mTOR (mammalian target of rapamycin) signaling pathway activity and their significance in human colon tumors

PhD Theses

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Introduction

1. The clinical significance, characteristics and treatment of colorectal tumours

Colorectal carcinoma (CRC) is the third most frequent type of tumour in men as well as in women, concerning their incidence and mortality rates, too. Based on data from 2015 the incidence of CRC in Hungary is 59/100,000 people. More than 90% of CRC cases is an adenocarcinoma. The treatment of CRC primarily requires a surgical intervention. After a successful surgical intervention a recidive tumour or a possible distant metastasis is formed in 25-60% of II and III stage CRC patients. The chance for a recidive tumour is decreased by a neoadjuvant and adjuvant chemotherapy and radiation treatment, administered before and after the operation. In accordance with current standards the basis of the treatment of III stage CRC patients is the oral or intravenous administration of fluoropyrimidine based chemotherapy, complemented with leucovorin. Currently the adjuvant treatment of CRC cases is performed based on the FOLFOX (leucovorin+5-FU+oxaliplatin) or the FOLFIRI (leucovorin+5-FU+irinotecan) standard. Nowadays thanks to the fast development of molecular oncology, biological therapies have become more prevalent, like EGFR- or VEGF-inhibition of colorectal tumours, using monoclonal antibody therapy. The survival of CRC patients is highly dependant on the stage in which the disease is diagnosed. For patients at early stages the 5-year survival rate is ~90%, for patients with regional metastases it is 70%, while for patients with distant metastases it is only 10%.

2. The tumour-biological role of the mTOR signalling pathway's regulating dysfunctions in colon carcinoma

The mTOR (mammalian/mechanistic target of rapamycin) is a 289-kDa serine-threonine protein kinase, integrating different extracellular signals from the pathways of different cell surface receptors and the effects of the signals monitoring the current condition of the cell. Therefore it plays a central role in the growth, proliferation, survival and metabolism of cells. The regulatory dysfunction of the PI3K/Akt/mTOR pathway is known in connection

with different processes (e.g. tumour formation, angiogenesis, insuline resistance, fatty acid synthesis or the activation of immune cells) and a number of diseases.

In cells mTOR is present in the form of two different multiprotein complexes. The structural build-up and function of these two complexes are different. The mTOR complex 1 (mTORC1) consists of the following proteins: the mTOR kinase, the mLST8, the Raptor, the PRAS40 and the Deptor. The mTOR complex 2 (mTORC2) is composed of the mTOR kinase, the Rictor, the mSIN1, the Protor1/2, the mLST8 and the Deptor. The two most important target molecules of mTORC1 are the 4E-binding protein (4EBP1) and the S6 kinases, p70S6K – S6K1 and the p90S6K - S6K2 isoforms. The mTORC1 plays a key role in the regulation of protein synthesis, and its effect of regulating autophagy is also well-known. The mTORC1 also participates in the regulation of other important cellular processes connected to metabolism, e.g. it increases transcription of the hypoxia-inducible factor 1-alpha (HIF1α). Through the production of other transcription factors it is also important in the positive regulation of lipid metabolism and pyrimidine synthesis. Out of the AGC kinases, one of the most important targets of mTORC2 is the Akt. Through the structural adjustment of the actin cytoskeleton, mTORC2 also participates in the regulation of the cell locomotion process.

Rapamycin, the first mTOR inhibitor was discovered in the late 1970s. Later it was shown, that it is immunosuppressive and has an antiproliferative effect. Currently rapamycin derivatives, the so-called rapalogs are widely used in treatment. Temsirolimus was approved to be used in the EU in the therapy of renal cell carcinoma in 2007, and currently it can already be used as a first-line treatment for patients with a poor prognosis. The use of Everolimus was approved in 2009 for advanced kidney cancer cases, where during or after the VEGF-inhibiting treatment a recidive tumour was formed. Also, it is used in the therapy of pancreatic neuroendocrine tumours, lung tumours and in heart transplantation. In cardiology Everolimus-eluting stents are also used.

Unlike rapalogs, which inhibit the mTOR kinase function allosterically, ATP-competitive inhibitors block the ATP-binding, therefore can inhibit the activity of both mTOR

complexes (e.g. the PP242 inhibitor). Due to the similar sequences of mTOR and PI3K certain competitive inhibitors may inhibit PI3K and Akt, too, in the same way as mTOR. These, so-called dual inhibitors generally decrease the activity of the pathway in the PI3K-Akt-mTOR signalling axis, and also reduce the activities (Akt or mTORC2 activities) remaining or augmented due to the feedback loop. NVP-BEZ235 and PF-04691502 are both dual PI3K-mTOR inhibitors, whose anti-proliferative effect, next to inhibiting other effects of signal transmission, has been proven in vitro as well as *in vivo*.

The abnormal activation of the PI3K/AKT/mTOR pathway plays a key role in the forming and progress, as well as the drug resistance of colorectal cancer, therefore in this case mTOR inhibition has also arisen as a possibility. The results of clinical trials performed so far imply that for CRC patients the mTOR inhibition therapy might be of some advantage. In the Everolimus phase II trial, with a 25% objective response rate, a 5.9 months longer average survival rate was achieved.

Objectives

Changes in the activity of the mTOR signal pathway contribute to the proliferation and survival of very different tumour cells. In the present paper I shall examine changes in mTOR activity and the amount of marker proteins for the changes in the activity of the mTOR1 and mTOR2 complexes in clinical CRC-samples and in vitro models, with the following purposes:

I. 1. Human clinical colon carcinoma in tissue samples:

- In situ examination of the expression of proteins connected to mTOR activity, using methods of immunohistochemistry;
- A statistical analysis of correlations between the protein expression data and the clinical survival data of the patients.

I. 2. Human colon carcinoma in cell lines:

- Description of the mTOR activity;
- In vitro examination of EGFR and mTOR inhibitor sensitivity and the effect of combination therapies with mTOR inhibitors

Methods

3.1.1. Examination of mTOR activity in human biopsy samples

I have examined the tissue samples of 103 colon carcinoma patients. After the operation the patients (50 females and 53 males) have received oxaliplatin and 5-FU complex treatment. The average age of the patients was 62 years (the median was 63 years), between the ages of 34 and 78. When examining the clinical data of patients the minimal patient follow-up time was 5 years, when analysing the survival data it was 10 years, with a median survival of 77 months. In 72 of the cases the tumours appeared in the colon, in 31 of the cases they appeared in the rectum. In the Dukes staging system the cases are classified as follows: 30 Dukes B2, 8 Dukes C1, 56 Dukes C2 and 9 Dukes D cases. Based on the international TNM (International Union Against Cancer) staging system there were 36 stage II, 60 stage III and 7 stage IV patients.

When determining the mTOR activity on a tissue level (in situ) we compared the amount of the signalling proteins and phosphoproteins to levels in the normal tissue. We have performed immunohistochemical reactions (mTOR, p-mTOR, Raptor, Rictor, p-S6, p-4EBP1, p-AMPK) on tissue microarrays (TMA-s). The immune reactions were detected with a Novolink (Novocastra) kit, with TBST and PBS buffer washing in between, then the peroxidase activity was made visible in the presence of diaminobenzidine (DAB) chromogen and hydrogen-peroxide substrate, finally the cell nuclei were stained with hematoxylin. The immune reactions were evaluated by three independent persons (2 pathologists and the author of the present paper, with the help of a pathologist), based on principles that had been defined in advance. In the case of any differences, the final values were established based on a consensus, after consulting with a third pathologist. Based on the intensity we established altogether four categories: negative, 1+ (mildly)/ 2+ (moderately)/ 3+ (strongly) positive. The reaction was considered to be positive if at least 10% of the tumour cells displayed the reaction of the specified intensity with the antibody connected to the mTOR signalling pathway or its activity. If the p-mTOR IHC was of 2+

or 3+ in intensity, then the case was assessed as having a high mTOR activity. If in the given case the p-mTOR assessment proved to be negative or only gave a mild (1+) reaction, then the case was considered to have a low mTOR activity. In the case of the Raptor and Rictor staining showing the amount of the two complexes, the Rictor/Raptor dominance was determined based on the intensity of immunostaining. In order to evaluate the amount of Rictors or Raptors to be dominant, all of the assessors had to indicate a difference of at least one + in intensity. For the TMA assessment we used the 3DHistech PanoramicViewer Program and a Nikon E200 microscope.

3.1.2. Statistics

The correlation between the survival data and the mTOR activity differences were examined using the Kaplan–Meier method, and the calculations were performed with PAST, which is a freeware. (http://folk.uio.no). A multivariate analysis was also performed: the different factors were analysed with the Cox regression model, using the SPSS program package (StatisticalPackagefortheSocialSciences, Chicago, IL, USA). The differences between the groups were also examined with the $\chi 2$ test and Pearson's chi-squared test. $P < 0.05$ was considered to be a statistically significant difference.

3.2. *In vitro* examiations using human colon carcinoma cell lines

3.2.1. *In vitro* cell lines and *in vitro* treatments

For the tests we have chosen human colon carcinoma cell lines of different genetic backgrounds, i.e. different mutation profiles (SW620, SW480, HCT116, RKO, Colo205, GC3, CaCo2, HT29).

The therapeutic sensitivity of cells was examined in 24-72 hour cetuximab, gefitinib, cisplatin, rapamycin, PP242 (ATP-competitive inhibitor, inhibits the activity of mTOR kinase in the mTORC1 as well as the mTORC2 complexes) and NVP-BEZ235 (dual ATP-

competitive PI3K and mTOR inhibitor) treatments. The rapamycin treatment was repeated on a daily basis due to its degradation.

3.2.2. *In vitro* proliferation and apoptosis tests

The changes in the proliferation of cells as a result of the treatments were examined by determining the changes in the number of cells, as well as the Alamar Blue proliferation assay. For measuring apoptosis we used flow cytometry. The results of the above measurements were evaluated using the Winlist software (Verity Software House). The so-called subG1 cells of low DNA content were considered to be apoptotic.

3.2.3. Examination of protein expression – Immunocytochemistry, Western blot and Duolink staining

For characterizing the mTOR activity of the *in vitro* cell lines we have examined the amount of proteins using several different methods. On the cytospin slides created out of the cells of the cell lines we used immunostaining, like in the case of the human biopsy samples.

In the case of certain treated and untreated cell lines we performed the quantitative comparison of the protein levels using the Western blot method, too.

In the case of certain cell lines we used the Duolink staining technique (a technique used for the quantitative detection of protein-protein interactions and protein modifications) for the complex detecting the phosphorylated S6 protein and the mTOR-Rictor protein, and also for determining their amounts.

3.2.4. The statistical assessment of the *in vitro* tests

After the given treatments the average proliferation change values and the SD values were calculated from a minimum of three independent parallel, and possibly from three or more parallel tests, depending on the examination methods used. We used the Student's t-test and the one-way variance analysis (ANOVA). $P \leq 0.05$ values were considered to be statistically significant.

Results

4.1. Examination of mTOR activity in human colon carcinoma biopsy samples

We have performed mTOR, p-mTOR, p-S6, p-4EBP1, p-AMPK, Rictor and Raptor immunohistochemical reactions on 103 TMA-s, and after that we summarized their independent assessments. The p-mTOR stainings showed a high mTOR (++ or +++ positivity) activity in 76 of the cases (73.8%).

4EBP-1 and p70S6K are well-known mTORkinase target molecules, and the phosphorylation of the proteins is a sign of the activity of the mTORC1 complex. However, based on tests performed on a wide variety of human tissues and biopsy samples, in most of the tests the most sensitive and most reliable mTOR and mTORC1 activity marker is considered to be the appearance of the target of p70S6K, the phosphorylated form of the ribosomal S6 protein (p-S6), which is the p-S6 positivity which can be shown with an immunohistochemistry test. In all of the cases the immunohistochemistry values of the p-S6, p-4EBP1 and the p-mTOR panels were examined together. All in all, out of the 76 cases showing an intense p-mTOR expression and evaluated to have a high mTOR activity, we found a p-S6 staining evaluated with a 2+/3+ positivity in 74 of the cases, and the assessment of the p-4EBP1 immunohistochemistry reaction yielded similar results. There were three cases showing a high mTOR activity, in which the p-4EBP1 staining proved to be negative, however, in these cases the p-S6 and p-mTOR stainings received a 2+/3+ evaluation from all of the pathologists. There were two cases in which, despite the high mTOR activity based on the p-mTOR staining, we were not able to detect the phosphorylated forms of neither the S6, nor the 4EBP1 proteins. In the cases with a low mTOR activity (27 out of the 103 cases, which is 26.2%) the negative or + assessment of p-S6 and p-mTOR immune reactions showing a good correlation with each other, also clearly indicated a low mTOR activity.

AMPK influences the mTOR activity negatively, and this was also supported by the results of our immunohistochemistry tests: in all of the cases with a low mTOR activity p-AMPK

positivity could be indicated (this is the active form of the kinase), while in the cases evaluated as having a high mTOR activity, p-AMPK positivity was shown in only one of the cases.

Besides the study of proteins characterizing the activity of the mTOR kinase and the mTORC1 complex, we also studied the expression of the Raptor-mTORC1 and Rictor-mTORC2 proteins, which typically appear in these two complexes. Based on the Raptor and Rictor stainings performed parallelly, we were able to classify the studied samples into 3 groups: a) tumour cells displaying a Rictor-dominant expression – in these cells the Raptor protein could hardly be detected (very weak Raptor staining) and we saw a significantly more intense Rictor staining (n=51, 49.5%); b) tumour cells showing a Raptor-dominant expression – these are the cases where in the tumour cells the Rictor showed no or only a low level of expression (n=14, 13.6%) and besides that we saw a typical Raptor staining; c) tumour cells displaying a balanced Rictor and Raptor expression – tumour cells in which we detected Rictor and Raptor staining (that is protein expression) of a similar intensity (n=38, 36.9%). In those two cases where we observed a high level of p-mTOR expression while the markers indicating the mTORC1 activity were not expressed (a low level of p-S6 and p-4EBP1 was not detectible), we could see a clear Rictor-dominance, which is typical of the mTORC2 complex. Out of the 76 cases having a high mTOR activity 39 showed a Rictor-dominance, 8 showed a Raptor-dominance, while in 29 of the cases we observed a similar level of Rictor- and Raptor-expression.

With statistical methods we were not able to show any significant correlations between high or low mTOR activity, the differences between the amounts of the two complexes, the sex and age of the patients and their stage (Dukes) at the time of the diagnosis. However, the patients' chance of survival showed a significant correlation with low mTOR activity. In the patient group with biopsies having a low mTOR activity the 5-year overall survival rate was 77.8% (OVS), while in the group with a high mTOR activity the same percentage was 46.1%, which is significantly worse. The best survival data were observed in the patient group where parallelly with a low mTOR activity we detected a dominant Raptor-

expression, that is a low mTORC1 activity. In this group after the diagnosis and after the treatment survival was more than 5 years for all of the patients. In the other two groups with much poorer prognoses – the Rictor-dominant group with a high mTOR activity, and the group with a high mTOR activity showing no dominance – we were not able to show any significant differences in the 5-year survival data (5-year OVS: 41%, 48.3%). Based on the foregoing the overall survival data are the worst for those patients whose biopsy samples showed a high mTOR activity as well as a high level of Rictor-expression, that is, in whose samples there are tumour cells with a high mTORC2 activity. The survival rates of the group with a high mTOR activity and with a dominant Raptor-expression were significantly better compared to other tumour cases showing a high mTORC2 complex expession. The 5-year survival rate of these patients was only worse compared to cases displaying a low mTOR activity without a dominant expression of the mTORC2 complex (5-year OVS: 62.5%).

Also, we have studied the OVS-data only in connection with the Raptor- and Rictor-expression, which show the amount of the two mTOR complexes. The Rictor-expression showed a correlation with the progress of the disease, even irrespectively of the values of the mTOR activity (assessment of the p-mTOR staining). If we only compare three groups (Raptor-dominant, Rictor-dominant and balanced complex expression), the worst survival rates (5-year survival: 49.5%) were observed in the patient group with tissue samples containing Rictor-dominant tumour cells.

The Kaplan-Meier curves prepared based on the data also show the correlation between the mTORC2 complex activity and the shorter periods of survival, in the case of a high mTOR activity with high Rictor-expression (dominant Rictor-expression or balanced Rictor- and Raptor-expression) in the tumour tissue. The significance data of the Cox regression analysis (taking into account variables like age, sex and stage) have shown, that a high mTOR activity and a high level of Rictor-expression (dominant or balanced Rictor-expression) are independent and stronger risk factors than the determination of the Dukes-stages, and that they can indicate a poor prognosis. Independently of the rest of the factors,

a detected high mTOR activity or Rictor-expression increased the risk of a shorter survival and a poor prognosis.

4.2. Results of the *in vitro* study of human colon carcinoma cell lines

4.2.1. Detecting the resistance to the EGFR inhibitor

Knowing the typical mutations of the colon carcinoma cell lines available in the cell bank of our institute (mKRAS – SW620, SW480, HCT116, mBRAF – RKO, Colo205, HT29; mPI3KCA – HCT116, RKO, HT29, mP53 – CaCo2, HT29, SW480, SW620, GC3) our hypothesis was that these cells might be resistant to a lot of treatments, therefore also to the EGFR inhibitors. During our in vitro tests a – for other, EGFR-inhibitor-sensitive cells – effective dose of neither gefitinib, nor cetuximab managed to inhibit proliferation or induced an apoptosis in the examined cell lines after a 72-hour incubation. However, a high-dose gefitinib treatment – during which already the non-specific kinase-inhibiting effects are also expressed – showed a significant proliferation-inhibiting effect in almost all of the cell lines, and in certain cells e.g. in HT29 and GC3 it showed an increase in the proportion of apoptotic cells. However, in most of the cases, similarly to the RKO cell line, even a high dose of grfitinib treatment resulted only in an inhibition of proliferation *in vitro*.

4.2.2. The rapamycin sensitivity and mTOR activity of colon carcinoma cell lines *in vitro*

Our protein-expression tests in the human colon carcinoma cell lines, similarly to the results of the in situ biopsy samples, have shown a high mTOR activity of the colon tumour cells with the Western blot, immunocytochemistry as well as the Duolink method. The cell lines have shown unique expression differences concerning the amounts of Rictors and Raptors, and accordingly, also in the Duolink stainings, characterizing the expression of the mTORC2 complex and the mTORC1 activity.

The expression of proteins marking mTOR activity – the active mTOR-kinase (p-mTOR), the typical Raptor- or Rictor-proteins of the mTORC1 and C2 complexes, the p-p70S6K

and p-p70S6K target proteins, phosphorylated ribosomal S6 (p-S6), connected to the activity of the mTORC1 complex – showed a correlation with the mTOR inhibitor sensitivity of the cells. The differences in sensitivity were shown through 72-hour rapamycin, PP242 (inhibiting mTORC1 and C2 complexes alike) and dual mTOR inhibitor (NVP-BEZ25) treatments. It was observed that cells producing Rictor in a big amount (+++ with immunocytochemistry), that is GC3, HCT116 and HT29 were less sensitive to the mTORC1 inhibitor treatment. In contrast, in colon carcinoma cells showing a low Rictor-expression (typical of the mTORC2 complex) besides treatments inhibiting both the C1 and C2 complexes, rapamycin, too, inhibited proliferation in tests in vitro, significantly. In cells showing no or hardly any Rictor-expression, e.g. in RKO cells, which are the most sensitive to mTOR inhibitors, dual inhibitor and C1-C2 complex inhibitor treatments proved to be more effective compared to the rapamycin treatment. In the RKO cells the amount of the p-S6 proteins, which are also considered to be the markers of mTORC1 activity, decreased already in 24 hours as a result of a rapamycin and NVP-BEZ235 treatment, while in the case of HT29 cells, which are less sensitive, only a 72-hour NVP-BEZ235 treatment was able to significantly reduce the amount of p-S6 proteins. The amount of p-S6 proteins was reduced by rapamycin, as well as NVP-BEZ235, while the amount of the mTORC2 complex Rictor-proteins could only be reduced significantly by the dual inhibitor NVP-BEZ235.

4.2.3. The effect of the mTOR inhibitor combined treatment to the human carcinoma cells *in vitro*

Resistance constitutes a clinical problem in the case of an increasing number of targeted treatments, including the EGFR inhibitors (EGFRI). Therefore we studied the proliferation inhibiting effects of EGFRI and rapamycin, as well as other mTOR inhibitor combinations in vitro, and any possible sensitizing effects of combined treatments in EGFRI resistant colon carcinoma cell lines . We showed that rapamycin and other mTOR inhibitors (e.g. NVP-BEZ235 and PP242), and EGFR inhibitor combinations can be effective in the

inhibition of tumour growth in the most resistant colon tumour cells (GC3, HCT116 and HT29). We also observed, that in the mTOR inhibitor sensitive cell lines, compared to the effects of the rapamycin treatment, the proliferation inhibiting effect cannot significantly be increased using an mTOR and EGFR inhibiting combination.

Finally, we tested if the mTOR inhibitor treatment can increase the effectiveness of other treatments used in colon carcinoma therapy. Therefore we examined the effects of combined treatments of mTOR inhibiting rapamycin, NVP-BEZ235 and cisplatin in vitro, in three EGFRI resistant colon carcinoma cell lines of different mTOR sensitivity. Results: a) we observed differences in cisplatin sensitivity between the cell lines, the RKO cells proved to be resistant; b) the mTOR inhibiting treatment (significant also in itself), most significantly the dual inhibitor NVP-BEZ235, reduced the proliferation of the EGFR inhibitor resistant RKO cells; c) the dual mTOR inhibitor treatment significantly intensifies the anti-proliferative effects of cisplatin, also in in vitro cultures of EGFR inhibitor resistant colon carcinoma cells (HT29 and SW620).

Conclusions

I. New insights gained by the study of the elements of the mTOR signalling pathway in clinical samples of colorectal cancer:

- The high level activity was observed independently of the Dukes stage and the grading.
- The expression of p-S6 is one of the best markers to ascertain the activity of mTORC1, or even mTOR kinase in formalin-fixed paraffin-embedded samples, if the detectability of p-mTOR or other, direct target proteins is questionable.
- In 2/3 of the studied colon carcinoma cases the high level of mTOR activity can be connected to the mTOR2 complex.
- We have hammered out an immunohistochemistry panel in which the detection of the p-mTOR is complemented with the study of the expression of p-S6, p-4EBP1, Rictor and Raptor. This panel is capable of the in situ description of mTOR activity in colon carcinoma tissue samples.
- A high mTOR activity with a Rictor-dominance (mTORC2 complex activity) shows a significant positive correlation with the poor prognosis of colon carcinoma (both parameters are independent prognostic factors), while the low mTOR activity connected to the mTORC1 complex may co-occur with a better outcome, or even the chance of recovery.

II. New insights in connection with the *in vitro* study of human colon carcinoma cell lines:

- In most of the studied EGFRI resistant colon carcinoma cell lines the dual (mTOR and PI3K) inhibitors and the mTORC1 and C2 dual inhibitor monotherapy have proved to be effective proliferation and tumour growth inhibiting treatments.

- We have managed to affirm in several tumour cell models, that in the treatment of colorectal tumours, mTOR inhibitor combinations can be useful in supporting an EGFR inhibiting therapy, or even the platinum based, traditional treatment.

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