Immunohistochemical expression of transient receptor potential vanilloid 1 in World Health Organization grade IV astrocytoma, oral squamous cell carcinoma and bladder carcinoma

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Patient consent for publication: patients were briefed about the study procedure and followup details. They were enrolled in the study after getting their consent. They were also informed that they will be a part of this important study which will be published.

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ABSTRACT

Transient receptor potential vanilloid 1 (TRPV1), an ion channel receptor, has been identified to have a variety of functions in cancer, with overexpression associated with tumor suppression as well as promotion, making it an attractive but challenging target for cancer research and therapy. The study aimed to evaluate the immunohistochemical expression of TRPV1 in various cancer grades, including astrocytoma, meningioma, bladder carcinoma, oral squamous cell carcinoma, and normal tissues. A total of 60 patients diagnosed with cancer from King Edward Medical University were studied. All the specimens were prepared for immunohistochemistry by fixing them in formalin and embedding them in paraffin. Tissue consecutive sections were collected on L-lysine-coated slides. To determine the labeling index (*i.e.*, % of labeled cells, LI) for the TRPV1 antibody, two observers independently assessed 10 random non-overlapping fields (×400 total magnification) for each sample and counted manually 100 tumor cells in each field by using an ocular grid. High expression of TRPV1 was seen in the advanced stage of bladder cancer, while decreased expression was seen in low-grade bladder cancer. Very low expression of TRPV1 was seen in breast cancer. Very high expression of TRPV1 was seen in tissue samples of World Health Organization grade 4 astrocytoma. Tissue samples of oral cancer also showed increased expression of TRPV1. Meningioma (negative control) had no expression of TRPV1, and colon cancer (positive control) had high expression. The current study demonstrates distinct patterns of TRPV1 immunohistochemical expression across several cancer types, underlining the context-dependent nature of TRPV1's function in cancer progression. Further studies should be conducted to further investigate the therapeutic potential of TRPV1.100.

Introduction

Transient receptor potential (TRP) family members respond to chemicals, stretch/pressure, oxidation/reduction, pH, and osmolarity and are ligand-gated cation-permeable ion channels (such as Mg^{2+} and Ca^{2+}) that mediate downstream signaling. TRP channels are known to exist in internal membranes and interact with proteins that are crucial for TRP channel trafficking and activity in addition to their

well-established function at the cell surface.[1] TRP channels are involved in the control of tissue-specific activities.[2] Different clinical conditions have been identified to exhibit inherited or acquired malfunction of these channels.[3] Therefore, TRP channels have been suggested as therapeutic targets for diseases of the central nervous system, inflammatory bowel disease, diabetes, and cancer.[4,5]

The vanilloid subfamily of TRP (TRPV) channels consists of six members and is divided into two groups based on sequence homology, TRPV1-4 and TRPV5-6. The transient receptor potential vanilloid 1 (TRPV1) also known as vanilloid receptor 1 is a non-selective calcium permeable cation channel.[6] Several endogenous or exogenous stimuli, such as anandamide, pro-inflammatory chemicals, eicosanoids, capsaicin, and resiniferatoxin may activate TRPV1 channels, and these channels primarily serve as polymodal receptors.[7] A growing number of research links changes in TRPV channel expression to the emergence and spread of cancer.[8,9] Particularly, human hepatoblastoma, cervical and bladder cancer cells, and breast tumor-derived endothelial cells all need TRPV1 and TRPV4 for migration.[10] On the other hand, there is proof that certain normal or tumor-cultured cells have a pro-apoptotic function for TRPV1 channels.[11] In particular, there was an inverse relationship seen between the expression of the TRPV1 channel and patients' grading and survival.[12] Vanilloids and cannabinoids are more commonly employed as therapeutic agents in high-grade astrocytoma, urothelial, and cervical cancer cells to promote apoptosis and inhibit invasion and growth of tumors.[13]

Astrocytoma arises from cells known as astrocytes that are involved in supporting nerve cells. World Health Organization (WHO) grade 4 astrocytoma is the deadliest malignancy in the body with a median survival rate of fewer than 18 months.[14] According to the European Association of Neuro-oncology and the 2021 WHO classification of central nervous system malignancies, WHO grade 4 astrocytoma is divided into IDH-mutant and IDH-wildtype subtypes; however, IDH-wildtype astrocytoma is isolated for glioblastoma.[15,16] Meningioma is a brain tumor that develops from the meninges, which is a membrane that covers the spinal cord and brain. Arachnoid cap cells are considered the normal analogs of meningioma.[17] Meningioma is divided into three classes by the WHO and comprises a large variety of histological subtypes.[18] It has been suggested that specific changes in cell signaling pathways and the genome are responsible for the development of meningioma.[19]

In Pakistan, urinary bladder cancer is among the top 10 cancers in men and the 9th most common cancer in the world.[20,21] Urothelial carcinoma accounts for 90% of bladder carcinomas, while 6-8% are squamous cell carcinoma, and 2% account for adenocarcinoma.[22] Currently different clinical markers play an important role in deciding the therapeutic strategies and for the evaluation of follow-ups and prognosis. However, the heterogeneity of bladder tumors and different behaviors of urothelial carcinomas made the prediction of clinical outcomes of patients very difficult.

TRPV1 channel is mainly found in primary sensory neurons that are involved in the nociception pathway and neurogenic inflammation; however, its expression is also found in non-neuronal cells, such as in the urinary bladder.[23,24] Where its expression has been found in afferent nerve terminals, apical and basal urothelial cells, and also in interstitial cells.[25,26] Many other studies have found the expression of TRP1 on epithelial and mesenchymal cells of skin (skin keratinocytes).[27,28] Studies have also associated the altered level of TRPV1 with oral squamous cell carcinoma (OSCC) of the tongue but there is still much more to explore.[29] The purpose of this study was to analyze TRPV1 immunohistochemical expression in astrocytoma, meningioma, bladder carcinoma, OSCC, and normal tissues in Pakistani patients. The association between TRPV1 channel expression and clinic-pathological features of patients was also studied.

Materials and Methods

Patients

A total of 60 patients diagnosed with cancer from King Edward Medical College were studied (Table 1). Out of 60, 10 patients had OSCC, 10 had bladder cancer, 10 had WHO grade 4 astrocytoma, and 10 had breast cancer. Ten patients were of meningioma, which was taken as a negative control, while 10 patients with colon cancer were taken as positive controls. The archived blocks containing formalin-fixed, and paraffin-embedded tissues were retrieved from the King Edward Medical College's archives. The relative slides stained with hematoxylin and eosin (H&E) were reviewed for representative tumor regions by a pathologist. For histopathology, the tumors were evaluated by immunohistochemistry for the Ki-67 index, used as a proliferation marker, and tumors were graded based on diagnostic criteria of the WHO classification system.[30] The human specimen used in this study was following the University Ethics Commission.

Table 1. Expression of transient receptor potential vanilloid 1 in oral, breast, astrocytoma, bladder, meningioma and colon cancer.

	Transient receptor potential vanilloid 1 expression					
	OSCC (10 cases)	Breast cancer (10 cases)	Astrocytoma (10 cases)	Bladder cancer (10 cases)	Meningioma (negative control, 10 cases)	Colon cancer positive control, (10 cases)
Mean age (yrs.)	52.1	49.6	60.5	59.1	46.1	56.2
WD	2 (20%) ++	2 (20%) +	0(0%) -	5 (50%) +	9(90%) -ve	2 (20%) +++
MD	4 (40%) +++	3 (30%) +	0(0%) -	0 (0%) -	0 (0%) -ve	6 (60%) +++
PD	4 (40%) +++	5 (50%) +	10 (100%) +++	5 (50%) +++	1(10%) -ve	2(20%) +++

WD, well differentiated; MD, moderately differentiated; PD, poorly differentiated; -ve, interpretation of TRPV expression: i) 0-10% = -ve (no staining/expression); ii) 10-30% = + (weak staining/expression); iii) 30-60% = ++ (moderate staining/expression); iv) 60-100% = +++ (strong staining/expression).

Immunohistochemistry

All the specimens were prepared for immunohistochemistry by fixing them in formalin and embedding them in paraffin. Tissue consecutive sections were collected on L-lysine-coated slides. For each sample, one segment was stained with H&E. Histological sections were then deparaffinized in xylene for immunohistochemical studies. Further, these sections were rehydrated in graded alcohols up to water. Sections were microwaved in a 0.01 M citrate buffer of pH 6 to retrieve antigens. Sections were treated for 20 minutes with 1% hydrogen peroxide to quench the endogenous activity of hydrogen peroxide. Sections were incubated with appropriate protein-blocking agents. Then sections were incubated with primary anti-TRPV1 antibody (IHC human) TRP cation channel subfamily V member 1, capsaicin receptor, vanilloid receptor 1, OTRPC1 [Abcam Anti-TRPV1 antibody (ab3487), rabbit polyclonal]. Counterstaining was done with Mayer's hematoxylin solution and sections were dehydrated and mounted. To ensure antibody specificity, negative controls included the omission of primary antibodies and substitution with non-immune serum. Control slides were invariably negative for immunostaining. Positive human inflammatory bowel for TRPV1-4 was used as the positive control.[30]

Scoring of immunohistochemical staining

To determine the labeling index (*i.e.*, % of labeled cells, LI) for TRPV1 antibody, two observers independently assessed 10 random non-overlapping fields (×400 total magnification) for each sample and manually counted 100 tumor cells in each field by using an ocular grid. From the cell counts, the immuno-positive stromal and endothelial cells were excluded. Immunohistochemical expression of TRPV1 was studied in consecutive sections of each sample. The mean value of LI was used as a cut-off value to categorize the tumors as showing low or high protein expression. Microphotographs were obtained using a Nikon DXM 1200C digital camera mounted on a Nikon Eclipse 80i microscope and ACT-1C software (Nikon Instruments Inc., Melville, NY, USA). The cytoplasmic staining intensity and expression were scored semi-quantitatively, according to a previously described method,[31] as follows: i) 0-10% = -ve (no staining/expression); ii) 10-30% = + (weak staining/expression); iii) 30-60% = ++ (moderate staining/expression); iv) 60-100% = +++ (strong staining/expression)

Statistical analysis

For statistical analysis, non-parametric methods were used. For investigating the predictive value of TRPV1 expression regarding the grades, *i.e.*, dependable variable; grade I *vs*. higher grades (II and III) Spearman's rho correlation was used. A p-value <0.05 was considered significant. SPSS package 27 (IBM, Armonk, NY, USA) was used for the statistical analysis.

Results

High expression of TRPV1 was seen in the advanced stage of bladder cancer, while decreased expression was seen in low-grade bladder cancer, as shown in Figure 1A.

Very low expression of TRPV1 was observed in all grades of breast cancer, as shown in Figure 1B.

Colon cancer was used as a positive control and high expression of TRPV1 was seen in the biopsy sample of colon cancer, as shown in Figure 1C.

Very high expression of TRPV1 was seen in tissue samples of WHO grade 4 astrocytoma (Figure 2A).

Samples of meningioma were used as negative control and there was very no expression of TRPV1 in meningioma tissues (Figure 2B).

Tissue samples of oral cancer showed increased expression of TRPV1 (Figure 3).

Table 1 shows the expression of TRPV1 in different grades of carcinomas. The mean age of participants in OSCC was 52.1, in breast cancer 49.6, in astrocytoma, 60.5, in bladder cancer, 59.1, in meningioma, 46.1, and in colon cancer, 56.2. In OSCC, 2 (20%) participants had well differentiated (++), 4 (40%) had moderately differentiated (+++) and 4 (40%) had poorly differentiated (+++) carcinoma. In breast cancer, 2 (20%) participants had well differentiated (+), 3 (30%) had moderately differentiated (+) and 5 (50%) had poorly differentiated (+) cancer. In astrocytoma, 10 (100%) participants had poorly differentiated (+++) cancer. In bladder cancer, 5 (50%) participants had well differentiated (+) while 5 (50%) had poorly differentiated (+++) carcinoma. In meningioma, 9 (90%) participants had well differentiated (-ve) while 1 (10%) had poorly differentiated (-ve) cancer. In colon cancer, 2 (20%) participants had well differentiated (+++), 6 (60%) had moderately differentiated (+++) and 2 (20%) had poorly differentiated (+++) cancer.

There was a strong positive correlation between the grades of OSCC and TRPV1 expression. TRPV1 expression and intensity increased with advancement in grading (0.745*, p=0.013). There was also a strong positive correlation between the grades of bladder cancer and TRPV1 expression. TRPV1 expression and intensity increased with advancement in grading (1.000**, p=0.000) (Table 2).

Discussion

TRPV channels are well recognized for their members' role as polymodal receptors detecting changes in the cellular environment; however, pharmacological manipulation of these channels in cancer cells has been documented.[13] Several studies show that the TRPV cation channel family is important in malignant cell growth and development *via* modulating cell survival and apoptotic cell death.[1,8,32,33]

Our results showed intense expression of TRPV1 in WHO grade IV astrocytoma. Stock *et al.* observed a similar role of TRPV1 and showed that high-grade (HG)-astrocytoma expresses high amounts of TRPV1 and that TRPV1 activation causes tumor cell death. Neural progenitor cells (NPCs) target HG-astrocytoma and emit fatty acid ethanolamides, which are anti-tumorigenic TRPV1 agonists.[34] They also showed that arachidonoyl-ethanolamide (AEA), a cannabinoid receptor agonist, and endogenous TRPV1 are mostly sourced by NPCs.[35,36] The researchers discovered that NPC-released factors evoke TRPV1-dependent Ca2+ responses in HG-astrocytoma, the tumor suppressive effect of NPC-conditioned medium is lost, and that NPC-induced HG-astrocytoma cell death is TRPV1 dependent *in vitro* and *in vivo*. They were

able to identify high levels of AEA and related acylethanolamides in undifferentiated NPCs. These findings are consistent with earlier studies showing that synthesized AEA causes cell death in HG-astrocytoma.[37]

In our study, there was no expression of TRPV1 seen in meningioma. Goutsou *et al.* found that grade III meningioma had significantly lower TRPV1 expression than grade I or grade II meningioma.[38] Although there were very few meningiomas in this cohort, the decreased expression of TRPV1 channels in anaplastic meningioma (WHO grade III) may suggest a relationship between these channels and the differentiation of meningioma cells. TRPV1 is implicated in cancer pain, in addition to its function in the creation and propagation of pain through nociceptive sensory neurons.[4,8] Although TRPV1 was not found in the leptomeninges in their investigation, other researchers found TRPV1 channel-positive nerve fibers and blood vessels in the dura mater, which may have an impact on the pathophysiology of migraine.[39,40] Intriguingly, TRPV1 channel expression was found in the blood vessels of meningioma in their investigation. Functional investigations may reveal the therapeutic value of TRPV1 inhibitors in the treatment of pain, such as headaches, in meningioma patients.

High expression of TRPV1 was seen in the advanced stage of bladder cancer in our study. TRPV1 mRNA and protein were discovered to be expressed in well differentiated papillary urothelial carcinoma and normal human urothelial cells but significantly downregulated in poorly differentiated J82 and EJ cell lines and undifferentiated TCCSUP urothelial carcinoma cell lines.[41]

Increased expression of TRPV1 was seen in OSCC. Similar results were seen by Marincsák *et al.*[29] They found TRPV1 immunoreactivity in the basal layers of healthy human tongue epithelium; however, it was weak and sparse. In contrast, they found significantly increased TRPV1 immunoreactivity in all layers of the epithelium in both precancerous and malignant samples. Furthermore, they demonstrated that the substantial overexpression of TRPV1 seen in all grades of OSCC had no relationship with the tumor's aggressiveness. Finally, the molecular expression of TRPV1 was discovered in an OSCC-derived cell line and was found to rise in tandem with the cells' rapid development.

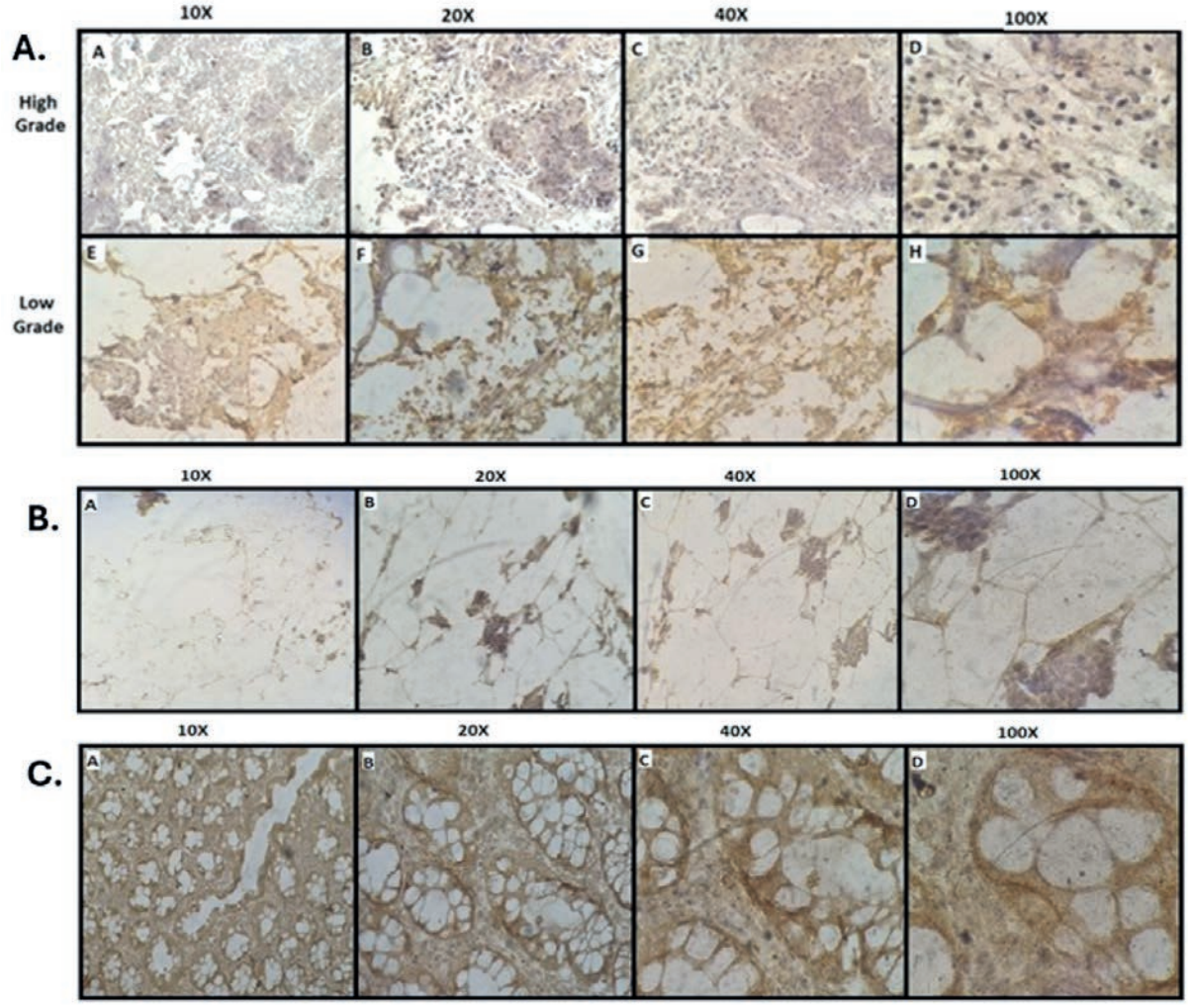

Figure 1. Immunohistochemical expression of transient receptor potential vanilloid 1 in bladder carcinoma (A), breast cancer (B) and colon cancer (C) at different magnifications (10-100×).

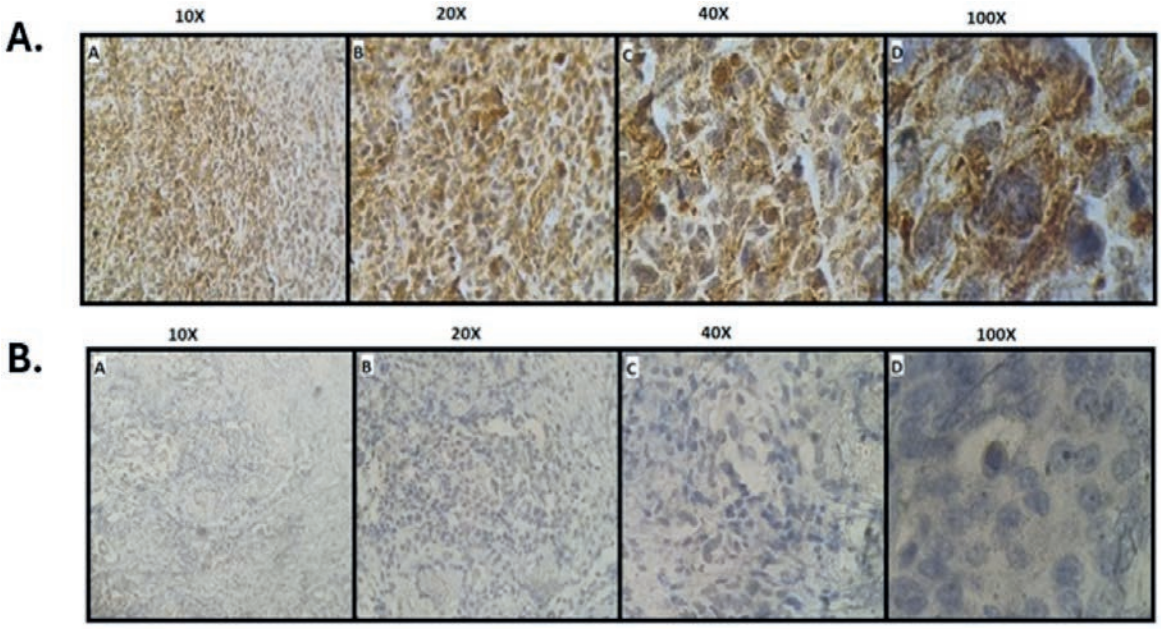

Figure 2. Immunohistochemical expression of transient receptor potential vanilloid 1 in World Health Organization grade IV astrocytoma (A) and negative expression in meningioma tissues (B) at different magnifications (10-100×).

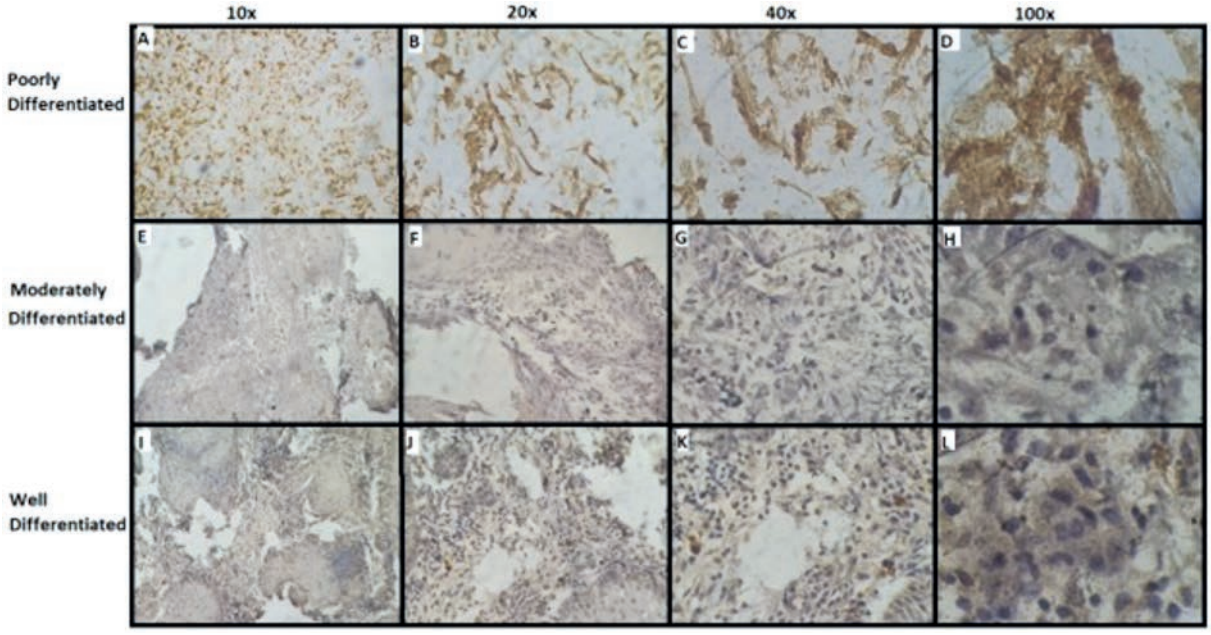

Figure 3. Immunohistochemical expression of oral squamous cell carcinoma (OSCC) at different magnifications (10-100×) (A-D), poorly differentiated OSCC (E-H), moderately differentiated OSCC, (I-L), well differentiated OSCC.

Table 2. Spearman correlation analysis of all cancers.

Correlation coefficient		TRPV1 expression	Grades of cancer
Oral squamous cell carcinoma			
TRPV1 expression		1.000	0.745*
	p	0	0.013
	N	10	10
*-Spearman's rho correlation is significant at the 0.06 level (2-tailed)			
Bladder cancer			
TRPV1 expression		1.000	1.000**
	p	0	0.000
	N	10	10
*-Spearman's rho correlation is significant at the 0.01 level (2-tailed)			
Meningioma (negative control)			
TRPV1 expression		1.000	0
	p	.	0
	N	10	10
Colon cancer (positive control)			
TRPV1 expression		1.000	0
	p	0	0
	N	10	10
Breast cancer			
TRPV1 expression		1.000	0
	p	0	0
	N	10	10
Astrocytoma			
TRPV1 expression		0	0
	p	0	0
	N	10	10

TRPV1, transient receptor potential vanilloid 1.

Conclusions

Our analysis demonstrates distinct patterns of TRPV1 immunohistochemical expression across several cancer types, underlining the context-dependent nature of TRPV1's function in cancer progression. According to our results, TRPV1 is a unique, prospective target molecule in supportive therapy and diagnostics of WHO grade 4 astrocytoma, meningioma, bladder cancer, and OSCC. Further studies should be conducted to further investigate the therapeutic potential of TRPV1.

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