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Short Communication

Investigation of the Possible Association Between Galectin and Apoptosis in Gastric Cancer Patients

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Abstract: Cancer is a type of disease that occurs as a result of the uncontrolled growth of cells, which has been very common in recent years, and some species have a poor prognosis. Galectin-3 is a multifunctional protein and is associated with the developmental process of tumors, including cell growth, adhesion, proliferation and metastasis. Galectin-3 has a broad effect on tumor development, including cell proliferation, apoptosis, cell adhesion, invasion, angiogenesis, and metastasis. Members of the BCLF-2 family are anti-apoptotic molecules required for the proteolytic degradation of the cell by caspases, which is the ultimate drive of programmed cell death, which plays a very important role in the regulation of the apoptotic pathway, ensures the integrity of the mitochondrial membrane and prevents the release of cytochrome C from the mitochondria. NF-kB, which is one of the important factors in cancer formation, is found in the cytoplasm, and there is a correlation between the protein levels of proinflammatory cytokines such as interlukin (IL)-1b, and IL-8, and the high incidence of cancer. There are two types of apoptotic caspases: initiator (apical) caspases and effector (executioner) caspases. Initiator caspases (e.g., caspase-2, -8, -9 and -10) cleave inactive pro-forms of effector caspases, thereby activating them. Effector caspases (e.g., caspase-3, -6, -7) in turn cleave other protein substrates within the cell resulting in the apoptotic process. At least fourteen caspases have so far been implicated in human apoptotic pathway cascade. Among these, caspase-3 is considered to be a major executioner protease in apoptosis. To examine this mechanism in more detail, we aimed to examine the difference between Galectin, BCLF-2, Kaspase3, Kaspas 8, Nfkb levels before and after treatment in operable gastric cancer patients with the Elisa test. In this study, We observed a statistical increase in Galectin, BCLF-2, Kaspase3, Kaspas 8, Nfkb levels when the control group was compared with the preoperative group. There was a statistically significant increase in Galectin, BCLF-2, Nfkb, Caspase3, Caspase 8 levels in the preoperative group compared to the control. There is a statistical increased in Galectin, BCLF-2, Kaspase3, Kaspas 8, Nfkb levels in the postoperative group compared to the control. Although there was no statistical difference in Galectin, BCLF-2, Caspase-3, Caspase-8, Nfkb levels between pre and postoperative groups, a significant decrease was observed in Galectin, BCLF-2, Nfkb levels. A very slight increase was observed in Caspase-3 and Caspase-8 levels. In conclusion, we think that Galectin-3 Bcl-2 and NF-kB may be markers for gastric cancer patients. We think that it is appropriate to conduct this study with more patient groups and a longer period.

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INTRODUCTION

In recent years, there have been great developments in the diagnosis and treatment of cancer, which is among the most common causes of death in the world. Despite this, some types of cancer, such as gastric cancer, have a poor prognosis and not much progress has been made in its treatment. Apoptosis and galectin, which are effective in tumor growth, spread, differentiation and metastasis, are of great importance (Parkin et al., 1999; Ribeiro et al., 2006). Galectin-3 is a multifunctional protein that is a member of the beta-galactosidase-binding lectin (Fukumori et al., 2006). It has been found in high amounts in many studies in human malignancies (Fukumori et al., 2006; Shimura et al., 2005). Galectins are mainly found in the nucleus and cytosol and are defined as 14 members. Galectins are basically divided into 3 subgroups. These are (a) prototype (galectin-1, -2, -5, -7, -10, -11, -13, and -14); (b) chimera type (galectin-3); and (c) tandem repetitive type (galectin-6, -8, -9, and -12) (Dandoo et al., 2007). Galectin-3 expression is increased in neoplastic cell types. Galectin-3 is associated with the developmental process of tumors, including cell growth, adhesion, proliferation, and metastasis (Califice et al., 2004). Galectin-3 has a wide effect on tumor development including cell proliferation, apoptosis, cell adhesion, invasion, angiogenesis and metastasis (Venkateshaiah et al., 2017). Galectin-3 is structurally and functionally related to the Bcl-2 protein (Kosoka et al., 2013) and has an antiapoptotic effect in some cells (Selemetjev et al., 2015). The biological behavior of each tumor depends on many factors, including programmed cell death (apoptosis). Thus, abnormality in proteins that regulate apoptosis may cause tumor progression and aggregation (Kosoka et al., 2013).

Members of the Bcl-2 family play a very important role in the regulation of the apoptotic pathway (Dandoo et al., 2007). The Bcl-2 protein is anti-apoptotic molecules required for the proteolytic degradation of the cell by caspases, the ultimate drive of programmed cell death, which maintains the integrity of the mitochondrial membrane and prevents the release of stochrome C from the mitochondria. Unlike Bcl-2, its homologue Bax allows disruption of mitochondrial membrane and caspase activation. A protein with such a pro-apoptotic function is formed. The ratio between Bcl-2 and Bax decides whether the cell will go to apoptosis (Selemetjev et al., 2015).

In recent years, protein-carbohydrate interactions have been considered crucial for the modulation of cell-cell and cell-

extracellular matrix (ECM) interactions that mediate various biological processes such as cell activation, growth regulation, cancer metastasis, and apoptosis (Ahmed et al., 2015).

NF-kB, which is one of the important factors in cancer formation, is found in the cytoplasm and its main activation causes the initiation, progression and development of cancer (Jayasooriya et al., 2013; Mesallamy et al., 2012; Lee et al., 2013). There is a relationship between the levels of nuclear factor-kB (NF-kB), proinflammatory cytokines (interlukin (IL)-1b, and IL-8) and the incidence of cancer (Bonizzi et al., 2004; Coussens et al., 2002; Calzado et al. 2007). The aims of this study were to investigate the Galectin, BCLF-2, Kaspase3, Kaspas 8, Nfkb levels in gastric cancer patients before and after operation, and to compare the gastric cancer patients patients with healthy controls with Elisa test.

MATERIALS AND METHODS

Our study consisted of people who applied to Dr. Abdurrahman Yurtaslan Oncology Hospital, who were over the age of 18, did not have a pre-existing chronic disease, and signed a consent form for those who had these standards and wanted to participate

Patients receiving neoadjuvant chemotherapy or chemoradiotherapy were included in the study. It consisted of 20 preoperative and postoperative groups diagnosed as malignant by biopsy, and 20 healthy volunteers as a control group. Cases diagnosed with malignant gastric cancer by taking biopsy samples and sending them to pathology were used in the study. Approximately 2 cc of blood was taken from the cases that were diagnosed as malignant by biopsy, during routine blood collection before treatment and during routine blood collection on the 30th day after treatment, in order to carry out our study.

The bloods were stored at -80 degrees and all were studied according to the same standards after the blood was completed. Galectin, BCLF-2, Kaspas-3, Kaspas-8, Nfkb levels in gastric cancer types before and after the treatment, which were collected blood later, were evaluated with the Elisa test (Elabscience, USA).

Galectin, BCLF-2, Kaspase-3, Kaspas-8, Nfkb kits were studied according to the sandwich-ELISA principle. Two antibodies are used in this technique. The first solid phase is covered and blocked by the capture antibody. The second enzyme-labeled antibody (conjugate) sandwich ELISA techniques are 2-5 times more sensitive than others. The sample was added and incubated for the antigen in it to bind. Afterwards, the unbound ones were removed by washing. The second antibody (conjugate) labeled with the enzyme was added and bound to the antigen-antibody complex. At this point the sandwich took shape. Washing was done and substrate was added. The reaction was stopped and quantified by measuring the intensity of the color formed. The absorbance intensity of the color formed is directly proportional to the concentration. The absorbance was read spectrophotometrically in an Elisa reader at a wavelength of 450 nm ± 2 nm.

The software SPSS for Windows, version 16.0 was used in the statistical analysis of the data. Associations between continuous variables were assessed by the Mann Whitney-U test. In all analyses, a p value of 0.05 was used as the cut off for significance.

RESULTS

In this study we have analyzed Galectin, BCLF-2, Caspase-3, Caspase-8, Nfkb levels in pre and post-op gastric cancer patient. We created this study from a control and case group (before and after treatment). There was no significant difference in age, gender and weight of these groups (p>0.05).

The comparisons between the control group and case groups (Table-1, Figure 1) were performed by Mann Whitney-U test. We observed a statistical increase in Galectin, BCLF-2, Kaspase3, Kaspas 8, Nfkb levels when the control group was compared with the preoperative group. There was a statistically significant increase in Galectin, BCLF-2, Nfkb, Caspase3, Caspase 8 levels in the preoperative group compared to the control. There is a statistical increased in Galectin, BCLF-2, Kaspase3, Kaspas 8, Nfkb levels in the postoperative group compared to the control. Although there was no statistical difference in Galectin, BCLF-2, Caspase-3, Caspase-8, Nfkb levels between pre and postoperative groups, a significant decrease was observed in Galectin, BCLF-2, Nfkb levels. A very slight increase was observed in Caspase-3 and Caspase-8 levels.

Table 1: Galectin, BCLF-2, Caspase-3, Caspase-8, Nfkb levels in gastric cancer

Gruplar	Nfkb (ng/mL)	BCLF-2 (ng/mL)	Kaspase3 (ng/mL)	Kaspas 8 (ng/mL)	Galektin-3 (ng/ml)
Control	1,42±0,2	1,71±0,2	1,19±0,1	1,03±0,06	1,36±0,1
Preoperative group	1,67±0,06 *	2,02±0,05 *	1,33±0,03 *	1,11±0,01 *	1,53±0,02 *
Postoperative group	1,65±0,09 *	1,99±0,06 *	1,35±0,01 *	1,11±0,01 *	1,52±0,02 *

* Significant relative to control (p>0,05)

Discussion

In recent years, cell-cell and extracellular matrix (ECM)-cell interaction, which mediates various biological processes such as protein-carbohydrate interactions, apoptosis, cancer metastasis, growth regulation, and cell activation, is thought to be very important for modulation (Ahmed et al., 2015).

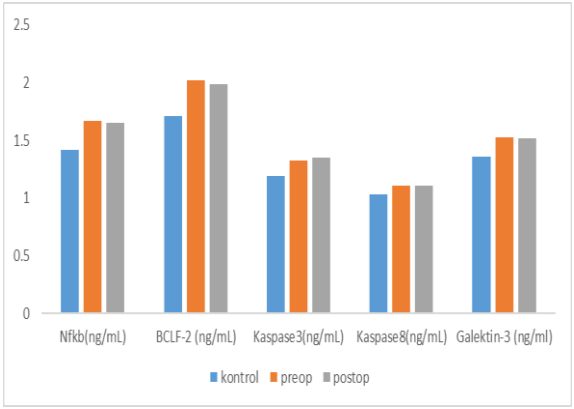

Figure 1: Galectin, BCLF-2, Caspase-3, Caspase-8, Nfkb levels in gastric cancer

Galectin-3 is a multifunctional protein and a member of the beta-galactosidase-binding lectin (Fukumori et al., 2006). It has been found in high amounts in many studies in human malignancies (Fukumori et al., 2006; Shimura et al., 2005). Although galectins do not have a typical secretory signal peptide, they are found not only in the cytoplasm but also in the ECM. Extracellular galectin-3 binds to laminin, fibronectin, CD29, CD66, α1β1 integrin and Mac-2-binding protein. Intracellular galectin-3 is bound to gemin 4, Bcl-2, nucling, synexin and β-catenin via protein-carbohydrate or protein-protein interactions (Ahmed et al., 2015). Galectin-3 expression is increased in neoplastic cell types. Galectin-3 is associated with the developmental process of tumors, including cell growth, adhesion, proliferation, and metastasis (Califice et al., 2004). Galectin-3 has a wide effect on tumor development, including cell proliferation, apoptosis, cell adhesion, invasion, angiogenesis, and metastasis (Venkateshaiah et al., 2017). Clinical data have shown a correlation between the presence of galectin-3 and malignant potential in certain tumor types such as colon cancer and thyroid cancer (Dondoo et al., 2017). There is a wealth of data on the roles of galectin-3 in the regulation of cellular homeostasis. This protein has been shown to modulate cell growth, control the cell cycle, and be involved in the regulation of apoptosis. Galectin-3 has been shown to migrate either from the cytosol or from the nucleus to the mitochondria after exposure to apoptotic stimuli and prevents apoptosis by blocking changes in mitochondrial membrane potential. It is stated that galectin-3 may show its anti-apoptotic activity by interacting with other apoptosis regulators that function in mitochondria (Nangia-Makker et al., 2007). In the human Gal-3 gene promoter domain, there are binding sites for transcriptional factors including Sp1, AP-1 and NF-kB, known as intermediates

of VEGF-C signaling (Noma et al., 2012). Liu et al. showed that NF-kB inhibitor, not Sp1 or AP-1 inhibitor, largely inhibited VEGF-C-enhanced Gal-3 expression, and NF-kB was the key pathway. They stated that VEGF-C increases Gal-3 protein expression via NF-kB (Liu et al., 2014).

Although the exact mechanism of apoptosis has not been fully explained, the most important event associated with apoptosis is the activation of caspases (Choen, 1997; Lee et al., 2000). Caspases constitute the most important part of the calcium-independent intracellular cysteine protease class (Mukae et al., 1998, Ozawa et al., 2002). These endoprostheses are found in the cell cytoplasm as inactive precursors and most of them are proapoptotic (Ozawa et al., 2002; Wang, 2000). Caspases are triggered by signals that activate apoptosis and take an active role in all three pathways of apoptosis (Ozawa et al., 2002, Zhang et al., 1997). It is also supported by recent studies that caspase 3 plays the most important role in the apoptotic process and caspase 9 has similar properties to caspase 3 (Keane et al., 2001; Li et al., 2000). Caspase 3, which causes DNAase activation in DNA fragmentation, is thought to have a direct role (Mukae et al., 1998; Nuttal et al., 2000). In another way in which apoptosis is triggered by external signals, it is triggered by binding to plasma membrane proteins of the tumor necrosis factor (TNF) receptor family, known as death receptors. The death receptor pathway of apoptosis is mediated by the association of TNF family cell surface receptors with their associated apoptosis-inducing ligands (TRAIL), Fas ligands, or their specific receptors in some malignant and normal cells. Death receptors; It belongs to the TNF (Tumor Necrosis Factor) receptor gene family. Adaptor proteins bind to caspases as a result of the signal from the receptor and activate. By binding of the sensitive ligands, the three TNFR or Fas molecules come together to form a complex, and the cytoplasmic portions of the TNFR and Fas trimers bind to the adapter proteins TRADD and FADD/Mort-1, respectively. The cytoplasmic portions of receptors, adapter proteins and proteases form the "Death Inducing Signaling Complex (DISC)". Activation of proteases produces the apoptotic signal. DISC leads to direct activation of caspase-8. Caspase-8 also activates caspase-3 and apoptosis occurs (Li et al., 1997).

Galectin -3 is structurally and functionally related to the Bcl-2 protein and has an antiapoptotic effect in some cells (Selemetjev et al., 2015). The biological behavior of each tumor depends on many factors, including programmed cell death (apoptosis). Thus, abnormality in proteins that regulate apoptosis may cause tumor progression and aggregation (Selemetjev et al., 2015). Members of the Bcl-2 family play a very important role in the regulation of the apoptotic pathway (Dondoo et al., 2017). The Bcl-2 protein is anti-apoptotic molecules required for the proteolytic degradation of the cell by caspases, the ultimate drive of programmed cell death, which maintains the integrity of the mitochondrial membrane and prevents the release of stochrome c from the mitochondria. Unlike Bcl-2, its homologue Bax allows disruption of mitochondrial membrane and caspase activation. Pro-apoptotic function is formed. The ratio between Bcl-2 and Bax decides whether the cell will go to apoptosis (Selemetjev et al., 2015). Bcl-2 translocation to the mitochondrial membrane blocks cytochrome c release, leading to antiapoptotic activity. It has been reported that galectin-3 can also inhibit cytochrome c release and subsequent activation of the caspase cascade when it inhibits nitric oxide-induced apoptosis in human breast carcinoma BT-549 cells. In addition, galectin-3 can bind to in vitro Bcl-protein and mimicking the ability of Bcl-2 family members. Therefore, galectin-3 may be a mitochondrial-associated apoptotic regulator through interaction with Bcl-2 in the cytoplasm. It has been reported that cincincin, a Ca2+ and a phospholipid-binding protein, is required for mitochondrial damage to inhibit galectin-3 and subsequently release cytochrome c after treatment of BT-549 cells with cisplatin (Noma et al., 2012).

NF-kB (nuclear factor kB) belongs to a family of heterodimeric transcription factors involved in inflammatory and stress responses as well as tumor cell resistance to apoptosis. NF-κB is a transcription factor in all cell types. It is inactive in the cytoplasm. When activated it is transported to the nucleus, there are 5 types: NF-κB1, NF-κB2, RelA (p65), RelB and c-Rel. Rel or NF-kappaB (NFkB) proteins consist of a family of eukaryotic transcriptions that control large amounts of normal cells and in organismal processes such as immune and inflammatory response, development process, cell growth and apoptosis. In addition, these transcription factors activate disease including cancer, arthritis, chronic inflammation, asthma, neurodegenerative diseases, and heart disease (Gochman et al., 2011). Activation of IκBα kinase (IKK), which is formed by the phosphorylation of bi-local serines (Ser 32 and Ser 36 in IκBα) on IκBα, is required for the activation of NF-kB. This phosphorylation of IκBα results in proteosomal degradation, nuclear transcription, and activation of NF-kB. This has been considered a classical pathway of NF-kB activation. Many alternative pathways regulating NF-kB activity have been described by NO and peroxy nitrite (Gochman et al., 2011). In some normal cells, such as B cells, some T cells, Sertoli cells, and some neurons, NFkB is mainly located in the nucleus. In addition, in many cancer cells (breast cancer, colon cancer, prostate cancer, lymphoid cancer) NF-kB is mainly active and located in the nucleus. In some cancers (such as some Hodgkins and diffuse large B-cell lymphoma cells), IkB genes may be mutated and damaged due to chronic stimulation of the IKK pathway. Moreover, the Rel/NF-kB transcription factors of many human lymphoid cancer cells proliferate or mutate, leading to activation of NFkB. Sustained Rel/NF-kB activity protects cancer cells from apoptosis and in some cases enables them to grow. Thus, many currents in antitumor treatments inhibit tumor growth by blocking NF-kB activity. Expression of galectin-3 in human T lymphotrophic virus-1 (HTLV-1) infected T-cells was increased by the galectin-3 promoter through interaction with NF-kB. Through the nuclear translocation process of NF-kB/p65, the NF-kB transcription factor causes regulation of galectin-3 expression via NF-kB (Gochman et al., 2011). In a study by Kosova et al., they compared pre and postop values in colon and thyroid cancer patient groups and reported that there was an increase in TSP-1, ES, NFκ-B, VEGF and MMP-9 levels in the preop group ($p < 0.05$) (Kosova et al., 2020). In our study, we investigated Galectin, BCLF-2, Kaspase3, Kaspas 8, Nfkb levels among control, pre- and postoperative gastric cancer patient groups. There was a statistically significant increase in Galectin, BCLF-2, Nfkb, Caspase3, Caspase 8 levels in the preoperative group compared to the control. There is a statistica difference in Galectin, BCLF-2, Kaspase3, Kaspas 8, Nfkb levels in the postoperative group compared to the control. Although there was no statistical difference in Galectin, BCLF-2, Caspase-3, Caspase-8, Nfkb levels between pre and postoperative groups, a significant decrease was observed in Galectin, BCLF-2, Nfkb levels. A very slight increase was observed in Caspase-3 and Caspase-8 levels.

Recent studies have reported that galectin-3 can bind to Bcl-protein and mimic the ability of Bcl-2 family members, and therefore, galectin-3 may be a mitochondrial-associated apoptotic regulator through interaction with Bcl-2 in the cytoplasm. It has also been reported that the galectin-3 promoter is increased through interaction with NF-kB.

In the light of this information, we see in literature studies that Galectin-3 Bcl-2 and NF-kB are effective in mitochondrial-related apoptosis and decrease apoptosis. In our study, we observed that Galectin-3, Bcl-2 and NF-kB levels increased in the postoperative gastric cancer group and decreased in the postoperative gastric cancer group. We observed that apoptosis decreased in the preoperative group, but increased apoptosis with the operation. In our study, we collected blood 30 days after the operation. If this study were carried out over a longer period, we think that we would observe that apoptozoin would increase more and that the proliferation of the tumor would decrease with apoptosis.

In conclusion, we think that Galectin-3 Bcl-2 and NF-kB may be early detection markers for gastric cancer patients. We think that it is appropriate to conduct this study with more patient groups

and a longer period. Thus, we think that early diagnosis can reduce the treatment time and contribute to the country's economy.

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