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ARAŞTIRMA MAKALESİ

The role and importance of galectin-3 in colon carcinoma metastasis

Galektin-3'ün kolon karsinom metastazindaki yeri ve önemi

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ABSTRACT

Aim: Galectin-3 is an endogenous β-galactoside binding protein which is an S-type lectin family member with intracellular and extracellular localization and has certain tasks for controlling cell adhesion, growth, proliferation, differentiation, migration, and apoptosis. In this study we aimed to elucidate the role of galectin-3 expression in metastasis biology and its role in predicting tumor metastasis in colon carcinomas.

Materials and Method: In this research, 80 cases with colon adenocarcinoma containing the transition of the normal mucosa-tumor tissue were included. The expression of galectin-3 in these cases was investigated immunohistochemically.

Results: There was no significant relationship between Galectin-3 expression and age, gender, and histological type, but there was a significant increase in the amount of galectin-3 expression while the histological grade increased. Galectin-3 expression of the adjacent normal mucosa and tumor was found to be significantly higher in patients with metastases than patients without metastases. There was also a correlation between the presence of vascular invasion and the increase of galectin-3 expression. The mean galectin-3 expression in metastatic foci was higher than that of the tumor area. These findings suggest that the cells with metastatic phenotype express a higher amount of galectin-3 and also galectin-3 has an indirect role in the pathogenesis of metastasis even if its place could not be determined currently.

Conclusion: In our study, it was concluded that the expression of galectin-3 may play a role in the metastatic process of colon carcinomas.

Keywords: Colon Adenocarcinomas, Metastasis, Galectin-3

ÖZ

Amaç: Galektin-3, hücre içi ve hücre dışı yerleşimli, hücre adezyonu, büyümesi, çoğalması, farklılaşması, göçü ve apoptozu kontrol etmek ve aralarındaki ilişkiyi düzenlemek gibi görevleri olan S tipi bir lektin ailesi üyesi olan endojen bir β-galaktozid bağlayıcı proteindir. Bu çalışmada galektin-3 ekspresyonunun metastaz biyolojisindeki rolünü ve kolon karsinomlarında tümör metastazını öngörmedeki rolünü aydınlatmayı amaçladık.

Gereç ve Yöntem: Bu çalışmaya normal mukoza-tümör dokusunun geçişini içeren kolon adenokarsinomu bulunan 80 olgu dahil edildi. Bu vakalarda galektin-3 ekspresyonu immünohisto-kimyasal olarak araştırıldı.

Bulgular: Galektin-3 ekspresyonu ile yaş, cinsiyet, histolojik tip arasında anlamlı bir ilişki olmadığı ancak histolojik derece arttıkça galektin-3 ekspresyon miktarında anlamlı bir artış olduğu görüldü. Komşu normal mukoza ve tümörün galektin-3 ekspresyonu, metastazı olan hastalarda metastazı olmayan hastalara göre anlamlı derecede yüksek bulundu. Vasküler invazyon varlığı ile galektin-3 ekspresyonunun artışı arasında da bir korelasyon tespit edildi. Metastatik odaklardaki galektin-3 ekspresyonunun ortalaması, tümör alanınındakinden daha yüksek bulundu. Bu bulgular metastatik fenotipli hücrelerin daha yüksek miktarda galektin-3 eksprese ettiğini ve galektin-3'ün metastaz patogenezinde henüz yeri belirlenememiş olsa da dolaylı olarak rolü olduğunu düşündürmektedir.

Sonuç: Çalışmamızda galektin-3 ekspresyonunun kolon karsinomlarının metastatik sürecinde rol oynayabileceği sonucuna varıldı.

Anahtar Kelimeler: Kolon Adenokarsinomları, Metastaz, Galektin-3

Introduction

Tumor metastasis is a complex process involving interactions between tumor cells, host cells, connective tissue components, and blood vessels with a step wise nature. Thus, all the steps involved in the metastatic process also guide the development of targeted therapies.

The galectins are a family of mediators that have crucial roles for the immune response and thus they have the capacity to regulate inflammatory processes. This regulatory impact can be both inflammatory and anti-inflammatory depending on the localization *(1, 2)*. Galectin-3 is an endogenous β-galactoside-binding protein with intracellular and extracellular localization that belongs to the S-Type lectin family. Its' main functions can be elaborated as cell growth, adhesion, proliferation, differentiation, migration, and apoptosis *(1, 2, 3)*. Galectin-3 is an Ig E binding protein, also known as CBP 35, CBP 30, MAC-2, RL-29, L-29, hL-31, IL-34, or LBP. It is a member of the β-galactoside-binding protein family that recognizes N-acetyllactosamine structures of various glycoconjugates *(3 – 7)*. Galectin – 3 is expressed in various diseases such as diabetes mellitus *(8, 9, 10)*, cardiac diseases *(11 – 17)*, neurodegenerative diseases *(18 – 23)* and tumor formation *(24 – 33)*.

Galectin – 3 is expressed by the tumor cells and may contribute to the aggressiveness, progression and metastasis of tumor tissue *(34 – 40)*. These are called tumor derived galectins and deteriorate the immune functions while enhancing inflammation. Regarding this fact one can state that the tumor-derived galectins have bipotential consequences on both tumor and immune cells *(39)*. In a tumor tissue the most prevalent immune cells are macrophages, and they are called tumor-associated macrophages *(TAMs) (40, 41, 42)*. In previous literature the increased number of tumor-associated macrophages has been interpreted as an indicator of poor prognosis. These macrophages secrete galectin – 3 into and leverage tumor tissue progression as galectin – 3 facilitates tumor angiogenesis by regulating vascular endothelial growth factor *(43)*. At this stage it should be mentioned that macrophages are not the only galectin – 3 expressing cells but this expression is also performed by tumor stroma. This secretion ratio may be in favor of tumor cells in the progressed neoplasms.

Galectin – 3 is abundant in the cell surface and in biological fluids such as serum and urine. It is also secreted by tumor cells, tumor-associated macrophages and inflammatory cells which make it both a diagnostic and prognostic biomarker *(25 – 28, 30, 31)*. Galectin – 3 has been utilized as a biomarker to detect glioma tumorigenesis *(24)*.

In previous studies the association between tumor presence, prognosis and galectin -3 levels have been identified thus this situation has been tumor type dependent. The expression of galectin – 3 is up-regulated in many types of cancers *(37)* and new therapeutic strategies may

be designed to facilitate the use of galectins as biological response modifiers to either tumor cells or immune cells *(38, 39, 40)*.

In this study we aimed to elucidate the role of galectin-3 expression in metastasis biology and its role in predicting tumor metastasis in colon carcinomas.

Materials & Method

Hematoxylin-eosin stained sections of 80 adenocarcinoma cases that were previously reported by the Istanbul Training and Research Hospital pathology clinic were re-examined under a Olympus BX51 light microscope. They were re-evaluated in terms of *histological type, histological grade, stage, lymph node and distant metastasis, and vascular invasion*. Grading was accomplished using the three values. TNM staging was re-evaluated according to American Joint Committee on Cancer *(AJCC)* 8th Edition.

We have chosen a representative colon adenocarcinoma containing the transition of the adjacent normal mucosa-tumor tissue block from each tumor for immunohistochemical analysis. Immunohistochemical study was also performed on one metastatic lymph node and distant metastasis section in all metastatic cases. We have utilized a 4 µm section from each formalin-fixed, paraffin-embedded tissue block and mounted on to positively charged slides. The slides were stained with Galectin-3 *(NCL-Gal3 Clone: 9C4)* mice monoclonal antibody *(Novo Castra Laboratories)* with the streptavidin-avidin-biotin method. The immune-histo-chemically stained sections were examined and scored by two different pathologists with light microscopy.

Both staining intensity and staining percentage were assessed for Galectin-3 in the center and invasive margin of the tumor, in the metastatic focus in the lymph node, and distant metastatic focus. According to the staining intensity, negative staining was evaluated as *Category 0*, mild staining as *Category 1*, moderate staining as *Category 2* and strong staining as *Category 3*. The percentage of staining was evaluated as the ratio of the stained area to the total tumor area. The following formula was used to calculate the mean staining density score for each assessed compartment. Mean staining density score: *(0x percentage of the negatively stained area) + (1x percentage of the weakly stained area) + (2xpercentage of the moderately stained area) + (3xPercentage of the strongly stained area) (10).*

Statistical Analysis

SPSS *(Statistical Package for the Social Sciences)* Windows 10.0 Software package was used for statistical analyses. Student's t-test, Mann Whitney U test, and Kruskal -Wallis test were utilized for comparisons. Pearson test was performed for correlation analysis. A p level less than 0,05 was considered statistically significant.

Results

The samples to be examined have been collected from 80 individuals. Of the 80 patients 47.5% *(n=38)* were male, 52.5% *(n=42)* were female. The mean age of the patients was 57.12 years *(ranging from 28 to 89 years)*. The mean age of the cases without metastasis was 55.6±11.02 and the mean age of the patients with metastasis was 58.72±10.50. No statistically significant relationship has been detected between age and metastasis. *(p=0.205).*

No significant difference have been observed between genders in terms of normal mucosa, tumor, invasion, and lymph node metastasis galectin score. There was no statistically significant difference between classical NOS and mucinous type adenocarcinoma in terms of galectin score values of normal mucosa, tumor, and invasive margin *(Table 1)*. The number of signet ring cells and undifferentiated carcinoma cases was insufficient for further statistical analysis.

Table 1: Relationship between histological type of tumor neighboring mucosa, tumor, invasive margin, and lymph node metastasis galectin score

Histological type	NOS	Mucinous	*p* value
Neighboring mucosa galectin score	2.77±0.39	2.81±0.24	0.776
Tumor galectin score	1.57±0.65	1.81±0.66	0.359
Invasive margin galectin score	2.09±0.82	2.31±0.39	0.478
Lymh node metastasis galectin score	2.43±0.47	2.76±0.39	0.138

Data expressed as mean ± SD

SD: Standard deviation

NOS: Not otherwise specified

The mean galectin scores of the invasive margin of the tumor with metastasis *(Stage III, IV, V)* were significantly greater than those of the cases without metastasis *(Stage I, II) (p=0.003)*. In addition, the galectin score of the neighboring mucosa was significantly greater in subjects with metastasis compared to those without *(p=0.001).* There was no significant difference between the subjects with or without metastasis with respect to the tumor galectin score in the whole tumor area *(p=0.83) (Table 2).* Lymph node metastases had a mean galectin score of 2.44.

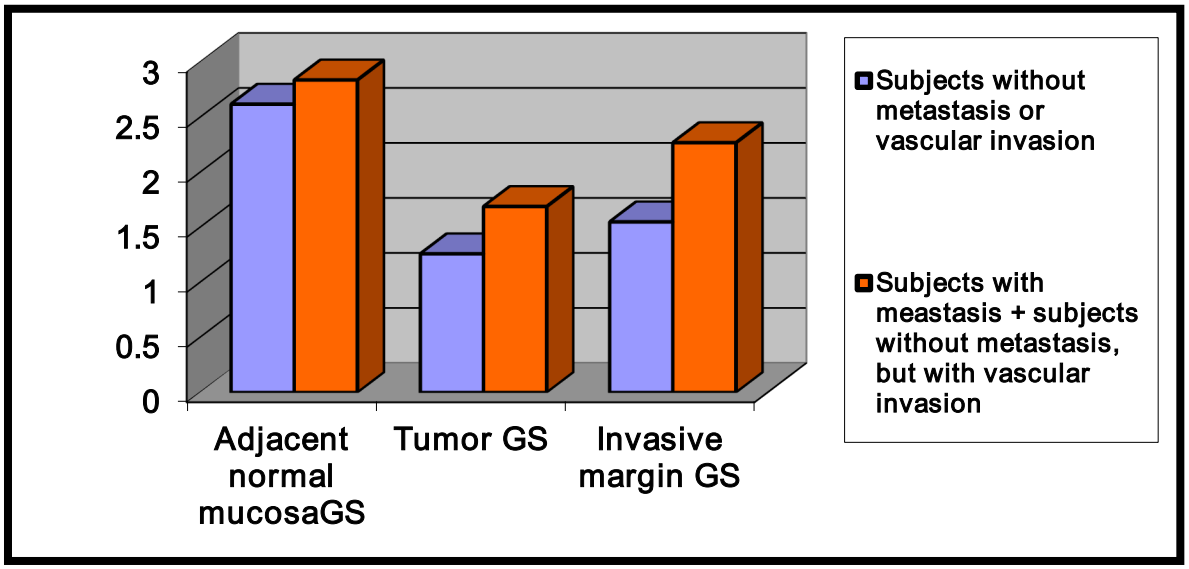
Table 2: Comparison of the adjacent normal mucosa, tumor, and invasive margin galectin scores of the subjects without metastasis with those of the "subjects with metastasis+subjects without metastasis but with vascular invasion" group.

Presence of metastasis Stage	Subjects without metastasis Stage I, II	Subjects with metastasis Stage III, IV, V	
			p value
Adjacent normal mucosa galectin score	2.64±0.46	2.90±0.22	0.001
Tumor galectin score	1.43±0.63	1.69±0.68	0.083
Invasive margin galectin score	1.77±0.80	2.30±0.76	0.003

Data expressed as mean ± SD

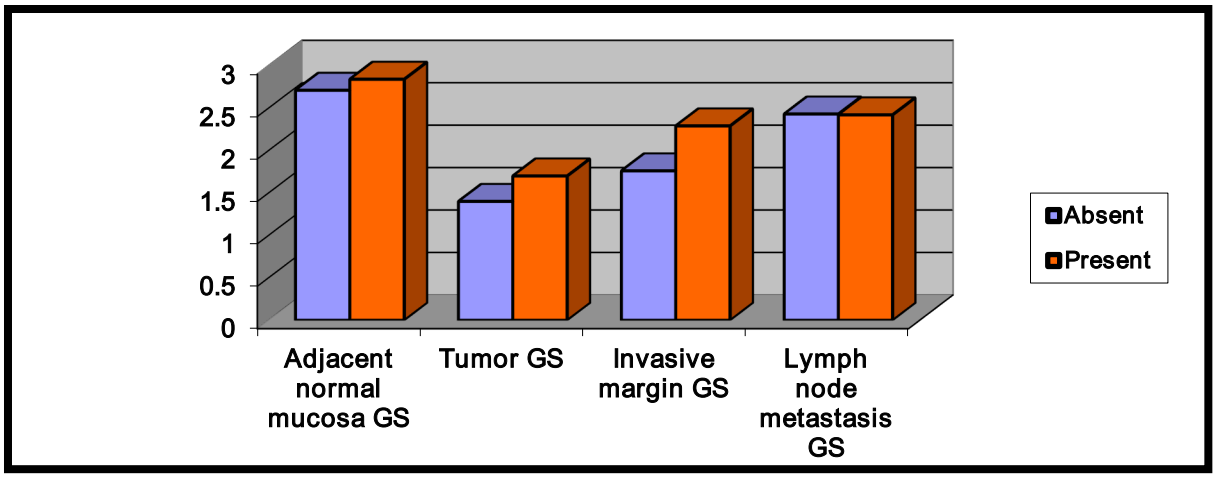
SD: Standard deviation

Crossover of the subjects with vascular invasion from the group of subjects without metastasis to those with metastasis led to a significantly greater normal mucosa, tumor, and invasion area galectin scores in subjects with metastasis than those without *(p=0.016, p=0.008, p<0.001) (Figure 1).* The tumor and invasive margin galectin scores were significantly greater in the subjects with vascular invasion compared to the subjects without vascular invasion *(p=0.048, p=0.004) (Figure 2).*



GS: Galectin score

Figure 1: Graphical comparison of the adjacent normal mucosa, tumor, and invasive margin galectin scores of the subjects without metastasis with those of the "subjects with metastasis+subjects without metastasis but with vascular invasion" group



GS: Galectin score

Figure 2: Comparison of the mean galectin scores of adjacent normal mucosa, tumor, invasive margin and lymph node metastasis between the subjects with and without vascular invasion.

The adjacent normal mucosa galectin scores of *Grades 2, and 3* cases were significantly higher than *Grade 1*. Tumor, invasive margin, and lymph node galectin score did not significantly differ with respect to tumor grade *(Table 3)*.

A strong cytoplasmic and strong nuclear staining for galectin-3 was observed in the upper parts of normal mucosa while there was weak nuclear staining for galectin-3 in the basal part. At the transformation zone from normal mucosa to adenoma, the galectin-3 expression was reduced, which was increased again in areas of dysplasia in parallel with the grade of dysplasia. The galectin-3 expression was greater in areas of carcinoma than adenomatous areas with dysplasia, with the greatest staining being in the deep invasion areas.

Table 3: Comparison of the mean galectin scores of adjacent normal mucosa, tumor, invasive margin and lymph node metastasis between the subjects with and without vascular invasion.

GRADE	GRADE 1	GRADE 2	GRADE 3	
				p value
Adjacent normal mucosa galectin score	2.55±0.59	2.78±0.34	2.91±0.19	0.012
Tumor galectin score	1.51±0.56	1.51±0.72	1.69±0.63	0.512
Invasive margin galectin score	1.86±0.79	1.98±0.90	2.31±0.66	0.156
Lymph node metastasis galectin score	2.32±0.36	2.41±0.42	2.46±0.64	0.863

Data expressed as mean ± SD

SD: Standard deviation

A correlation analysis showed that the adjacent normal mucosa galectin score was correlated to tumor stage and grade. Invasive margin galectin score showed a positive correlation with stage at the same time, invasive margin galectin score also had greater than adjacent normal mucosa and tumor galectin scores. The lymph node metastasis score was also correlated to invasion and tumor galectin score *(Table 4).*

Table 4: Correlation coefficients (r)

	Age	Stage	Grade	Histological Type	Adjacent Normal Mucosa galectin score	Tumor galectin score	Invasive margin galectin score
Adjacent normal mucosa galectin score	0.009	0.359	0.321	0.115			
Tumor galectin score	-0.002	0.169	0.073	-0.074	0.189		
Invasive margin galectin score	0.080	0.316	0.149	-0.166	0.245	0.711	
Lymph node metastasis galectin score	0.099	0.135	-0.038	-0.256	0.050	0.306	0.516

A comparison of the sensitivities and specificities of adjacent normal mucosa, tumor, and invasive margin galectin scores based on the stage revealed that the invasive area galectin score had the greatest sensitivity. When adjacent normal mucosa, tumor, invasive margin galectin score values are compared according to stages in terms of sensitivity and specificity; the invasive margin galectin score value is the parameter with the highest sensitivity. Even after adding vascular invasion to the cases without metastasis, the invasive margin galectin score still had the greatest sensitivity *(Figure 3).*

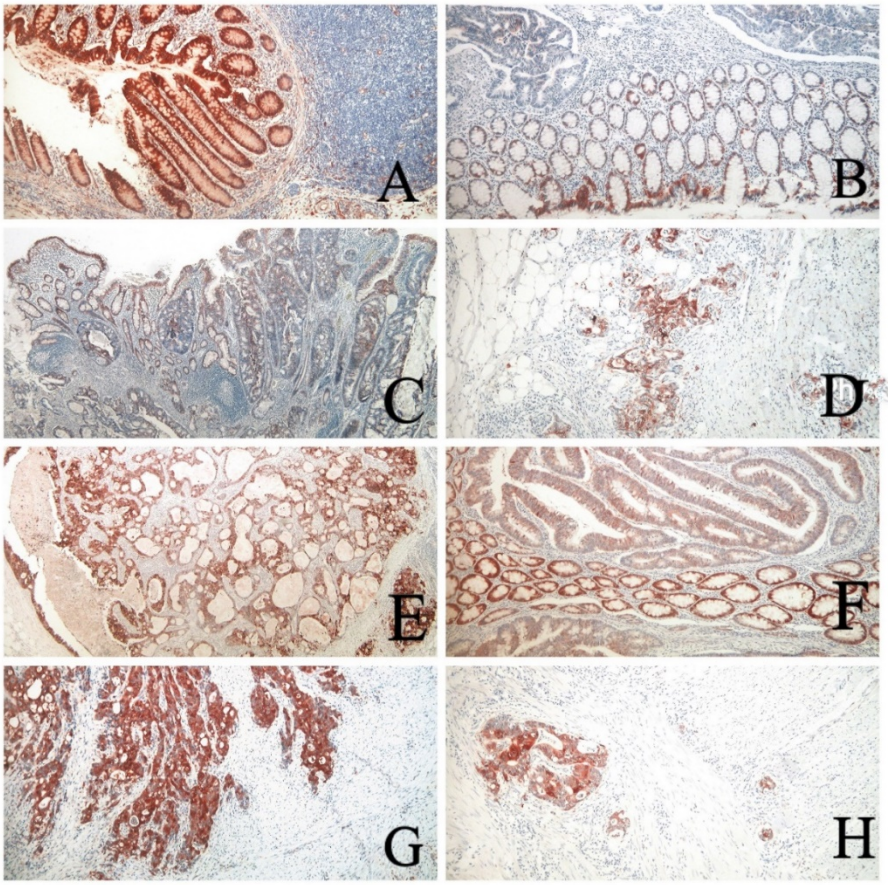


Figure 3: Galectin-3 immunohistochemical results. A: Score 3 galectin-3 expression, more severe and cytoplasmic, on the crypt surface in normal colonic mucosa. In addition to the epithelium, strong expression is also observed in some lymphocytes, stromal cells, and endothelial cells (IHKX4). B: Tumor galectin-3 expression score of 0,4 and normal mucosa galectin-3 staining pattern in a case without metastasis (IHKX4). C: Score 1,6 galectin-3 expression on the tumor surface in a patient with metastasis. Normal mucosa tumor transition area and generally superficial tumor area are observed (IHKX4). D: Score 2,6 galectin-3 expression in the invasive margin in the same case as in C (IHKX4). E: Score 2,8 galectin-3 expression in lymph node metastasis of the same patient as in C (IHKX20). F: Score 1,9 galectin-3 expression in the superficial tumor area in a patient without metastasis but with vascular invasion (IHKX4). G: Invasive margin galectin-3 expression score of 3, which was the strongest staining (IHKX4). H: Score 2,8 galectin-3 expression in the invasive tumoral area and vascular invasions in the same case as in F (IHKX10).

Discussion

Galectin-3 is a carbohydrate-binding protein that belongs to the S-type lectin group and has an affinity for β-galactoside sugars. Disorders on the cell surface or in glycoproteins to which galectin-3 is bound, such as mucins, play an important role in carcinogenesis in the gastrointestinal system *(25)*. Increased galectin-3 levels have been reported in some neoplasms and this finding has been suggested to relate to disorders of cell growth, transformation, and metastasis *(26)*.

Although the biological functions of galectin-3 have not been fully elaborated, it has been found to induce tumor progression and metastasis by means of carbohydrate-mediated homotypic aggregation and inhibition of apoptosis *(1,2,27)*.

Most colorectal adenocarcinomas develop on the basis of adenomas, rather than de novo development *(28)*. Furthermore, only part of the cells in a tumor possesses metastatic phenotype and a heterogeneous cell population is formed within a tumor. Considering this, a score encompassing the whole tumor area may not reflect the actual galectin-3 expression. Thus, we separately scored the invasive margin of the tumor area with the highest metastatic potential *(30)*. As a result, overall galectin-3 expression detected in a tumor did not show a significant correlation to its metastatic capacity, while an expression in the invasive component showed a positive correlation to the presence of metastases. This was considered to be a result of a heterogeneous population within the tumor *(29)*.

In very early stages of galectin research promising data have been published by various investigators. Iramura and Lee have reported in separate studies that there existed a direct relation between galectin-3 expression and tumor stage *(44,45)*. Similarly, Schoeppner et al. showed that galectin-3 expression was increased in proportion to an increase in stage and was correlated with reduced survival *(46*), hence, studies on some malignancies other than colorectal carcinomas have reported opposite results. Lotan et al. showed in gastric carcinomas *(47)* and Vandenbrule et al. showed in ovarian carcinomas *(48*) that metastatic properties and the clinical course did not correlate to galectin-3 levels. Unlike the studies on colon carcinomas, Lotz et al. found that reduced galectin 3 expressions were associated with tumor progression *(49)*. Invasion of vascular structures by tumor cells is one of the metastasis steps *(26,28)*. The cases having no metastasis in the resection material, namely the cases in stage I and II were included in the group with vascular invasion in the metastatic process to form a separate case group. When we separately analyzed that group, we observed a more significant relationship between galectin-3 and metastasis.

Taking vascular invasion as a single parameter, the significant association between vascular invasion and tumor invasion and galectin scores can be explained by the increased cell population that can invade vessels during the metastatic process. This significant relationship, however, also suggests a role of galectin-3 in the heterotypic-homotypic aggregation of tumor cells with each other and thrombocytes during the entry into the vessel lumen and tumor embolization *(30, 31)*.

It has been reported that there was generally a strong galectin-3 staining in the upper 2/3 of the normal colonic mucosa and negative or weak staining in the base of crypts, and the staining was usually nuclear in the basal part and cytoplasmic and nuclear on the surface *(34, 35, 38)*. The sole presence of nuclear staining in the basal part may be linked to a higher rate of cellular proliferation and an increased nuclear galectin-3 concentration as a component of ribonucleoprotein particles during cellular proliferation *(37)*. The galectin-3 expression on the surface may be attributed to a greater mucin content in the crypt surface as well as the presence of galectin-3 as an anti-receptor of mucins in glycoprotein structure *(9,10)*.

Since colorectal carcinomas were among the best examples of malignancies to identify the adenoma-dysplasia-carcinoma they provide a unique opportunity for carcinogenesis studies *(39)*. Some of our subjects clearly demonstrated the typical morphogenetic transformation from normal mucosa to carcinoma. While a reduction in expression was observed in the areas of adenoma, dysplasia, and carcinoma compared to normal mucosa, a strong cytoplasmic expression similar to normal mucosa was noted in the deepest and least differentiated infiltration areas of the tumor. Similar findings have also been observed in areas of deep myometrial invasion in endometrial adenocarcinomas. This was the result of the accumulation of cells with metastatic ability through genetic mutations at the deepest site, by virtue of their potential for degrading the extracellular matrix and inhibiting cellular adhesion and migration. In this study there was no significant relationship between age, gender, histological type, histological grade, and galectin-3 expression level; but as the grade increased, the amount of normal mucosal galectin expression increased significantly.

Some studies have examined the use of galectin-3 in the differential diagnosis of some malignancies such as thyroid carcinoma and anaplastic large cell lymphoma, albeit with conflicting results *(40, 43)*. Galectin-3 expression may occur as a result of malignant transformation, but malignant transformation may also induce galectin-3 expression *(41, 42)*. In our study, normal mucosa galectin score correlated with the increase in tumor stage and grade. This finding may be due to the normal mucosa from the periphery of the tumor undergoing some mutational changes that would lead to the development of a high-grade tumor. The mean galectin-3 expression was higher in the metastatic foci than in other tumoral regions, suggesting that cells with metastatic phenotype express a greater amount of galectin-3 and galectin-3 indirectly plays an important role in the pathogenesis of metastasis.

Conclusion

Exploring tumor markers that can predict tumor metastasis and prognosis is important for effective treatment guidance. Galectin-3 may predict prognosis in some solid tumors. In

targeted treatment of cancer patients, anti-invasion and anti-metastatic agents can be improved by identifying inhibitors capable of preventing apoptosis escape, cell adhesion, growth, differentiation, and angiogenesis, such as anti-galectin 3.

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Competing interests

The authors declare that they have no competing interests.

Ethics Statement

Bağcılar Eğitim Araştırma Hastanesi Girişimsel olmayan Klinik Araştırmalar Etik Kurulu
23/09/2022
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Authorship Contributions

Concept: UK, MK, Design: UK, MK, Supervising: MK, HD, Financing and equipment: UK, MK, HD, Data collection and entry: MK, HD, Analysis and interpretation: MK, HD, Literature search: UK, Writing: UK, Critical review: MK, HD

Abbreviations:

AJCC: *American Joint Committee on Cancer*
NOS: *Not otherwise specified*
SD: *Standard deviation*
SPSS: *Statistical Package for the Social Sciences*
TAM: *Tumor-associated macrophages*
TNM: *Tumor Nodes and Metastasis*
GS: *Galectin score*

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