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THE RELATIONSHIP BETWEEN THE EXPRESSION ACTIVITY OF GENES ENCODING VIMENTIN AND ACTIN-BINDING PROTEINS IN PATIENTS WITH SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK WITH LYMPHOGENOUS METASTASIS.

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Abstract

Aggressive head and neck squamous cell carcinoma is characterized by a high metastatic potential, with the epithelial-mesenchymal transition acting as a central driving process. The epithelial-mesenchymal transition during metastasis is driven by the remodeling of the cytoskeleton, primarily through the action of actin-binding proteins. There are no available methods for assessing the risk of head and neck squamous cell carcinoma metastasis; therefore, the study of the molecular characteristics of head and neck squamous cell carcinoma metastasis remains extremely relevant. The purpose of the study was to examine the relationship between the mRNA expressions of vimentin and actin-binding proteins (cofilin-1, profilin-1, adenylate cyclase-associated protein 1, fascin-1 and ezrin) in tumor tissue of head and neck squamous cell carcinoma patients with lymph node metastases.

Material and Methods: The analysis was carried out using RT-PCR in paired samples from The analysis was performed using reverse transcriptase PCR in paired samples from 44 patients with head and neck squamous cell carcinoma: Thirty seven patients with laryngeal squamous cell carcinoma and seven patients with oropharyngeal squamous cell carcinoma. All patients were divided into subgroups with and without lymph node metastases.

Results: Profilin-1 mRNA levels were found to be seven times higher in patients with lymph node metastases than in patients without metastases. Ezrin mRNA levels were not correlated with lymph node metastasis, but correlated with tumor stage. Vimentin mRNA levels were independent of disease stage and the presence of lymph node metastasis. High vimentin mRNA levels correlated with elevated expression of fascin-1 and adenylyl cyclase-associated protein 1 and contributed to a stronger association between cofilin-1 and profilin-1.

Conclusion: Thus, the relationship between vimentin and actin-binding protein gene expression indicates active cytoskeletal reorganization during head and neck squamous cell carcinoma metastasis.

Keywords: *epithelial-mesenchymal transition, actin-binding proteins, head and neck squamous cell carcinoma, vimentin, intermediate filament proteins, metastasis*

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INTRODUCTION

Head and neck squamous cell carcinoma (SCC) is the 6-th most common cancer worldwide. Head and neck SCC cases are anticipated to increase by 30% by 2030, reaching over 1 million new cases annually. Currently, there is no specific screening for diagnosis and prognosis of this disease, and a thorough physical examination remains the main diagnostic approach. Head and neck SCC represents over 90% of all head and neck cancers, arising from the mucosal epithelium of the larynx, oral cavity, and oropharynx. The head and neck SCC mortality remains high due to local recurrence, distant metastasis, and significant resistance to standard chemoradiotherapy [*Romanenko I.G. et al, 2021; Coca-Pelaz A. et al, 2026*]; therefore, the identification of new prognostic factors with the analysis of biological characteristics of this tumor is crucial for improving survival rates.

Head and neck squamous cell carcinoma is characterized by its high aggressiveness, which is largely driven by its ability to metastasize, a process closely linked to the epithelial-mesenchymal transition (EMT). Initiation of the EMT during metastasis leads to changes in the expression of various genes, including those associated with cytoskeleton reorganization. It is known that for tumor cells of epithelial origin, activation of molecular biological processes associated with the EMT most specifically reflects malignant transformation [*Kalluri R et al., 2009; Gaponova A et al, 2020*]. The epithelial-mesenchymal transition process is accompanied by a cascade of various changes in molecular genetic events, in particular, the activation of transcription factors (Snail-1, Twist, Zeb-1/Zeb-2 etc.), increased production of tissue metalloproteinases, loss of intercellular contacts, changes in the content of actin-binding proteins and other intracellular events [*Chikina A et al., 2018; Morris H et al., 2015; Kakurina G et al, 2018; Suzuki T et al., 2023; Yang J et al., 2020*]. All these processes ultimately lead to the reorganization of the actin cytoskeleton, which is the final step before the onset of tumor cell invasion [*Datta A et al., 2020*].

Vimentin, an intermediate filament protein, is believed to be primarily expressed in fibroblasts, endothelial cells, and lymphocytes [Sharma P et al, 2019; Pimm ML, et al, 2020]. There is evidence that vimentin is involved not only in regulating the EMT during tumor growth but also in regulating the Wnt/β-catenin and glycogen synthase kinase-3 (GSK-3)/Snail signaling pathways. It is believed that vimentin is mainly expressed in fibroblasts, endothelial cells and lymphocytes. Cytoskeleton remodeling is known to be mediated by multiple actin-associated proteins (AAPs) [*Peltanova B et al., 2019; Chikina A et al, 2018; Mokin Y et al, 2024*], including cofilin, fascin, profilin, ezrin, adenylyl-associated protein-1 (CAP1), which have different functional roles in the cell [*Kakurina G et al, 2016; Kakurina G et al, 2018; Mokin YI et al, 2024*]. In particular, cofilin-1 (CFL1) and CAP1 are functionally related and have the ability to cut actin filaments [*Kakurina G et al, 2016; Kakurina G et al 2018; Kolegova E et al, 2020*]. Profilin -1 (PFN1) is a protein that binds actin monomers and enhances the growth of actin microfilaments [*Coumans J et al, 2018*]. Fascin (FSCN1) is an actin binding protein that is involved in the formation of fibrillar actin bundles [*Kolegova E et al, 2020; Zhang Y et al, 2018*]. Ezrin (EZR), a protein of the ezrin-radixin-moesin (ERM) family, acts as a linker between the plasma membrane and the actin cytoskeleton [*Michie K et al, 2018; Hinojosa L et al, 2017; Brambilla D et al, 2009*]. In response to extracellular and intracellular signals, actin-binding proteins and vimentin regulate cytoskeleton reorganization, thereby participating in cancer cell invasion and metastasis [*Sharma P et al., 2019*]. There is virtually no data on the combined effect of vimentin and the cytoskeleton proteins on head and neck SCC metastasis. In addition, given that laboratory-specific methods for predicting Laryngeal SCC metastasis have not yet been introduced into practice, this area of research remains relevant.

The assessment of the relationship between the expression of genes encoding vimentin and the expression activity of genes encoding cytoskeleton proteins in the head and neck SCC tissue, as well as the evaluation of their relationship with lymph node metastasis will be useful as new approaches in diagnostics or search for new therapeutic targets. Therefore, the aim of the study was to assess the relationship between the levels of vimentin and cytoskeleton proteins: cofilin-1 (CFL1), rofiling-1 (PFN1), ezrin (EZR), fascin-1 (FSCN1) and adenylyl-associated protein-1 (CAP1) in head and neck SCC tissue, as well as the association of the expression of these

genes with head and neck SCC metastasis.

Material and methods

The study included 37 patients with laryngeal squamous cell carcinoma and 7 patients with oropharyngeal squamous cell carcinoma, who were treated at the Cancer Research Institute of Tomsk National Research Medical Center from 2017 to 2021. The median age of the patients was 54.7 (41:67) years. The proportion of men in the study group was 89%. Tumor samples (stage T1-4N0-1M0) and normal tissue samples obtained during videolaryngoscopy were the study material. All patients with histologically verified SCC were divided into the group with regional metastases (n=25) and the group without metastases (n=19). The study was conducted in accordance with the Helsinki Declaration of the World Medical Association "Ethical Principles for Medical Research Involving Human Subjects" with the amendments of 2000 and the "Rules of Clinical Practice in the Russian Federation" approved by Order of the Ministry of Health of the Russian Federation No. 266 (06/19/2003). Informed consent was obtained from each patient and permission from the Ethics Committee of the Oncology Research Institute of the TNRMC (extract from protocol No. 7 dated 06/24/2019). The obtained tissue samples were placed and stored in RNAlater solution (Ambion, USA).

Extraction of mRNA and preparation of cDNA: The CCR-50 kit (Biosilica, Novosibirsk) was used to extract the total mRNA pool from paired tissue samples according to the manufacturer's instructions. The concentration and purity of mRNA were assessed using a NanoDrop-2000 spectrophotometer (Thermo Scientific, USA). cDNA synthesis on the RNA matrix was performed using the OT-1 reverse transcription reagent kit (Synthol, Moscow) according to the manufacturer's instructions, and the resulting mixture was then used to perform quantitative real-time polymerase chain reaction (RT-PCR).

Real-time PCR: The level of gene mRNA expression was assessed by RT-PCR using Sybr Green technology on an iCycler amplifier (Bio-Rad, USA). Primers (Table 1) were selected using the Vector NTI Advance 11.5 program (Thermo Fisher Scientific, USA) and the NCBI database (http://www.ncbi.nlm.nih.gov/nuccore). Melting curve analysis (Melt) was used to assess the final PCR product for the presence of primer-dimers or non-specific products.

The housekeeping gene of glyceraldehyde-3-phosphate dehydrogenase (GAPDH) enzyme was used as a reference gene to normalize the expression of the studied genes. mRNA (cDNA) isolated from morphologically altered laryngeal epithelium was used as a calibrator. Expression analysis was performed using the 2-ΔΔCT method [*Livak K, 2001*].

Statistical analysis of the results was performed using the Statistica 6.0 and IBM SPSS Statistics 22.0 software packages. Differences were considered statistically significant at $p<0.05$. The results are presented as Me (Q1; Q3), where Me is the median and Q1; Q3 is the interquartile range (25% and 75% quartiles), and Mean±SD, where Mean is the average value and SD is the standard deviation. The number of patients in the group is n. P (U-test) is the nonparametric Mann-Whitney U-test. Spearman correlation analysis was used to analyze the relationships.

Table 1.

Primer sequences for the studied genes

Genes	Amplicon	Sequences
Vimentin (VIM) NM_003380	176 p.n.	**S** 5′- CAGATGCGTGAAATGGAAGA-3′ **A** 5′- CTGTAGGTGGCAATCTCAATGT-3′
Ezrin (EZR) NM_001111077	273 p.n.	**S** 5′- CTTGATGTGATGTGGCAGGA-3′ **A** 5′- GGAATGAGTGGGCGGAA-3′
Profilin-1(PFN1) NM_005022	134 p.n.	**S** 5'-TGGAGCAAACCCTACCCTT-3 **A** A 5′- AGCCCAGACACCGAACTTT -3′
Cofilin-1(CFL1) NM_005507	144 p.n.	**S** 5′- CTGCCGCTATGCCCTCTA-3′ **A** 5′- TTCTTCTTGATGGCGTCCTT-3′
Adenylyl-associated protein-1 (CAP1) NM_001105530	278 p.n..	**S** 5′- CCAAACGAGCCACAAAGAA-3′ **A** 5′- ACCCATTACCTGAACTTTGACAT-3′
Fascin-1(FSCN1) NM_003088.4	167 p.n.	**S** 5′- TCAGAGCTCTTCCTCATGAAGCT **R** 5′- GTCCAGTATTTGCCTGTGGAGTC
GAPDH NM_001256799.2	138 p.n.	**S** 5′- GGAAGTCAGGTGGAGCGA-3′ **A** 5′-GCAACAATATCCACTTTACCAGA-3′

Note: *NM – RNA sequence number in NCBI Nucleotide Database (http://www.ncbi.nlm.nih.gov/nuccore); S – forward primer; A – reverse primer; p.n. - pairs of nucleotides*

RESULTS

No significant differences in the studied parameters between patients with laryngeal SCC and Oropharyngeal SCC were found. (Table 2)

The groups were combined and further analyzed in the overall sample of head and neck SCC patients. A 7-fold increase in the level of profilin-1 mRNA was observed in tumor tissue of head and neck SCC patients with lymph node metastases compared to those without metastases. The level of cofilin-1 mRNA in tumor tissue of head and neck SCC patients tended to increase in comparison with that observed in patients without metastases (Table 3). No significant differences in the level of vimentin mRNA between patients with lymph node metastases and patients without metastases were found.

TABLE 2.

The mRNA levels of actin-binding proteins and vimentin in tumor tissue of patients with laryngeal squamous cell carcinoma (LSCC) and oropharyngeal squamous cell carcinoma (OSCC)

	LSCC, n= 37			OSCC , n=7			P
mRNA	Me	Q1	Q3	Me	Q1	Q3	(U-test)
Vimentin	0.89	0.04	21.93	0.90	0.04	12.81000	0.23
Fascin-1	0.19	0.03	8.60	0.68	0.04	7.02000	0.21
Ezrin	2.46	0.06	17.99	1.69	0.05	17.01000	0.51
Profilin-1	1.48	0.01	14.69	2.51	0.12	18.82000	0.51
Cofilin-1	2.38	0.04	17.75	1.16	0.12	25.59000	0.36
CAP1	3.69	0.12	27.33	2.65	0.09	28.64701	0.68

Note: a p-value is a significance level of differences (Mann–Whitney U test), CAP1 - adenylyl cyclase-associated protein 1

The correlation analysis revealed that metastasis affected the strength and number of correlations between expressed genes encoding cytoskeletal proteins. Thus, in head and neck SCC patients with lymph node metastasis, a strong positive correlation between the mRNA level of profilin 1 and cofilin 1 was found r=0.9; p≤0.04) (Fig. 1).

In head and neck SCC patients with lymph node metastases, positive correlations were found between the expression levels of almost all the genes studied (r=0.4-0.7; p≤0.05). The VIM mRNA expression positively correlated with the expression of the FSCN1, EZR, PFN1 and CAP1 genes (r=0.7; p≤0.04). A positive relationship was established in the group of functionally related ABPs encoding PFN1, CAP1 and CFL1. The extent of tumor involvement correlated with ezrin mRNA expression, which was almost 16.8 times lower in patients with stage T3-4N0-2M0 compared to

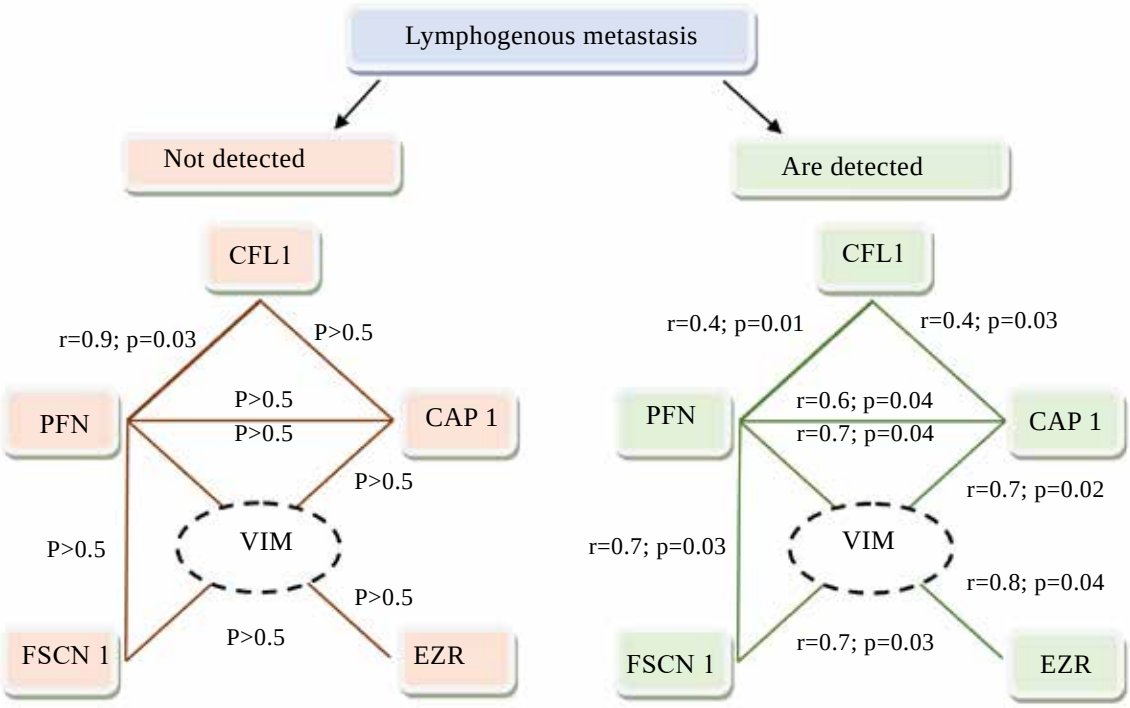

FIGURE 1. *Expression of genes encoding cytoskeleton proteins in tumor tissue of patients with head and neck SCC: Spearman correlation coefficients. Note: ( )Positive correlation; r – The Spearman's rank correlation coefficient; p – level of statistical significance.*

Table 3.

The relative mRNA levels of actin-binding proteins and vimentin in tumor tissue of head and neck SCC patients with and without lymph node metastasis.

mRNA	Without metastases, T1-4N0M0 Me(Q1; Q3)	Metastases, T1-4N1-2M0 Me(Q1; Q3)	P (U-test)
Vimentin	0.39(0.01; 40.93)	1.44(0.22; 18.00)	0.08
Fascin-1	0.32(0.04; 6.60)	1.73(0.21; 14.40)	0.11
Ezrin	3.47(0.06; 20.99)	1.53(0.07; 8.17)	0.51
Profilin-1	0.40(0.01; 4.69)	2.50(0.76; 25.99)	0.01
Cofilin-1	0.39(0.04; 7.75)	3.12(0.19; 27.10)	0.06
CAP1	3.51(0.22; 29.33)	4.51(1.07; 28.61)	0.39

Note: *a p-value is a significance level of differences (Mann–Whitney U test);* CAP1 - adenylyl cyclase-associated protein 1

Table 4.

The expression levels of actin-binding proteins in head and neck SCC tissue depending on the extent of the tumor involvement.

mRNA	T1-2N0-1M0 Me(Q; Q3)	T3-4N0-2M0 Me(Q; Q3)	P (U-test)
Vimentin	0.31 (0.01; 41.93)	1.27(0.22; 7.31)	0.58
Fascin-1	1.31(0.03; 7.15)	0.90(0.12; 8.00)	0.70
Ezrin	12.53(0.57; 34.34)	0.75(0.04; 4.67)	0.03
Profilin-1	1.19(0.01; 7.67)	2.09(0.18; 18.82)	0.22
Cofilin-1	1.57(0.08; 13.77)	1.16(0.19; 7.60)	0.74
CAP1	5.41(1.07; 27.93)	3.33(0.10; 29.15)	0.67

Note: a p-value is a significance level of differences (Mann–Whitney U test), CAP1 - adenylyl cyclase-associated protein 1

Table 5.

Expression of the gene encoding vimentin in tumor tissue of head and neck SCC patients

Groups of patients	Level of VIM mRNA		Total number of patients
	<0.63 U	≥0.63 U	
Lymph node metastasis			
no	12	13	25
yes	9	10	19
Total number of patients	21	22	44

Table 6.

The expression levels of actin-binding protein genes in tumor tissue of patients with laryngeal cancer depending on the different expression activity of the gene encoding vimentin

mRNA	below 0.63 U			above 0.63 U			P (U-test)
	Me	Q1	Q3	Me	Q1	Q3	
Fascin-1	0.12	0.03	0.26	1.73	0.68	7.02	0.02
Ezrin	0.52	0.02	3.48	4.05	0.09	17.03	0.07
Profilin-1	0.75	0.02	18.82	2.80	0.40	14.91	0.21
Cofilin-1	1.16	0.14	26.29	1.89	0.08	5.54	0.18
CAP1	0.14	0.02	10.10	5.34	1.61	26.93	0.01

Note: a p-value is a significance level of differences (Mann–Whitney U test), CAP1 - adenylyl cyclase-associated protein 1

those with stage T1-2N0-1M0 (Table 4). No significant changes in the gene expression levels depending on the tumor grade and size were found.

Head and neck SCC patients were divided into the groups with low VIM mRNA expression (below 0.63 U) and high VIM expression in tumor tissue (above 0.63 U) (Table 5).

High VIM mRNA levels were observed in 10 head and neck SCC patients with lymph node metastasis (N1-2) and in 13 patients without metastasis. A similar distribution was observed in patients with low VIM mRNA levels (Table 5). Although VIM mRNA levels did not correlate with the presence of lymph node metastasis, their increase was associated with a significant increase in CAP1 and FSCN-1 expression. (Table 6).

It was found that at low VIM mRNA levels (below 0.63 U), there was one weak positive correlation between PFN1 and CFL1 mRNAs (r=0.4; p=0.04) (Fig. 2). While high VIM gene expression was associated with an increase in the number and strength of correlations between CFL1, PFN1, FSCN1, and EZR mRNA levels, the strength of correlations between the functional partners of CFL1 and PFN1 increased almost twofold (r=0.9; p=0.03).

The study showed that lymph node metastasis in head and neck SCC did not correlate directly with the expression of the gene encoding vimentin. However an increase in Vimentin mRNA was associated with a significant increase in PFN1 mRNA (Table 3). The correlation analysis revealed that high vimentin mRNA levels enhanced the positive relationships between the mRNA levels of CFL1 and PFN1 and contributed to a stronger positive association between mRNA expressions of PFN1-FSCN1 – EZR. The observation of multiple positive relationships between vimentin and other protein mRNA expression levels during cancer metastasis supports the understanding that

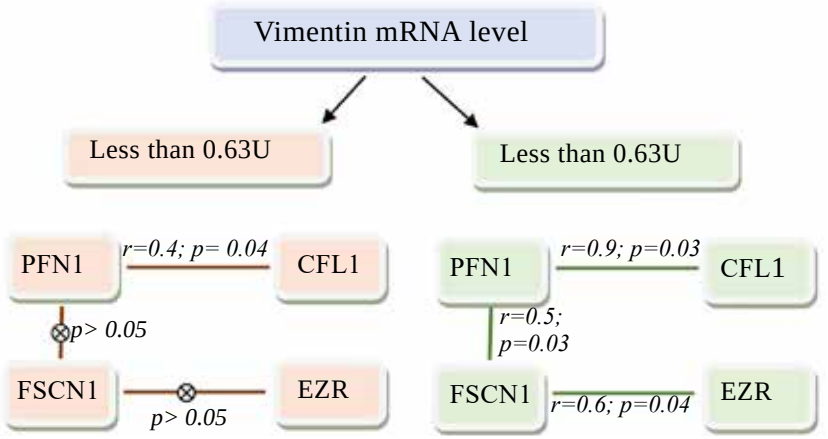

Figure 2. Effect of vimentin mRNA level on co-expression of genes encoding cytoskeletal proteins in head and neck SCC tissue.
Note: (——) Positive correlation; r – The Spearman's rank correlation coefficient; p – level of statistical significance.

vimentin acts as a key coordinator or "master regulator" of an entire metastatic program, often through indirect mechanisms.

DISCUSSION

Cytoskeletal proteins are known to not only regulate cell motility but also participate in transcription. There is evidence that proteins involved in actin polymerization can migrate across the nuclear membrane. The cell nucleus contains monomeric actin, the amount of which depends on key actin-binding proteins - profilin and cofilin. Nuclear actin, regulated by actin-associated proteins, is involved in transcription, RNA processing, apoptosis, chromatin organization, nuclear membrane assembly, and other nuclear effects on external signals. [Kristó I et al, 2016; Mokin Y et al, 2024].

Our study demonstrated that high vimentin mRNA levels correlated with elevated expression of FSCN1 and CAP1 and contributed to a stronger association between PFN1 и CFL1. Moreover, a positive correlation was found between FSCN1 and EZR and PFN1. Our results are consistent with other recent studies, highlighting the co-expression and role of CAP1**,** PFN1**,** and CFL1 in the metastatic cascade [*Coumans J et al, 2018; Joshi P et al, 2018; Kolegova E et al, 2020*].

We found a 16.8-fold decrease in ezrin mRNA expression between stages from T1-2N0-1M0 and T3-4N0-2M0, despite the low statistical significance (p=0.5). Ezrin, a protein which links the cell cytoskeleton, membrane, and extracellular matrix, is involved not only in cell locomotion, but also in processes such as adhesion, differentiation, proliferation, signaling, blebbing, and entosis [*Buenaventura R et al, 2023; Li J et al, 2015; Hinojosa L et al, 2017*]. There is a significant amount of data indicating a link between high ezrin levels and tumor progression, including metastasis [*Buenaventura R et al, 2023; Zhu Y et al, 2024*]. Our results obtained contradict the literature data. To analyze the relationship between EZR and tumor progression, it is likely necessary to take into account the presence of mutations in its gene, as well as the expression activity of genes of the ERM (ezrin-radixin-moesin) family [*Michie K et al, 2019*]. In addition, the decrease in ezrin expression may be associated with a disruption of the adhesive properties of tumor cells, which is important for invasion and metastasis [*Shevlyuk N et al, 2020*]. The role of ezrin in the processes of invasion, metastasis, progression and drug resistance of tumors is still being studied both in vivo and in vitro [*Buenaventura R et al, 2023; Zhu Y et al, 2024*]

CONCLUSION

Our study has extended the knowledge of molecular genetic mechanisms of head and neck SCC metastasis. Specific patterns in the correlations between the expression activity of genes encoding vimentin and ABPs have been identified. The results obtained indicate the activation of cytoskeletal reorganization during head and neck SCC metastasis. Cytoskeletal reorganization during any type of cellular locomotor activity is known to be controlled by various signaling systems. Therefore, further in vitro studies are needed to more fully analyze possible mechanisms and confirm the obtained results. These studies will expand our understanding of the role of actin-binding proteins in head and neck SCC progression. Nevertheless, the discovered relationships may contribute to our general understanding of cancer development and progression, which will be useful in the development of new diagnostic methods or therapeutic targets.

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