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Original Article

Immunohistochemical Evaluation of Apoptosis and Multidrug Resistance-Related Markers in Gallbladder Dysplasia and Carcinoma

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ABSTRACT

Objective: The search for treatment success in gallbladder carcinomas, which is one of the tumors with the most aggressive course, poor prognosis, and tendency to show resistance to treatment, continues today. Treatments targeting pathways related to genetic changes detected in most solid tumors offer new hope in the treatment of these tumors. Some of these treatment modalities target apoptosis-related pathways, and mammalian target of rapamycin (mTOR), p38, Bcl-2, and caspase-3 are important components of this pathway.

Methods: In the study, mTOR, caspase-3, p38, Bcl-2, LL-37, MDR1, multidrug resistance protein (MRP)1, MRP6, and MRP7 immunohistochemical staining were applied to paraffin blocks of 27 gallbladder cancer and 62 cases with gallbladder dysplasia. The immunohistochemically stained sections were evaluated and scored.

Results: mTOR, p38, and caspase-3 expressions were found to be significantly increased in dysplasia and tumor groups, and in dysplastic and malignant cells. While there was no significant difference in the expression of MRP1 and MRP7, MRP6 was significantly overexpressed.

Conclusion: In this study, increased expression of mTOR, p38, and caspase-3 in the dysplastic and malignant cells of the gallbladder may show that it has a role in the carcinogenesis process in the gallbladder. The study also shows that MRP6 may also play a role in the development of drug resistance in gallbladder carcinoma.

INTRODUCTION

Gallbladder cancer (GBC) is the most common and aggressive malignancy of the biliary tract associated with poor prognosis and chemotherapy resistance.[1] Most cases are diagnosed in advanced stages and the response to traditional chemotherapy and radiotherapy is limited. Identifying the treatment-related genetic changes in tumors ensures the continuity of the search for hope for the treatment of tumors with a poor prognosis, such as GBC. Treatment options acting through apoptosis-related pathways constitute one group of this search. Mammalian target of rapamycin (mTOR), a member of the PI3K-Akt-mTOR signaling pathway, which is one of the main apoptosis-related pathways, regulates cell apoptosis, and plays an important role in carcinogenesis by activating cell cycle, growth, size, movement, and invasion ability.[2,3] Furthermore, p38 has the ability to phosphorylate Bcl-2 and this results in inhibition of the antiapoptotic potential of Bcl-2. p38 Mitogen-activated protein kinase (MAPK) activation and Bcl-2 phosphorylation are synchronous and result in caspase activation and cellular apoptosis.[4] The multidrug resistance proteins (MRPs)

play an important role in chemotherapy resistance in the colon[5] and lung[6] cancers[7] and play functions that mediate the active cellular efflux of xenobiotics (such as chemotherapy drugs) and their metabolites.[1,7] Although MRP6 has previously been shown to be associated with chemotherapy resistance, a treatment resistance relationship has not yet been defined in GBCs. Determination of mTOR, p38, Bcl-2, and Caspase-3 expression in dysplastic and malignant epithelial cells in the gallbladder may give an idea about the treatment possibilities associated with apoptosis in GBCs. Furthermore, determining the expression of MRPs may help explain the mechanism of possible resistance to treatments.

MATERIALS AND METHODS

All the procedures were approved by the Kartal Dr.Lütfi Kırdar City Hospital Ethics Committee (Project Approval Form Number:2020/514/170/2). Seven thousand five hundred and thirty-five gallbladder specimen was re-examined from the archive of the pathology laboratory of Kartal Dr.Lütfi Kırdar City Hospital. Twenty-seven adenocarcinoma and 62 gallbladder dysplasia were diagnosed in the gallbladder and were included in this study. Two paraffin blocks were selected for each case and for immunohistochemical studies. The Ventana BenchMark ULTRA IHC System (Ventana Medical Systems, AZ, USA) was used. Included antibodies were p38 (clone: p38α/β, 1:150 dilution, Santa Cruz, OR, USA), mTOR (clone:FRAP1, 1:250 dilution, Merk, Darmstadt, Germany), Caspase-3 (clone:P10, 1:500 dilution, Boster Biological Technology, CA, USA), Bcl-2 (clone: Bcl-2, 1: 100 dilution, Boster Biological Technology, CA, USA), LL-37 (clone: D-5, 1: 50 dilution, Santa Cruz, Oregon, USA), MDR1 (clone: Polyclonal, 1: 50 dilution, Bioss, Massachusetts, USA), MRP1 (clone: MRP1/1343, 1: 750 dilution, Boster Biological Technology, CA, USA), MRP6 (clone:M6II-7, 1: 300 dilution, Abcam, MA, USA), and MRP7 (clone: Polyclonal, 1: 500 dilution, Boster Biological Technology, CA, USA). All antibodies were diluted with Ventana Antibody Diluent (251–018, Ventana Medical Systems, AZ, USA). The intensity of staining on the surface epithelium was scored semiquantitatively, according to the following degrees of staining: 0 (none), 1 (mild), and 2 (marked). All statistical assessments were performed with SPSS® version 21 for Windows®. The Pearson Chi-square test was used for evaluation. The statistical significance level was established at $p<0.05$ and the confidence interval was 95%.

RESULTS

Twenty-seven adenocarcinomas and 62 dysplasias were diagnosed in the gallbladder. The incidence of gallbladder carcinoma was 0.35% and incidence of dysplasia was 0.82%. The ratio of female cases-to-male cases is 23/4 for adenocarcinoma and 51/11 for dysplasia. The average age of cancer cases was 65.7 (Male: 60.0y and female 66.8y). The average age of dysplasia cases was 52.3 (Male: 49.8y and female 52.8y). In dysplasia and tumor cases, expressions in normal epithelium and dysplastic epithelium were compared. In the tumor group, normal epithelium, dysplastic epithelium, and tumor cells were compared separately. Normal epithelium and dysplastic epithelium in dysplasia and tumor cases were also compared and statistical comparisons are shown in Table 1. There was no significant difference in the expression of any markers in normal epithelium, in dysplasia and tumor groups.

In the comparison of dysplasia and tumor groups, the expression of p38 was significantly higher, and Bcl-2 was significantly lower in the dysplastic epithelium. When the expressions in normal and dysplastic epithelium are compared in the dysplasia group; the number of cases and of p38, mTOR, and caspase-3 expressed cases and intensity of expressions (Fig. 1a-f). Significant loss of expression was

Table 1. Comparison of p values of immunohistochemical expressions of epithelial subgroups

	Dysplasia group	Dysplasia group versus tumor group		Tumor group		
	Normal versus dysplastic epithelium	Normal epithelium	Dysplastic epithelium	Normal versus dysplastic epithelium	Normal epithelium versus tumor	Dysplastic epithelium versus tumor
mTOR	0.000↑	0.269	0.478	0.162	0.008↑	0.06
p38	0.000↑	0.064	0.003↑	0.013↑	0.001↑	0.303
Bcl-2	0.000↑	0.282	0.007↓	a	a	a
Caspase-3	0.000↑	0.781	0.476	0.015↑	0.000↑	0.003↑
LL-37	0.038↑	0.329	0.329	0.310	0.102	3.00
MDR1	0.004↑	0.836	0.836	0.012↑	0.153	1.21
MRP1	0.065	0.143	0.143	0.125	0.157	0.02↑
MRP6	0.000↑	0.845	0.845	0.001↑	0.02↑	1.94
MRP7	0.012↑	0.641	0.641	0.254	0.115	0.26

a: No statistics are computed because Bcl-2 is a constant. No staining was observed in any of the patients in the tumor group. ↑Significance in the direction of increase. ↓Significance in the direction of decrease.

observed in the tumor cells and staining with Bcl-2 was not observed in any of the cases.

In the comparison of expressions in the dysplastic and normal epithelium in patients in the dysplasia group, the

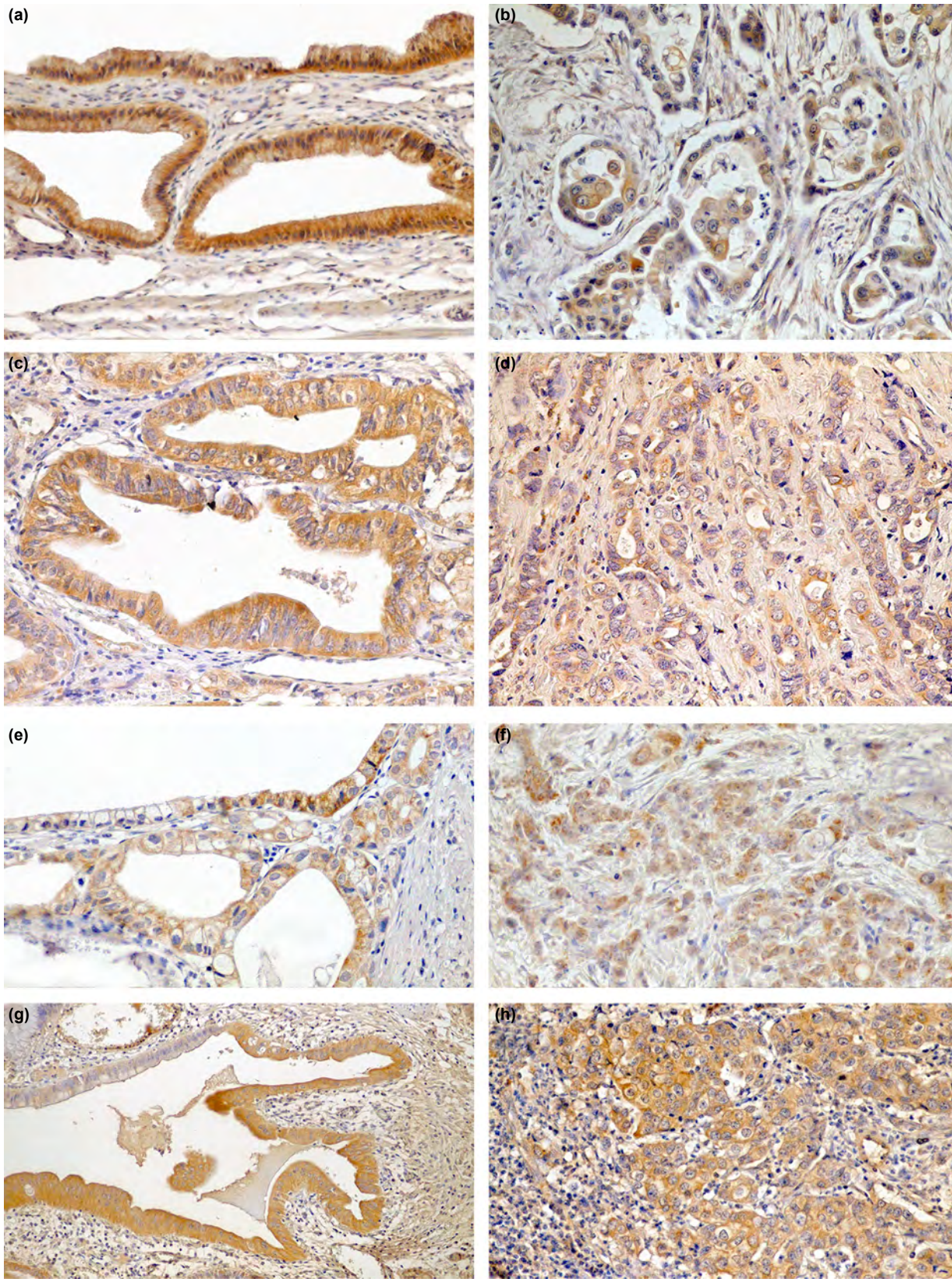

Figure 1. mTOR, p38, caspase-3, and MRP6 immunohistochemical expression in the dysplastic epithelium **(a, c, e,** and **g** respectively**)**, and gallbladder cancer cells **(b, d, f,** and **h,** respectively**)** (Magnification of all sections ×200).

number of p38, mTOR, and caspase-3 expressed cases and intensity of expression was significantly higher in dysplastic epithelium than in the normal epithelium. Bcl-2 expression was mild and the number of dysplastic cases expressing bcl-2 was higher than normal.

In the tumor group, the number of p38 and caspase-3 expressed cases and intensity of expression were significantly higher in dysplastic epithelium than in the normal epithelium. The number of p38, mTOR, and caspase-3 expressed cases and intensity of expression were significantly higher in tumor cells than in the normal epithelium, and the number of caspase-3 expressed cases and intensity of expression were significantly higher in tumor cells than in the dysplastic epithelium. There was no significant difference in mTOR and p38 expression in dysplasia and tumor cells. No staining of Bcl-2 in cancer cells was observed in any of the patients in the tumor group. MRP1 expression was present at mild expression intensity in more tumors than dysplastic epithelium. Comparing the expressions in the normal and dysplastic epithelium in the dysplasia group, number of MRP6, LL-37, MRP7 expressed cases and intensity of expression, and number of cases expressing MDR1 were significantly higher. In the comparison of normal and dysplastic epithelium in the tumor group, the number of cases expressing MRP6 and expression intensity in the dysplastic epithelium and the number of cases expressing MDR1 were significantly higher. When normal epithelium and tumor were compared in the tumor group; the number of cases expressing MRP6 in tumor cells and the expression intensity was significantly higher (Fig. 1g and h). In the comparison of dysplastic epithelium and tumor in the tumor group, no significant difference was observed in MDR expression.

DISCUSSION

Understanding pathogenetic mechanisms and molecular targets for gallbladder carcinoma as well as searching for effective treatment are the focus of current research.[8] p38 is one of the subgroups in the Mitogen-activated protein (MAP) kinase family, and p38α and p38β variants are ubiquitously expressed on tissues.[2] p38 has an effect that described as the pleiotropic, and important for the outcome and the sensitivity to drug therapy.[9] Various extracellular stimuli that activate the p38 pathway activate the p38α pathway differently in different cell types, regardless of the type of stimulus.[2,10] There is an evidential link between the p38 pathway with inflammation, apoptosis, cell cycle, cell hypertrophy and development, cell differentiation, tumorigenesis, senescence, and continuous cell proliferation in the cancers.[2,11] Inhibition of downregulation of caspase-3 was reported to be the mechanism of apoptosis underlying oral carcinogenesis.[12] While p38 signaling has been shown to promote cell death in some cell lines, in different cell lines, p38 has been shown to enhance survival, cell growth, and differentiation. Hence, the role of p38 in apoptosis is cell type and stimulus-dependent.[2,10,13] Activation of p38 MAP kinase activities has been shown to occur during hypertrophy, and a possible role of the p38 pathway in the development of hypertrophy and heart failure has been suggested.[8] If the stress stimulus persists, the balance between hypertrophic and apoptotic signaling is disrupted and cardiomyocytes enter the cell death pathway.[14]

The normal epithelium in the dysplasia group and tumor group shows the different expression of p38, Bcl-2, caspase-3, and mTOR from dysplastic cells and tumor cells. The fact that dysplastic epithelium expresses p38 more than normal epithelium in tumor cells means that the MAPK pathway may have a role in gallbladder carcinogenesis. The similarity of p38 and mTOR expressions may also mean that it could indicate that both paths may have been activated at the same time in the mechanism of dysplasia and carcinogenesis. The higher expression of p38, mTOR, and caspase-3 in the dysplastic epithelium in dysplasia cases means that the pathway may have a role in the dysplasia-carcinogenesis sequence starting from the dysplasia stage. Consistent with this, it has been suggested that MAPK and mTOR signaling pathways might be a potent therapeutic for GBC patients; particularly, those that have both pathways activated. Activation of the AKT/mTOR pathway promotes tumor growth and metastasis.[3,15,16] Similarly, when the normal and dysplastic epithelium in the tumor group are compared, the increase in p38 and caspase-3 expression and decrease in Bcl-2 expression in the dysplastic epithelium is the expected expression pattern, which means that Bcl-2 may play a role in the development of dysplasia, but not in tumorigenesis.[17,18] Phosphorylated p38 proteins can activate several transcription factors, that are involved in controlling cytoplasmic and/or nuclear signaling networks and response to cytokines, growth factors, toxins, and pharmacological drugs.[19] p38δ enhances cell migration and invasion in human cholangiocarcinoma and plays an important role in the metastasis, but not in the developing tumor and tumor cell proliferation.[20] p38α and p38ß are implicated in an IL-6-mediated cell proliferation and survival pathway in benign and malignant cholangiocytes and aberrant p38 MAPK signaling promotes transformed cell growth in malignant cholangiocytes.[21]

Bcl-2 is phosphorylated by p38 and this phosphorylation reduces the anti-apoptotic potential of Bcl-2. Bcl-2 phosphorylation is synchronous with p38 MAPK activation and results in caspase activation.[4] The Bcl-2 expression has been shown to be inversely associated with apoptosis in many tumor types.[22] Bcl-2-mediated inhibition of apoptosis may be an important factor in the tumorigenesis and upregulated Bcl-2 oncoprotein has been identified in some tumors such as oral squamous cell carcinoma.[23] Active caspase-3 expression in GBC was shown.[18,24]

LL-37 is an important antimicrobial peptide regulate and balance immune response to micro-organisms, promotes wound healing, and participates in the tumor surveillance system.[25] It has been documented that LL-37 is upregulated in ovarian cancer, lung cancer, breast cancer, prostate cancer, pancreatic cancer, malignant melanoma, and skin

squamous cell carcinoma and is down-regulated in colon cancer, gastric cancer, hematologic malignancy, and oral squamous cell carcinoma. This suggests that LL-37 has a tumorigenic effect by being upregulated in some organs and has an anti-cancer effect by being downregulated in some organs.[25] The higher expression of LL-37 in dysplastic epithelium compared to the normal epithelium of the gallbladder suggests that it may play a role in the development of dysplasia in the gallbladder epithelium. However, the lack of expression difference between cells in the tumor group suggests that the development of gallbladder tumors and dysplasia may be independent of LL-37. The MRP1 protein molecules playing functions that mediate the active cellular efflux of xenobiotics and their metabolites.[1,7] MRP1 did not show any difference in expression between normal, dysplastic epithelial, and tumor groups, which indicates that it has no role in drug resistance in gallbladder tumors. In the tumor group, it was concluded that the same intensity of staining compared to the dysplastic epithelium in more tumor cases was not significant in terms of drug resistance. Although MRP6 has previously been shown to be associated with chemotherapy resistance in the colon[5] and lung[6] cancers, a treatment resistance relationship has not yet been defined in GBCs. The higher expression of MRP6 in the dysplastic epithelium in our study than in normal epithelium and in the dysplastic epithelium in tumors may indicate its role in increasing drug resistance in the dysplasia-tumor cascade. The fact that MDR1 and MRP7 expression was higher in the dysplastic epithelium than in the normal epithelium in the dysplasia group, but did not differ in the tumor group suggests that they do not have a role in drug resistance in gallbladder tumors.

CONCLUSION

This study showed that increased p38 expression in the dysplastic cells of the gallbladder was increased and p38 activation may have an effect on the development of dysplasia and gallbladder carcinoma. These pathways may be activated in gallbladder epithelial dysplasia and carcinoma, but this does not indicate that dysplasia or cancer develops as a result. However, it may mean that effective therapies can be used through these pathways. The study also shows that MRP6 may also play a role in the development of drug resistance in gallbladder carcinoma.

Ethics Committee Approval

This study approved by the Kartal Dr. Lütfi Kırdar Training and Research Hospital Clinical Research Ethics Committee (Date: 28.01.2020, Decision No: 2020/514/170/2).

Informed Consent

Retrospective study.

Peer-review

Externally peer-reviewed.

Authorship Contributions

Concept: K.B., S.O.; Design: K.B., S.O.; Supervision: S.O., D.D., A.K.K.; Fundings: K.B., S.O.; Materials: K.B.; Data: K.B., S.O., A.K.K.; Analysis: K.B., D.D., S.O., A.K.K.; Literature search: K.B., D.D., S.O., A.K.K.; Writing: K.B.; Critical revision: K.B., D.D.

Conflict of Interest

None declared.

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Safra Kesesi Displazi ve Kanserlerinde Apopitoz ve Çoklu İlaç Direnci İlişkili Belirteçlerin İmmünohistokimyasal Olarak Değerlendirilmesi

Amaç: En agresiv seyir gösteren, kötü prognoza sahip ve tedavi direnci göstreme eğiliminde olan tümörlerden biri olan safra kesesi karsinomlarında (SKK) tedavi başarısı arayışı günümüzde devam etmektedir. Solid tümörlerin çoğunda saptanan genetik değişikliklerle ilgili yolakları hedef alan tedaviler bu tümörlerin tedavisinde yeni ümit olmaktadır. Bu tedavi modalitelerinden bazıları apopitoz ilişkili yolakları hedeflemekte olup, mTOR, p38, Bcl-2 ve caspase-3 bu yolağın önemli bileşenlerindendir.

Gereç ve Yöntem: Çalışmada 27 SKK ve 62 safra kesesi displazisi tanısı olan olguların parafin bloklarına mTOR, caspase-3, p38, Bcl-2, LL-37, MDR1, MRP1, MRP6, and MRP7 immünohistokimyasal boyaması uygulandı. İmmünohistokimyasal olarak boyanmış kesitler değerlendirildi ve skorlandı.

Bulgular: mTOR, p38 ve caspase-3 ekspresyonları displazi ve kanser gruplarında, displastik ve malign hücrelerde istatistiksel olarak anlamlı artmış bulundu. MRP1 ve MRP7 nin ekspresyonlarında anlamlı farklılık yokken, MRP6 anlamlı olarak fazla eksprese ediliyordu.

Sonuç: Bu çalışmada safra kesesi displastik ve malign hücrelerinde mTOR, p38 ve caspase-3 ekspresyonunun artması, safra kesesinde karsinogenez sürecinde rolü olduğunu gösterebilir. Çalışma ayrıca MRP6'nın safra kesesi karsinomunda ilaç direncinin gelişmesinde rol oynayabileceğini de göstermektedir.

Anahtar Sözcükler: Apopitoz; çoklu ilaç direnci; safra kesesi displazisi; safra kesesi karsinomu.