mTOR inhibitor combinations (e.g. everolimus, ridaforolimus) are tested in addition to the registered aromatase inhibitor and trastuzumab (anti-HER2+ therapy) combination. In the future, the combinations can be successful in breaking the resistance problems, but their use may be influenced by the side-effect profiles and the individual sensitivity.

In our studies, we examined two tumour types, which have significant importance regarding to both therapeutic and mTOR hyperactivity, gliomas with high malignancy, poor prognosis and different molecular subtypes of breast adenocarcinomas.

Gliomas represent the most common type malignant tumours of the central nervous system in adults. Gliomas can be categorised as astrocytomas, oligodendrogliomas and ependymomas. Grade I/II type astrocytomas are more manageable, slow-growing tumours, but can be transformed into higher grade. Grade III anaplastic astrocytomas and glioblastomas (grade IV) are difficult to treat due to their rapid, aggressive growth. Grade IV glioblastoma multiforme is the most common and an extremely aggressive primary brain tumour with a very short survival (an average of 15 months). The

former groups can be divided into additional prognostic subgroups based on molecular subtyping.

In 2016, an important factor was introduced in the classification of gliomas – accordingly is the gain of function mutation of the isocitrate dehydrogenase (IDH) genes leads to D-2-hydroxyglutarate (2-HG) oncometabolite production (epigenetic and other metabolic changes promoting the tumour growth). The IDH mutation is commonly detected in grade II astrocytomas and oligodenrogliomas; its presence is associated with better prognosis in primary glioblastomas (grade IV). However, IDH-mutant gliomas with better prognosis may develop higher grade secondary glioblastomas during progression. These may include increased activity of certain signalling pathways (PI3K/Akt/mTOR) and amplification of several genes (*MYC*, *MET*, *EGFR*).

Currently, the therapy of gliomas includes surgical, radiation and chemotherapy (temozolomide). The therapeutic options are quite limited; despite the recent improvements (e.g. bevacizumab and mTOR inhibitor phase trials), there is no real breakthrough. Increased aerobic glycolysis (Warburg effect) and glutaminolysis have been observed in gliomas as metabolic changes. mTORC1/2 activity is also involved in the regulation of glycolysis and glutaminolysis. Numerous *in vitro* and *in vivo* experiments also demonstrate the potential inhibitory effect of dual, third-generation mTOR inhibitors and temozolomide combinations on tumour growth of glioma cells. PFKP and PDK1 are the most promising glycolysis targets in glioblastomas. However, the metabolic plasticity of glioblastoma cells and the rearrangement of glycolytic processes towards OXPHOS can often obstruct the

success of metabolic inhibitors. The importance of glutamine utilisation is even less revealed. The significance of glutamine utilisation in IDH1-mutant tumours is well-characterised which explains the demonstrated anti-tumoural effect of glutaminase inhibitors. It is also well-known that in addition to *de novo* lipid synthesis, which supports the proliferation, glioma cells are also able to absorb and utilise exogenous lipids from the microenvironment by mitochondrial β-oxidation. The importance of the above is confirmed by the fact that acetate, in addition to the increase in ACSS2 expression, could also be a source of carbon in glioma cells. In summary, the glycolytic capacity of glioma cells is elevated, moreover, glioma cells are also capable of using glutamine, fatty acids and acetate, which indicates potential metabolic plasticity and additional adaptation mechanisms.

Recently, the treatment protocols of breast cancers patients have been changed and improved. Nevertheless, the therapy of poor prognosis and therapy-resistant breast tumours requires further improvements and efforts. Based on the status of hormone, estrogen and progesterone receptor (HR, ER and PR, respectively) and the expression of human growth factor receptor 2 (HER2), three groups can be distinguished clinically: HR-positive (HER2-negative, about 70%), HER2-positive (ER-negative or positive 10-20%) and triple negative (ER, PR, HER2-negative 10-20%).

In line with the gene expression profile, breast cancers can be divided into four molecular subtypes: luminal A, luminal B, HER2-positive and basal type. The relative location of tumour cells and basal membranes is also an important aspect in the pathomorphological characterisation and clinical behaviour of breast tumours.

Based on this, *in situ* (DCIS, LCIS) and invasive carcinomas can be distinguished. Prognostically, tumour stage determination is important, which depends on the size of the tumour (T), the involvement of the surrounding lymph nodes (N) and the presence of distant metastases (M).

In addition to conventional chemotherapeutic agents (e.g. taxanes, anthracyclines), targeted anti-HER2 and hormone therapies are the most decisive in the pharmacological treatment of breast tumours.

According to the observations of metabolic pathways in breast cancers, metabolic characteristics of these malignancies could be either subtype-dependent or independent. However, the organisation of these results and the classification of breast tumours by metabolic subtypes have not been published yet. Based on other studies, metabolic symbiosis and the reverse Warburg effect are associated with OXPHOS activity in ER+ breast tumours. It is common that endocrine therapy resistance develops in case of ER+ cancer patients. The ER pathway may affect the genes that regulate glycolysis, glutaminolysis and OXPHOS.

HER2+ and triple negative (TN) breast tumours generally have high levels of GLUT1 expression with increased LDHA and MCT1 expression. HER2+ tumours tend to produce fatty acids, while TN tumours are characterised by increased lipid uptake.

Tissue studies in relation to the expression of glutaminase in breast tumours are contradictory, accordingly glutamine utilisation cannot be linked to certain subtypes. Based on previous observations, trastuzumab treatment reduces glucose uptake and lactate release, the intensity of the Warburg effect and lapatinib reduces the expression of GLUT1 and GLUT4

transporters. These indirect effects of inhibiting aerobic glycolysis are also related to the *in vitro* anti-proliferative effects of glycolysis inhibitors (e.g. GLUT1 inhibitor).

Glutaminase inhibitors could reduce the proliferation of TN breast cancer cell lines *in vitro* and *in vivo*. So far tumour type and contradictory results have been reported in relation to the inhibition of fatty acid metabolism (e.g. FASN inhibition). However, β-oxidation inhibitors may provide new possibilities in radiotherapy-resistant cases. Tumour growth reduction as an off-target effects of mitochondrial inhibitors such as metformin or certain antibiotics (e.g. doxycycline) have also been described in cancers. Metabolic inhibitor treatments are not the most appropriate alternatives monotherapy, but they can be combined with current therapies to assist in therapeutic developments.

2. Aims

We aimed to characterise the mTOR activity and the metabolic alterations of glioma and breast cancers *in situ* and *in vitro*; and in addition, to investigate the sensitivity of glioma and breast cancer cell lines to mTOR and metabolic inhibition.

Besides testing and comparing quantitative changes in mTOR activity and certain metabolic enzyme proteins of human glioma samples and cell lines, examining the intracellular metabolite concentration differences *in vitro*. To investigate the susceptibility and the combined effects of mTOR inhibitor, temozolomide and metabolic inhibitor in glioma cell lines *in vitro*.

Performing the characterisation of mTOR activity, metabolic protein expression and intracellular metabolite concentrations by using different subtypes of human breast cancer cell lines. In line with this, to compare the sensitivity of breast cancer cells to mTOR and metabolic inhibitor treatments *in vitro*. Based on our previous studies, we propose to select immunohistochemical markers for the characterisation of metabolic and mTOR activity of clinical tissue samples; and in parallel, to compare the tissue characteristics with patients' clinicopathological data. Additionally, to test the effects of mTOR and metabolic inhibitor combinations on breast cancer tumour models *in vitro* and *in vivo*.

3. Methods

***In vitro* studies –** studied cell lines: U87 MG, U373-U MG, *IDH1* wild-type U251 MG and *IDH1*-mutant U251 MG human high grade glioma cell lines; MCF7, T47D (LumA); ZR75.1, BT474 (LumB); SKBR3, MDA-MB453 (HER2+); and MDA-MB231, MDA-MB468, BT549, HS578T (TN) breast adenocarcinoma cell lines. We tested the mTOR (rapamycin (RAPA), NVP-BEZ235, PP242, GDC-0068 (GDC)) and other metabolic pathway inhibitors (BMS-303141, etomoxir, 3-bromopyruvate (3BP), BPTES doxycycline (Doxy) and chloroquine). Temozolomide (TMZ) was used as a chemotherapy agent for glioma cell lines, while doxorubicin (Doxo) was applied in the study of breast carcinoma cells. Proliferation of cell cultures was tested with Alamar Blue or sulforodamine B assays.

***In vivo* studies:** ZR75.1 xenografts were established by injecting cells subcutaneously in SCID mice. We compared tumour sizes and final tumour masses in the following groups: Rapamune, doxorubicin, doxycycline, Rapamune + doxorubicin and Rapamune + doxycycline.

Protein expression studies: immunohistochemical (IHC) examination of formalin-fixed paraffin-embedded biopsy samples was performed with the following antibodies: p-mTOR (Ser2448), p-S6 (Ser 235/236); Rictor; p-Akt-(Ser473), GLS, LDHA, CPT1A, FASN, ACSS2.

Western blot and WES Simple techniques were also used to study protein expression of cell lines. In the Western blot analysis, anti-β-actin, as loading control, and p-mTOR, p-S6, Rictor, Raptor, mTOR, S6, LDHA, GLS, GLUT1, β-F1-ATP-ase, GAPDH, pan-Akt, p-(Ser473)-

Akt, PFKP, HK2, ASCT2, LDHB, CPT1A, FASN, ACSS2, PDH, p-Acly, COXIV, LC3 and anti-p-AMPK primary antibodies were used.

Determination of metabolites by liquid chromatography-mass spectrometry: lactate, pyruvate, citrate, α-KG, succinate, fumarate, malate, glutamate and aspartate concentrations were determined with using calibration curves, the values were added as ng/10^6 cell.

Analysis of Kaplan-Meier plotter data: using the Kaplan-Meier Plotter database (KM plotter; http://www.kmplot.com), we analysed mRNA expression data certain mTOR and metabolic pathway-related enzymes in breast cancer patients.

Statistical analysis: Mann-Whitney U-test, Fisher test, log-rank test and Kaplan-Meier curve analysis were used for prognostic tests (IBM SPSS Statistics software). Hazard Ratio, Cox regression analysis and Student t-test were also applied. $p \leq 0.05$ was considered statistically significant.

4. Results

Human glioma studies

According to our immunohistochemical examination performed in normal peritumoural cerebrum (n=4) and IDH wild and mutant human glioma samples (n=10, n=8), low levels of p-mTOR, p-S6 and (p-Ser473)-Akt were detected in normal brain tissues whereas moderate expression was showed in IDH-mutant and high in IDH wild-type gliomas. IDH wild-type gliomas are characterised by high general metabolic enzyme expression (CPT1A, ACSS2, LDHA, FASN except for GLS) which indicates a potential substrate usage flexibility in these cells. In correlation with the elevated mTOR-related protein levels, mTORC1/C2 and dual mTOR inhibitors showed significantly higher proliferation inhibition than rapamycin and temozolomide in the four studied glioma cell lines.

U87 and the genetically modified IDH-mutant U251 cells were found to be the least TMZ and mTOR inhibitor sensitive *in vitro*. Among the enzymes that indicate metabolic alterations, the levels of HK2, FASN and GLS were reduced by mTOR inhibitor treatments, while a simultaneous enhanced expression change was observed in case of CPT1A and ACSS2. The metabolic rearrangement effects of TMZ were less characteristic, however, significant individual differences were detected in cells. Comparing to the other two cell lines, U251 IDH wild and mutant cells showed lower glycolytic (HK2, LDHA) activity and higher GLS expression in parallel. Between U251 wild and IDH-mutant cell lines significant differences were not observed in the expression of

metabolic proteins. In accordance with the quantitative differences between HK2 and LDHA U87 cells showed the highest lactate/malate ratio.

Rapa and chloroquine treatments caused cell line-dependent growth inhibition. BPTES, doxycycline and etomoxir monotherapy treatments did not show any significant protein or phospho-protein expression changes. In case of TMZ resistance, increased mTORC2 activity (p-(Ser473)-Akt and Rictor), elevated CPT1A and LC3 expressions were observed. After Rapa treatment, the expected mTOR activity change (mTORC2 activation) and in case of TMZ addition increased CPT1A and LC3 expression were assessed.

The anti-proliferative effect of chloroquine has been enhanced by other inhibitors and the combination of TMZ. Rapa was more effective in combinations than in monotherapy. The effect of Rapa + TMZ was either synergistic in U251 and U373-U cells or additive in U87, furthermore, the combination of Rapa + Doxy was also successful. At protein level, the level of FASN decreased, but there was no increase in CPT1A levels in parallel. The increase in TMZ-induced mTORC1 activity was completely suspended by Rapa and even the increase in mTORC2 activity – p-(Ser)-Akt – was not observed. The level of β-F1-ATP-ase – required for OXPHOS activity – was also significantly reduced by the highly effective Rapa + TMZ combination which could be an interesting therapeutic perspective in the breakthrough of TMZ resistance.

Human breast adenocarcinoma studies

Changes of mTOR and metabolic protein expression with mTOR and other metabolic inhibitors

were also investigated in ten breast cancer carcinoma cell line *in vitro*. Alterations in mTOR activity-related proteins and the proliferation effects of the used inhibitors (Rapa, PP242, and GDC) were evaluated together. The most effective anti-proliferative effects were observed after PP242, mTORC1 and C2 inhibitor treatments. 3BP, the glycolysis inhibitor, was the most effective metabolic inhibitor. Three triple negative of the ten cell lines (MDA-MB468, BT549, HS578T) proved to be the most glycolytic (Warburg phenotype) ones based on the intracellular lactate/malate ratio. High LDHA protein expression was observed in all cell lines, while the level of LDHB showed significant individual differences. FASN was higher in non-triple negative groups, whereas high CPT1A and ACSS2 were characteristic for all cell line. Regardless of these subtypes, breast carcinoma cell lines show significant individual metabolic differences.

For characterising the mTOR and the metabolic activity of breast tumours *in situ*, we examined the tissue volume and the distribution of proteins p-S6, Rictor, LDHA, GLS, CPT1A, FASN proteins in nearly 100 human biopsy samples comparing with clinicopathological data. Tumour cells and normal tissues were characterised by high Rictor level, in contrast increased p-S6, FASN and CPT1A expressions were only observed in the studied tumour specimens. The most characteristic intra- and intertumoural differences were observed in case of p-S6 IHC stainings.

Homogeneous cytoplasmatic LDHA and granular, mitochondrial GLS expression were characteristic in normal and tumour tissues. Patients were divided into groups with low and high H-scores based on the median H-score values of stainings. Elevated LDHA expression

(Warburg glycolysis) was associated with HR-, while high CPT1A and FASN expressions showed significant correlations with HR+ status. High p-S6 correlated with the presence of distant metastasis, the age of patients and the shorter metastasis-free and shorter overall survival subtype independently. LDHA showed significant association with subtype, grades and stages. The analysis of CPT1A and FASN H-score values and survival data also showed certain tendencies and differences. Higher CPT1A was a feature of worse therapeutic outcome, on the contrary, FASN was correlated with better prognosis.

We also performed combined evaluation methods to identify mTOR activity and other metabolic pathways markers. Cases with high H-score of mTOR and at least two other metabolic pathway markers were classified as a good metabolic adaptability group. Based on these, good metabolic adaptability was correlated with shorter distant metastasis-free and overall survival. We also confirmed our results by using mRNA expression, survival and clinical data analysis of the KM plotter database.

The most effective treatments of gliomas have been tested on ZR75.1 LumB human breast tumour cells *in vitro* and *in vivo*. The three studied combinations (Rapa + Doxy, Rapa + Doxo, and Doxo + Doxy) significantly reduced cell proliferation compared with monotherapies *in vitro*. Rapa + Doxy combination was the most effective treatment *in vivo*, this is the first *in vivo* result regarding to the *in vivo* tumour growth inhibitory effect of rapamycin and doxycycline.

5. Conclusions

Results on mTOR activity and metabolic characteristics of human glioma tissues and cell lines:

1. Compared to the lower mTOR activity of normal brain tissue, increased mTORC1 and mTORC2 complex activity was observed in association with the progression of gliomas. We detected that moderate mTOR activity is a feature for IDH-mutant gliomas, while in IDH wild-type gliomas significantly increased mTOR expression could be described.
2. In parallel with mTOR activity, increased amount of CPT1A and ACSS2 proteins was observed in gliomas at tissue level. Furthermore, an overall significant increase was detected in metabolic enzyme levels of IDH wild-type tissues. These results highlight both the possibility of bioenergetic adaptability in high-grade gliomas and the importance of other nutrient utilisation pathways beside glucose consumption.
3. The low sensitivity of glioma cell lines to temozolomide, mTOR and other metabolic inhibitor monotherapies is associated with the *in vitro* detected metabolic enzyme expression changes (metabolic plasticity) and mTOR complex activity rearrangement, (mTORC2 activity shift).
4. Administrating simultaneously multiple inhibitors, anti-metabolic treatment combinations significantly decrease tumour growth via preventing the metabolic rearrangement in glioma cell lines. In addition to temozolomide + rapamycin, other rapamycin + anti-metabolic inhibitor combinations (e.g. rapamycin + doxycycline or rapamycin + chloroquine treatments) have complex additive, synergistic effects that

significantly increase the inhibition of tumour growth and the effectiveness of conventional treatments.

Results on mTOR and metabolic characterisation of different subtypes of breast cancer cell lines and human biopsy samples:

1. The examined breast tumour cell lines are characterised by individual, subtype independent mTOR activity and metabolic enzyme expression which are associated with the *in vitro* detected inhibitor sensitivity differences.
2. Based on the metabolic enzyme expression profiles and intracellular metabolite concentrations of the studied cell lines, the Warburg phenotype may also be characteristic feature for subtypes with better prognosis.
3. According to our results on mTOR activity and metabolic plasticity of breast tumours, we selected six IHC stainings (p-S6, Rictor, GLS, LDHA, CPT1A, FASN) from our *in vitro* studies:

a. Subtype independent high mTOR activity and high p-S6 H-score showed significant correlation with shorter metastasis-free and overall survival.

b. LDHA expression (Warburg glycolysis) is rather characteristic for HR-subtypes.

c. High CPT1A expression correlates with worse, while high FASN expression is associated with a better prognosis in breast cancer patients.

d. The studied six stainings in combination with the assessment of metabolic plasticity could help to identify patients requiring a more accurate follow-up of HR+ breast tumours with a good prognosis based on the subtype or contribute to rethink their future, post-relapse therapy.

6. Publications

Publications in context of the thesis:

1.) Petővári G, Hujber Z, Krencz I, Dankó T, Nagy N, Tóth F, Raffay R, Mészáros K, Rajnai H, Vetlényi E, Takács-Vellai K, Jeney A, Sebestyén A. Targeting cellular metabolism using rapamycin and/or doxycycline enhances anti-tumour effects in human glioma cells. Cancer Cell Int. 2018 Dec 19; 18:211. doi: 10.1186/s12935-018-0710-0. eCollection 2018. IF: 3.439

2.) Petővári G, Dankó T, Krencz I, Hujber Z, Rajnai H, Vetlényi E, Raffay R, Pápay J, Jeney A, Sebestyén A. Inhibition of Metabolic Shift can Decrease Therapy Resistance in Human High-Grade Glioma Cells. Pathol Oncol Res. 2019 Jun 11. doi: 10.1007/s12253-019-00677-2. [Epub ahead of print]. IF: 2.433

3.) Petővári G, Dankó T, Tőkés AM, Vetlényi E, Krencz I, Raffay R, Hajdu M, Sztankovics D, Vellai-Takács K, Jeney A, Kulka J and Sebestyén A. In situ metabolic characterisation of breast cancer and its potential impact on therapy. Under review

4.) Hujber Z, Petővári G, Szoboszlai N, Dankó T, Nagy N, Kriston C, Krencz I, Paku S, Ozohanics O, Drahos L, Jeney A, Sebestyén A. (2017) Rapamycin (mTORC1 inhibitor) reduces the production of lactate and 2-hydroxyglutarate oncometabolites in IDH1 mutant fibrosarcoma cells. J Exp Clin Cancer Res, 36(1):74. IF: 6.217

5.) Hujber Z, Horváth G, Petővári G, Krencz I, Dankó T, Mészáros K, Rajnai H, Szoboszlai N, Leenders WPJ, Jeney A, Tretter L, Sebestyén A. (2018) GABA, glutamine, glutamate oxidation and succinic

semialdehyde dehydrogenase expression in human gliomas. J Exp Clin Cancer Res, 37(1):271. IF: 5.646
Other publications:
1.) Hujber Z, Jeney A, Oláh J, Szoboszlai N, Baranyai L, Környei J, Petővári G, Sebestyén A. (2015) Measuring 14C-glucose and 14C-acetate oxidation in tumour cells and tumorous host organism. Magyar Onkol, 59(4); 292-301.
2.) Sticz T, Molnár A, Dankó T, Hujber Z, Petővári G, Nagy N, Végső G, Kopper L, Sebestyén A. The Effects of Different mTOR Inhibitors in EGFR Inhibitor Resistant Colon Carcinoma Cells.Pathol Oncol Res. 2019 Oct;25(4):1379-1386. doi: 10.1007/s12253-018-0434-4. Epub 2018 Jun 7. IF: 2.433

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