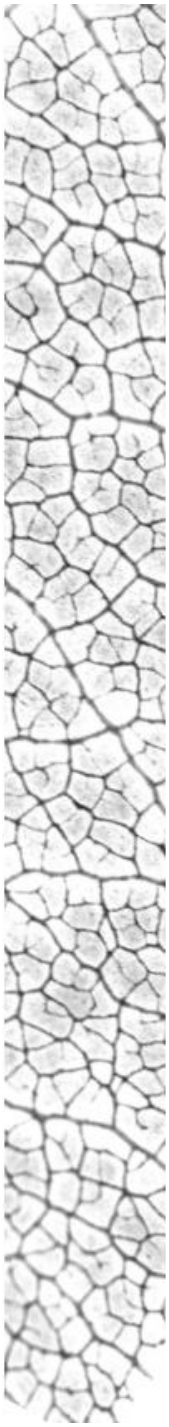

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Serum levels of galectin-9 in patients with oral squamous cell carcinoma

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Abstract

Aim: Understanding the process of tumor cell proliferation and metastasis will have a substantial influence on management of the aggressive oral squamous cell carcinoma (OSCC).The role of galectin-9 is well-known in several aspects of cancer progression, such as apoptosis, cell adhesion and immune system responses. The aim of the present study was to investigate whether the serum levels of galectin-9 play a significant role in the pathogenesis of OSCC. **Method and material:** This was a cross sectional study. The data were obtained from 60 patients with histological confirmed OSCC who had medical document in Khalili hospital, Shiraz, Iran, and 28 healthy donors as control group who refer to Blood Transfusion Center, Shiraz, Iran. The levels of galectin-9 were measured by Elisa sandwich assay, following the manufacturer's protocol. Student t test was used to identify significant difference between two groups according to age, sex and serum levels of galectin-9.To evaluate association between location and grade of tumor lesions with the levels of galectin-9, one way ANOVA was used. **Results:** The mean levels of galectin-9 in patients with OSCC (6.42± 2.08) were less than control subjects (6.65 ± 2.05), while there is not any significant difference between them (P value=0.0564).we did not find any significant relation between stage, grade and location of tumor lesions with the serum levels of galectin-9. **Conclusion:** Serum levels of galectin-9 do not seem to play any significant role in the pathogenesis of oral squamous cell carcinoma.

Keywords: serum levels, oral squamous, cell carcinoma

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INTRODUCTION

Oral cancer is the 11 most common cancers in the world (Ghantous and Abu 2017). Different malignant tumors with variant cellular origin can be seen in the oral cavity. Among these squamous cells carcinoma (SCC) constitutes a significant proportion compromising 95% of head and neck cancers (Jadhav and Gupta 2013). Oral SCC (OSCC) may presents clinically as leukoplakia, erythroplasia, necrotic ulcer or as a broad exophytic mass (Pires et al. 2013). Despite significant advances in the treatment protocols, OSCC still characterized by poor prognosis and a low survival rate approximately 50% after 5 years (Le Campion et al. 2017, Noguti et al. 2012). The best prognostic indicators of OSCC are the size and extent of tumor metastasis (Le Campion et al. 2017). Understanding the process of tumoral cell proliferation and metastasis will have a substantial influence on management of the aggressive OSCC (Boonkitticharoen et al. 2008). Neoplastic cells with metastatic capacity acquired distinct cellular capability

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such as the ability to proliferate without limit, to evade apoptosis, to escape immune surveillance and to express factors that alter the growth of blood and lymphatic vessels to create conduct for tumor metastasis (Brabletz et al. 2005).

Galectins are a family of non-integrin β-galactoside-binding letcins (Chang et al. 2017). The 15 family members of galectins are now classified according to the structure and numbers of carbohydrate Recognition Domains (CRD) (Vladoiu et al. 2014). Only galectin-1, -2, -3, -4, -7, -8, -9, -10 and -12 have been identified in humans. Galectins are involved in physiologic and pathological events such as cell proliferation and differentiation, apoptosis, immune response and tumor progression (Yang et al. 2008). One of the first clues that galectins were involved in cancer was published more than 25 years ago when it was observed that they were differentially regulated in normal and cancer tissues. The best understood of galectins in terms of cancer is galectin-3 and galectin-8 (Astorgues-Xerri et al. 2014).

Galectin-9 was first detected in Patients with Hodgkin's disease (Türeci et al. 1997). The structures of Galectin-9 is similar to that of other members of the galectin family such as galectin -4 and 8, which contain two homologous CRD domains secreted by a linker peptide (Yang et al. 2014). The role of Galectin-9 is well-known in several aspects of cancer progression, such as apoptosis, cell adhesion and immune system responses. Therefore, the levels of galectin-9 expression can have an effect on tumor cell proliferation, metastasis and survival rate (Fujita et al. 2017). In addition; galectin-9 is increasingly recognized as prognostic marker for some of the malignancies. Also it was reported that the levels of expression of galectin-9 can predict distant metastasis better than lymph node status (Irie et al. 2005). A decreased expression of galectin-9 in malignant cells as compared to their normal ones had been reported in the previous studies; for example in Lahm et al. study cancer cell lines of breast, melanoma, renal, lung, adrenal and prostate showed decreased or complete absence of Galectin-9 (Lahm et al. 2001).

An increased expression of Galectin-9 has only been reported in colon cancer and leukemia cell lines. In the tumors of the ovaries and nervous system the expression of Galectin-9 varied based on the particular subtypes of the tumoral cell lines (Heusschen et al. 2013, Serkova et al 2019).

While there is lack of evidence regarding serum level of galectin-9 in patients with OSCC, we designed a study to identify and compare the serum levels of Galectin-9 in patients with OSCC and healthy control subjects.

METHODS AND MATERIALS

Subjects

This was a cross sectional study. The data were obtained from 60pateints with histologically confirmed OSCC who had medical document in Khalili hospital, Shiraz, Iran, and 28 healthy donors as control group who refer to Blood Transfusion Center, Shiraz, Iran. Case and control subjects were matched according to sex and age. Subjects with a history of cancers in other parts of the body, systemic disease and immune insufficiency, chemotherapy or phototherapy were excluded from the study. This research was approved by the local ethics committee (IR.SUMS.REC.1395.S1182) and written consent was obtained from all participants.

Clinico-pathological Findings

To evaluate the relationship between the serum level of galectin-9 and clinic-pathological profile of OSCC lesions the data were collected from patients' medical documents. Size of the lesions, lymph node involvements and location of the tumors were recorded from the patients' documents. Tumor sizes, lymph node metastasis and clinical staging of cases were determined according to the tumor, node, and metastasis (TNM) staging system of the American Joint Committee on Cancer (AJCC) (ANNEROTH et al. 1987).The histopathological grade of oral SCC was determined based on World Health Organization (WHO) criteria (Akhter et al. 2011).

Blood Sampling

Native peripheral venous blood was collected from all patients with OSCC (n=60). Control blood samples were taken (n=28) anonymously from healthy donor with permission of blood Transfusion Center after receiving their written informed consent. The donor health status was identified before venipuncture by case history. The collected blood samples were centrifuged for 10 min at 1500 rpm to separate cellular elements. The serum was decanted, aliquoted and stored at -70C ◦ until analysis.

Elisa Assay

The levels of galectin-9 were measured by Elisa sandwich assay, following the manufacturer's protocol (BM S 279; Bender Med System GmbH, Germany).In the first step 100 µl of assay diluents RD-1 solution was added to wells and 100 µl of recombinant human galectin-9 and serum samples were added to wells subsequently. The wells were covered and incubated for 2 hours on shaker. The superficial layer was removed and the wells were washed 3 times using 400 µl of wash buffered. 200 µl of HRP-conjugated poly colonel anti galectin-9 was added to each well and incubated for 2 hours in room temperature. After 3 times washing with 400 µl of wash buffer, 200 µl of substrate A and substrate B were added to wells and incubated in dark room at 37 C for 30 minutes. Finally, 50 µL of stop solution was added to each well to terminate the

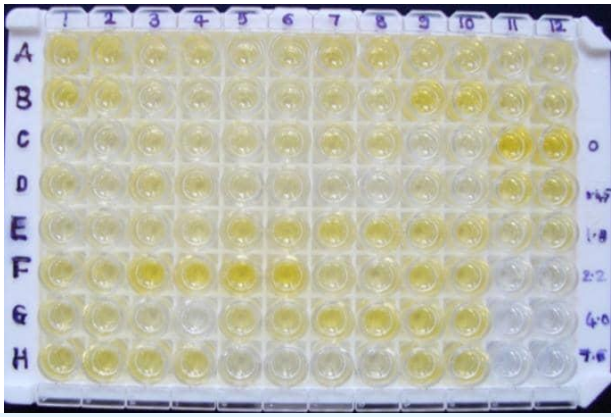

Fig. 1. Serum samples preparing for Elisa test

Table 1. Demographic data and the mean levels of galectin-9 in patients with OSCC and control groups

variables	OSCC patients Mean±SD	Control group Mean±SD	P - Value
Age	62 ± 12.02	58.07 ± 10.27	0.11
Sex	Male : Female 42 :18	Male : Female 19 : 9	0.48
Galectin-9	6.42 ± 2.08	6.65 ±2.05	0.56

reaction. Optical density of the wells was measured at 450 nm with Elisa micro plate's reader (MBG labtech) according to **Fig. 1**.

Statistical Analysis

Kolmogorove-Smirnov test was used to assess the normality assumption for quantitative variables. Mean age and Galectin-9 levels were compared between cases and controls using Independent sample t test. In this case, Chi-square test was employed to compare sex ratio. One way ANOVA F and Independent sample t test were used to compare mean Galectin-9 between different classifications of Oral SCC patients. SPSS version 18.0(PASW SPSS, SPSS Inc., Chicago, IL, USA) was employed for data analysis. All tests were two sides and α were considered to be 0.05.

RESULTS

Demographic data and the levels of Galectin-9 in case and control groups were shown in **Table 1**. Two groups were matched according to sex (p value=0.83) and age (p value=0.11).The mean levels of Galectin-9 in patients with OSCC (6.42 ± 2.08) was less than control subjects (6.65± 2.05), while there is not any significant difference between them (p value=0.564).

Clinico-pathological data were shown in **Table 2**. Half of the patients had SCC of grade I+II and the other had grade III+V. Lymph node involvement was not present in most of the patients(68%) and the remaining had only one lymph node metastasis.35 % of the patients diagnosed with well differentiated SCC, 36% moderate differentiated and 15% poor differentiated. The data regarding tumor differentiation were not available for 13% of the patients. In this study 35% of the patients had SCC in region of the tounge, 32% larynx and 11% in the oral cavity.

Table 2. The relation between galectin-9 serum levels and size, lymph node involvement, grade, stage and location of tumor lesions

	Frequency	Mean of Galectin-9 (µg /ml)	P-Value
Tumor size			
t1+t2	39(65%)	6.30 ± 2.33	0.576
t3 +t4	21(35%)	6.62 ± 1.53	
Lymph node			
N0	41(68.3%)	6.00 ± 1.50	0.073
N1	19(31.7%)	6.30 ± 2.82	
Grade			
G1	21(35%)	6.23 ± 2.32	
G2	22(36%)	6.28 ± 1.76	
G3	9(15%)	7.00 ± 2.54	0.801
Unreported	8(13.1%)	6.62 ± 1.90	
Stage			
I+II	30(50%)	6.05 ±1.60	0.177
III+IV	30(50%)	6.78 ±2.44	
Location			
Tongue	21(35%)	6.53 ± 2.49	
Larynx	32(53%)	6.45 ±1.93	0.680
Oral cavity	7(11%)	5.78 ±1.41	

We did not find any significant relation between stage, grade and location of tumor lesions with the serum levels of galectin-9 (**Table 2**). Only one patient had metastasis. Therefore the statistical analysis regarding levels of galectin-9 and metastasis were not performed.

DISCUSSION

The aim of this study was to identify the serum levels of galectin-9 in patients with OSCC and normal healthy subjects and if there is any significant relation between the serum levels of galectin-9 and pathogenesis of OSCC. Galectins are involved in different biological and pathological events such as embryogenesis, cell adhesion and proliferation, apoptosis and immune system responses (Dar et al. 2018, Kacimi et al. 2020, Xu et al. 1995). Tumorogenesis and anti-tumor activity of galectins were shown in different studies (Choi et al. 2017, Jiang et al. 2013, Kageshita et al. 2002, Sabatos et al. 2003, Sanchez-Fueyo et al. 2003, Zhu et al. 2005). As an example Induction of apoptosis of Tim-3 $^{+}$ T cells as the ligand of T cell immunoglobulin by the galectin-9 was shown in several studies, mentioning tumorogenesis of galectin-9 (Sabatos et al. 2003, Zhu et al. 2005, Sanchez-Fueyo et al. 2003). On the other hand Kageshita et al. (2002) and Irie et al. (Irie et al. 2005, Abagale et al. 2019). in their study reported anti-tumoral activity of galectin-9 in human melanoma cell lines and breast cancers respectively. Different patterns of expression and variety of galectins structures in different cellular lines lead to these two opposite biological activity (John and Mishra 2016).

Different galectins have been shown to either promote or inhibit cellular adhesion, depending on the galectin member studies as well as experimental condition. For instance galectin-1 inhibits cell adhesion

of myoblasts and human smooth muscles, while it can promote cell adhesion of ovarian carcinoma cell and human melanoma cells (Hughes 2001). More specific about galectin-9, the cell adhesion mechanism is indirect, such as regulating Integrins function or localization (Kasamatsu et al. 2005). Some studies reported decrease in expression of galectin-9 and E-Cadherin during transformation of normal epithelium cells to neoplastic ones. This promotes defects in adhesion mechanism and increase tumor metastatic potential (Liang et al. 2008). Kasamatus showed that expression of galectin-9 was decreased in CA-22, HSC-2 and HSC-3 as different Oral SCC cells in comparison with normal oral keratinocytes. He reported galectin-9 as an important metastatic factor in OSCC. Decreased levels of galectin-9 and its association with increased metastatic potential of tumor cells had been reported in breast, kidney, adrenal and prostate cancers (Kasamatsu et al. 2005). On the other hand, some studies did not find significant role of Galectin-9 on cell adhesion and metastatic potential of OSCC (Chang et al. 2014, Hossaka et al. 2014). Increased in Galectin-9 levels in different cancer cells such as colon and leukemia were reported (Lahm et al. 2001). These studies showed that Galectin-9 have 3 isoforms, gal-9L, gal-9 M and gal-9S.Gal-9L decreased the expression of E selection while 9M increased E selection. Therefore, biological behavior of Galectin-9 is different according to their variants and their mRNA arrangement (Zhang et al. 2009).

The other mechanism of Galectin-9 is the regulation of apoptosis. This mechanism can act as two opposite sides of a coin. This means that it could lead to apoptosis of cancer cells and in some cases it could be increased proliferation of cancer cells by apoptosis of T cells. Galectin-9 can induce apoptosis in myeloma cells through activation of JNK pathway 38MAPK and 9, 3, and 8 caspases. These kinases lead to phosphorylation, hydroxylation and segmentation of DNA and finally apoptosis of myeloma cells (Kobayashi et al. 2010). On the other hand, the releasing galectin-9 from EBV in nasopharynx carcinoma promotes apoptosis in TH 1 cells with binding of galectin-9 to Tim 3 receptor on T cells. As TH1 cells inhibit the proliferation of malignant cells, the proliferation potential of malignant cells increase through apoptosis of TH1 cells (Klibi et al. 2009).

Another mechanism of galectin-9 is its role in the immune system. Galectin-9 similar to cytokines can modulate the activity and function of different types of immune cells.

Galectin-9 is well characterized as an eosinophilic chemo-attractant. It was known that the presence of Eosinophil in malignancies is a marker for good prognosis, because of anti tumoral activity of these immune cells. The increased numbers of eosinophil often observed in the colon and hematological cancers. It seems that the expression of Galectin-9 indeed mediated the infiltration of eosinophil in the tumor microenvironment and on the other hand the absence of galectin-9 in some of the solid tumors allows tumoral cells to escape from anti-tumoral activity of eosinophil (Sato et al. 2002, Wedemeyer and Vosskuhl 2008).

In this study we did not find significant correlation between the serum levels of galectin-9 and pathogenesis of Oral SCC, as there was no significant difference between the levels of galectin-9 in patients with oral SCC and normal subjects. In addition, there was not any significant correlation between serum concentration of galectin-9 and location, size, stage and grade of tumoral lesions. Hossaka et al. in their study reported increased expression of galectin-3 in oral SCC, while they did not find significance difference between galectin-9 expression in oral SCC and normal epithelial cells (Hossaka et al. 2014). Weber et al reported that High Gal3 expression in oral SCC is associated with tumor size (T-status) and parameters of malignancy (N-, L-status, grading) (Weber et al. 2017). In contrast to Weber findings, Andishe-Tadbir et al mentioned that there was no apparent correlation between serum galectin-3 concentration and clinico-pathological features such as stage, tumor size, nodal status, distant metastasis and histological grade (Andisheh Tadbir et al. 2010). As we mentioned previously, we also did not find significant correlation between serum levels of Glacetin-9 and cliniopatholic profile of Oral SCC.

To interpret the results of the present study some of the limitations should be considered.

1) While the expression of galectin-9 can be different in intra and extracellular fluids, it may be more precise to use histological techniques in addition to the hematological ones. 2) As this study was cross sectional and we could not follow the patients during the study, the serum samples of cases with recurrent tumor were not checked. It is recommended that in case of recurrence the levels of Galectin-9 to be compared before and after the recurrence. 3) Galectin-9 has 3 isoforms as previously mentioned. Their expression and role are different in various cancers. It would be better to evaluate the 3 isoform separately in the study. 4) In the present study the subjects with metastasis were rare (n=1) and we could not find a statistical correlation between the serum levels of galectin-9 and metastasis. It is suggested that in future studies the relation between metastasis and serum levels of galectin-9 to be investigated more precisely. As a conclusion the serum levels of galectin-9 were lower in patients with Oral SCC than the control subjects, but the difference was not significant. This marker does not seem to play any significant role in the pathogenesis of Oral squamous cell carcinoma.

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REFERENCES

Abagale SA, Atiemo S, Abagale FK, Ampofo A, Amoah CY, Aguree S, Osei Y (2019) Pesticide Residues Detected in Selected Crops, Fish and Soil from Irrigation Sites in the Upper East Region of Ghana.

Akhter M, Hossain S, Rahman QB, Molla MR (2011) A study on histological grading of oral squamous cell carcinoma and its co-relationship with regional metastasis. Journal of oral and maxillofacial pathology: JOMFP 15(2): 168.

Andisheh Tadbir A, Fattahi MJ, Khademi B, Pourshahidi S, Ebrahimi H, Sardari Y, Fattah Z. (2010) Serum Level of Galectin-3 in Patients with Oral Squamous Cell Carcinoma. Middle East Journal of Cancer 1(2): 77-81.

Anneroth G, Batsakis J, Luna M (1987) Review of the literature and a recommended system of malignancy grading in oral squamous cell carcinomas. European Journal of Oral Sciences 95(3): 229-49.

Astorgues-Xerri L, Riveiro ME, Tijeras-Raballand A, Serova M, Neuzillet C, Albert S, Raymond E, Faivre S (2014) Unraveling galectin-1 as a novel therapeutic target for cancer. Cancer treatment reviews 1;40(2): 307-19.

Boonkitticharoen V, Kulapaditharom B, Leopairut J, Kraiphibul P, Larbcharoensub N, Cheewaruangroj W, Chintrakarn C, Pochanukul L (2008) Vascular endothelial growth factor A and proliferation marker in prediction of lymph node metastasis in oral and pharyngeal squamous cell carcinoma. Archives of Otolaryngology–Head & Neck Surgery 134(12): 1305-11.

Brabletz T, Hlubek F, Spaderna S, Schmalhofer O, Hiendlmeyer E, Jung A, Kirchner T (2005) Invasion and metastasis in colorectal cancer: epithelial-mesenchymal transition, mesenchymal-epithelial transition, stem cells and β-catenin. Cells tissues organs 179(1-2): 56-65.

Chang SW, Kallarakkal TG, Abraham MT (2014) Changed expression of E-cadherin and galectin-9 in oral squamous cell carcinomas but lack of potential as prognostic markers. Asian Pacific Journal of Cancer Prevention 15(5): 2145-52.

Chang WA, Tsai MJ, Kuo PL, Hung JY (2017) Role of galectins in lung cancer. Oncology letters 14(5): 5077-5084.

Choi SI, Seo KW, Kook MC, Kim CG, Kim YW, Cho SJ (2017) Prognostic value of tumoral expression of galectin-9 in gastric cancer. Turk J Gastroenterol 28: 166-170.

Dar AA, Dwivedi AK, Iyer PK, Khan A (2018) Indole derived “turn-on” fluorometric probe for dual detection of Hg2+ and Cu2+ ions at nanomolar level. Asian Journal of Green Chemistry 2(3. pp. 171-280): 171-180.

Fujita K, Iwama H, Oura K, Tadokoro T, Samukawa E, Sakamoto T, Nomura T, Tani J, Yoneyama H, Morishita A, Himoto T (2017) Cancer therapy due to apoptosis: Galectin-9. International journal of molecular sciences 1;18(1): 74.

Ghantous Y, Abu IE (2017) Global incidence and risk factors of oral cancer. Harefuah 156(10): 645-9.

Heusschen R, Griffioen AW, Thijssen VL (2013) Galectin-9 in tumor biology: a jack of multiple trades. Biochimica et Biophysica Acta (BBA)-Reviews on Cancer 1836(1): 177-85.

Hossaka TA, Ribeiro DA, Focchi G, André S, Fernandes M, Carapeto FC, Silva MS, Oshima CT (2014) Expression of Galectins 1, 3 and 9 in normal oral epithelium, oral squamous papilloma, and oral squamous cell carcinoma. Dental research journal 11(4): 508.

Hossaka TA, Ribeiro DA, Focchi G, André S, Fernandes M, Carapeto FC, Silva MS, Oshima CT (2014) Expression of Galectins 1, 3 and 9 in normal oral epithelium, oral squamous papilloma, and oral squamous cell carcinoma. Dental research journal 11(4): 508.

Hughes RC (2001) Galectins as modulators of cell adhesion. Biochimie 83(7): 667-76.

Irie A, Yamauchi A, Kontani K, Kihara M, Liu D, Shirato Y, Seki M, Nishi N, Nakamura T, Yokomise H, Hirashima M (2005) Galectin-9 as a prognostic factor with antimetastatic potential in breast cancer. Clinical Cancer Research 11(8): 2962-8.

Irie A, Yamauchi A, Kontani K, Kihara M, Liu D, Shirato Y, Seki M, Nishi N, Nakamura T, Yokomise H, Hirashima M (2005) Galectin-9 as a prognostic factor with antimetastatic potential in breast cancer. Clinical Cancer Research 11(8): 2962-8.

Jadhav KB, Gupta N (2013) Clinicopathological prognostic implicators of oral squamous cell carcinoma: need to understand and revise. North American journal of medical sciences 5(12): 671.

Jiang J, Jin MS, Kong F, Cao D, Ma HX, Jia Z, Wang YP, Suo J, Cao X (2013) Decreased galectin-9 and increased Tim-3 expression are related to poor prognosis in gastric cancer. PLoS One 8:e81799.

John S, Mishra R (2016) Galectin-9: from cell biology to complex disease dynamics. Journal of biosciences 41(3): 507-34.

Kacimi R, Khouzami K, Abram T, Bejjit L, Bennani MN, Bouachrine M (2020) Electro-Optical and Photovoltaic Properties of Oligothiophene and Derivatives; Experimental and Theoretical Investigations. *Chemical Methodologies 4*(2. pp. 115-219): 203-219.

Kageshita T, Kashio Y, Yamauchi A, Seki M, Abedin MJ, Nishi N, Shoji H, Nakamura T, Ono T, Hirashima M (2002) Possible role of galectin-9 in cell aggregation and apoptosis of human melanoma cell lines and its clinical significance. Int J Cancer 99: 809-816.

Kasamatsu A, Uzawa K, Nakashima D, Koike H, Shiiba M, Bukawa H, Yokoe H, Tanzawa H (2005) Galectin-9 as a regulator of cellular adhesion in human oral squamous cell carcinoma cell lines. International journal of molecular medicine 16(2): 269-73.

Klibi J, Niki T, Riedel A, Pioche-Durieu C, Souquere S, Rubinstein E, Le Moulec S, Guigay J, Hirashima M, Guemira F, Adhikary D (2009) Blood diffusion and Th1-suppressive effects of galectin-9–containing exosomes released by Epstein-Barr virus–infected nasopharyngeal carcinoma cells. Blood 113(9): 1957-66.

Kobayashi T, Kuroda J, Ashihara E, Oomizu S, Terui Y, Taniyama A, Adachi S, Takagi T, Yamamoto M, Sasaki N, Horiike S (2010) Galectin-9 exhibits anti-myeloma activity through JNK and p38 MAP kinase pathways. Leukemia 24(4): 843.

Lahm H, André S, Hoeflich A, Fischer JR, Sordat B, Kaltner H, Wolf E, Gabius HJ (2001) Comprehensive galectin fingerprinting in a panel of 61 human tumor cell lines by RT-PCR and its implications for diagnostic and therapeutic procedures. Journal of cancer research and clinical oncology 127(6): 375-86.

Le Campion AC, Ribeiro CM, Luiz RR, da Silva Júnior FF, Barros HC, dos Santos KD, Ferreira SJ, Gonçalves LS, Ferreira SM (2017) Low survival rates of oral and oropharyngeal squamous cell carcinoma. International journal of dentistry.

Liang M, Ueno M, Oomizu S, Arikawa T, Shinonaga R, Zhang S, Yamauchi A, Hirashima M (2008) Galectin-9 expression links to malignant potential of cervical squamous cell carcinoma. Journal of cancer research and clinical oncology 134(8): 899-907.

Noguti J, De Moura CF, De Jesus GP, Da Silva VH, Hossaka TA, Oshima CT, Ribeiro DA (2012) Metastasis from oral cancer: an overview. Cancer Genomics-Proteomics 9(5): 329-35.

Pires FR, Ramos AB, Oliveira JB, Tavares AS, Luz PS, Santos TC (2013) Oral squamous cell carcinoma: clinicopathological features from 346 cases from a single oral pathology service during an 8-year period. Journal of Applied Oral Science 21(5): 460-7.

Sabatos CA, Chakravarti S, Cha E, Schubart A, Sanchez-Fueyo A, Zheng XX, Coyle AJ, Strom TB, Freeman GJ, Kuchroo VK (2003) Interaction of Tim-3 and Tim-3 ligand regulates T helper type 1 responses and induction of peripheral tolerance. Nat Immunol 4: 1102-1110.

Sanchez-Fueyo A, Tian J, Picarella D, Domenig C, Zheng XX, Sabatos CA, Manlongat N, Bender O, Kamradt T, Kuchroo VK, Gutierrez-Ramos JC, Coyle AJ, Strom TB (2003) Tim-3 inhibits T helper type 1-mediated auto- and alloimmune responses and promotes immunological tolerance. Nat Immunol 4: 1093-1101.

Sato M, Nishi N, Shoji H, Seki M, Hashidate T, Hirabayashi J, Kasai KI, Hata Y, Suzuki S, Hirashima M, Nakamura T (2002) Functional analysis of the carbohydrate recognition domains and a linker peptide of galectin-9 as to eosinophil chemoattractant activity. Glycobiology 12(3): 191-7.

Serkova, E. I., Voronin, A. M., Salankova, S. Y., Bychkova, N. V., Klyuikov, V. V., & Savin, A. V. (2019). Design-Oriented Education Environment as a Means of Improving the Quality of Undergraduate Education in Terms of the Competency-Based Approach. Journal of Environmental Treatment Techniques, 7(4), 601-612.

Türeci Ö, Schmitt H, Fadle N, Pfreundschuh M, Sahin U (1997) Molecular definition of a novel human galectin which is immunogenic in patients with Hodgkin's disease. Journal of Biological Chemistry 272(10): 6416-22.

Vladoiu MC, Labrie M, St-Pierre Y (2014) Intracellular galectins in cancer cells: potential new targets for therapy. International journal of oncology 1;44(4): 1001-14.

Weber M, Büttner-Herold M, Distel L, Ries J, Moebius P, Preidl R, Geppert CI, Neukam FW, Wehrhan F (2017) Galectin 3 expression in primary oral squamous cell carcinomas. BMC cancer 17(1): 906

Wedemeyer J, Vosskuhl K (2008) Role of gastrointestinal eosinophils in inflammatory bowel disease and intestinal tumours. Best Practice & Research Clinical Gastroenterology 22(3): 537-49.

Xu XC, El-Naggar AK, Lotan R (1995) Differential expression of galectin-1 and galectin-3 in thyroid tumors. Potential diagnostic implications. The American journal of pathology 147(3): 815

Yang J, Zhu L, Cai Y, Suo J, Jin J (2014) Role of downregulation of galectin-9 in the tumorigenesis of gastric cancer. International journal of oncology 45(3): 1313-20.

Yang RY, Rabinovich GA, Liu FT (2008) Galectins: structure, function and therapeutic potential. Expert reviews in molecular medicine 10.

Zhang F, Zheng M, Qu Y, Li J, Ji J, Feng B, Lu A, Li J, Wang M, Liu B (2009) Different roles of galectin-9 isoforms in modulating E-selectin expression and adhesion function in LoVo colon carcinoma cells. Molecular biology reports 36(5): 823-30.

Zhu C, Anderson AC, Schubart A, Xiong H, Imitola J, Khoury SJ, Zheng XX, Strom TB, Kuchroo VK (2005) The Tim-3 ligand galectin-9 negatively regulates T helper type 1 immunity. Nat Immunol 6: 1245-1252.