DOI: https://doi.org/10.54393/pjhs.v5i11.1927

PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (P): 2790-9352, (E): 2790-9344
Volume 5, Issue 11 (November 2024)

Original Article

OPEN ACCESS

Immuno-Histochemical Analysis of PDGFRβ in OSCC: Clinical Significance and Prospects for Targeted Therapy

Sarah Rabbani[1], Aman-Ur-Rehman[2], Rabia Anjum[1], Nauman Rauf Khan[1] and Saima Chudhary[3*]

[1]Department of Oral Pathology, University of Health Sciences, Lahore, Pakistan
[2]Department of Oral Pathology, Shaikh Zayed Postgraduate Medical Institute, Lahore, Pakistan
[3]Department of Oral Pathology, The University of Lahore, Lahore, Pakistan

ARTICLE INFO

Keywords:
Platelet-derived Growth Factor Receptor Beta, Squamous Cell Carcinoma, Immunohistochemistry, Clinical Significance

How to Cite:
Rabbani, S., Rehman, A. ur, Anjum, R., Khan, N. R., & Chudhary, S. (2024). Immuno-Histochemical Analysis of PDGFRβ in OSCC: Clinical Significance and Prospects for Targeted Therapy: Immuno-Histochemical Analysis of PDGFRβ in OSCC: Clinical Significance . Pakistan Journal of Health Sciences, 5(11). https://doi.org/10.54393/pjhs.v5i11.1927

***Corresponding Author:**
Saima Chudhary
Department of Oral Pathology, The University of Lahore, Lahore, Pakistan
drsaimach@outlook.com

Received Date: 25th September, 2024
Acceptance Date: 18th November, 2024
Published Date: 30th November, 2024

ABSTRACT

The most prominent and key cells in cancer development are fibroblasts, known as cancer-associated fibroblasts. Limited data available on Head and Neck Cancer showed the presence of platelet-derived growth factor receptor beta as the most prevalent marker. Furthermore, therapies can be targeted against this receptor for the treatment of cancer. **Objectives:** To evaluate the expression of Platelet-derived growth factor receptor beta as a specific marker of cancer-associated fibroblasts in different grades of oral squamous cell carcinoma through immunohistochemistry. **Methods:** This descriptive study included 51 cases of squamous cell carcinoma of the head and neck region. Platelet-derived growth factor receptor beta expression was assessed based on the extent and intensity of immune-labelling in a tumor. SPSS was used to determine the association between the grade of tumor and Platelet-derived growth factor receptor beta expression. **Results:** Mean age was found as 53.65 + 17.15 years and there were 30 (58.8%) male and 21 (41.2%) female. The most commonly affected sites were glottis and supra-glottis areas accounting for 18.9% of total cases followed by the tongue which accounts for 13.2% of cases. The majority of the patients 34 (66.7%) patients had an intermediate grade of squamous cell carcinoma. In most cases, the degree of staining was strongest, with intermediate-grade tumors exhibiting the highest platelet-derived growth factor receptor beta staining. **Conclusions:** It was concluded that platelet-derived growth factor receptor beta emerges as a promising tumor marker in head and neck squamous cell carcinoma, with its expression levels increasing proportionately with the tumor grade.

INTRODUCTION

Oral squamous cell carcinoma (OSCC) is the most common cancer oral cavity cancer, with 177,000 deaths yearly worldwide [1]. It is the sixth most common cancer globally. The incidence of OSCC is highest in South and Southeast Asia and is increasing in developed countries [2]. Pakistan is a major Centre for this disease and, alongside China and India, is among the top three countries with the highest incidence of oral cancer [3]. The tongue, the floor of the mouth, and buccal mucosa are the most common sites of OSCC. Male is affected more than females with a ratio of 3:1 and have a mean age of 61±12 years. The most common risk factors for OSCC include tobacco, alcohol, and certain viruses including human papillomavirus (HPV) infection [4].

Platelet-derived growth factor beta (PDGFRβ) is a sub-type of receptors that are a part of the class III receptor tyrosine kinase family. PDGFRβ is an important biomarker of cancer-associated fibroblasts (CAFs) that play a crucial role in the tumor invasion and growth. It is a critical regulator of various cellular processes such as proliferation, differentiation, and survival. It becomes activated upon binding with its ligand, Platelet-Derived Growth Factor (PDGF), which triggers downstream signalling pathways that drive cell growth and angiogenesis. While PDGFRβ normally plays an essential role in tissue repair and development, its abnormal activation has been linked to the development of several

DOI: https://doi.org/10.54393/pjhs.v5i11.1927

cancers, including OSCC [5]. A variable expression of PDGFRβ has been observed across various tumors, including breast cancer, colon cancer, and lung tumors. However, it is most commonly found in colon and lung tumors where PDGFRβ is involved in promoting tumor growth and metastasis. Its role in remodeling the tumor stroma and facilitating angiogenesis makes it a promising target for therapy. Studies have shown that PDGFRβ expression is frequently elevated in cancerous tissues compared to normal tissues, which is associated with more aggressive disease and a worse prognosis. In OSCC, PDGFRβ is recognized as a significant factor in the tumor microenvironment, affecting both tumor cell behaviour and the surrounding stromal components [6]. PDGFRβ expression is upregulated and associated with worse survival in squamous cell carcinoma [5, 7]. However, Valle et al in 2023, found a low PDGFRβ expression in advanced stages of OSCC [8]. Targeting PDGFRβ has become a focal point in cancer therapy due to its involvement in tumor progression. PDGFRβ inhibitors, such as Imatinib and Sunitinib, have proven effective against various other cancers and are now being investigated for treating OSCC. Targeting PDGFRβ in OSCC holds the potential for therapeutic benefits, including reduced tumor growth, lower rates of metastasis, and improved patient survival [9].

This study aimed to evaluate the expression of PDGFRβ as a specific marker of CAFs in different grades of OSCC through immunohistochemistry. The aggressiveness of the tumor and its spread can be estimated and thus the prognosis. Furthermore, therapies can be targeted against this marker if PDGFRβ is found to be sensitive to OSCC.

METHODS

This cross-sectional study was conducted in the Department of Oral Pathology, UHS, and Pathology Department of Sheikh Zaid Hospital, Lahore after getting approval from the Ethical Review Committee of UHS vide letter no UHS/REG-18/ERC/469. The duration of the study was one year from April 2018 to May 2019. Paraffin-embedded blocks of 51 cases were recruited including both males and females of all age groups. A written informed consent was taken by the patients for the use of the blocks. However, the blocks of the patients who underwent chemotherapy or radiotherapy were excluded from the study. The demographic data consisting of age, gender, and tumor site was noted. The tumor was graded using Byrne's grading system based on the degree of keratinization, polymorphism, mitotic activity, and pattern of invasion [10]. The paraffin-embedded tissue blocks of all samples were cut into 4 µm sections and immunohistochemistry was performed with rabbit polyclonal anti- PDGFRβ antibody. Tissue sections along with positive control (human breast cancer) were taken. PDGFRβ expression was evaluated by using two different quantification systems. According to Kwon et al., PDGFRβ expression was determined based on proportion and staining intensity [11]. The total score (Score 0 – Negative; Score 1-2 - weak positive +1; Score 3-4 - moderate positive +2; Score 5-6 - strong positive +3) for each case was calculated by adding the proportion score (PS)(0 - less than 5% immune-reactive; 1 - less than 33% immune-reactive; 2 - 33%-66% immune-reactive; 3 - greater than 66% immune-reactive) and intensity score (IS)(0 - no staining; 1 – mild; 2 – moderate; 3 – Intense) of that particular case. The scoring system proposed by Shinohara et al. in 2007 was also used for PDGFRβ staining [12]. The labelling score (Low degree – 0 to 199; High degree – 200 to 300) of PDGFRβ was calculated by multiplying the intensity score (1 – Weak; 2 – Moderate; 3 – Intense) by percent area. SPSS version 20.0 was used for data analysis, including demographic data like age and gender. The grade of the tumor was analyzed along with its morphological parameters. PDGFRβ staining was analyzed according to its presence or absence, and the total score of PDGFRβ staining was seen using two scoring systems. The relationship between tumor grade, PDGFRβ staining scores, and gender was examined through bivariate analysis. The chi-square test of independence was applied, and ≤ 0.05 was taken as a significant p-value at a confidence level of 95%.

RESULTS

A total of 51 cases were enrolled in this study. Out of these, 17 were younger than 45 (32.1%), and 34 were 45 or older (67.9%). The mean age was 53.65 years, with the standard deviation of 17.152. The study included patients aged 16 to 87 years. Male was 30 (58.8%) and female was 21 (41.2%). This revealed a greater prevalence of SCC in men than in women, with a male-to-female ratio of 1.4:1. The highest examined sites were glottis and supra-glottis areas accounting for 18.9% (10) of total cases. Tongue was the next most frequent area of involvement, i.e., 7(13.2%). The least involved areas were the alveolus, cheek, and lip, accounting for one patient of each site. Out of 51 cases, most of the cases 34 (66.6%) were of grade 2 followed by 13 (25.4%) cases of grade 3 and 4 (7.8%) cases of grade 1 respectively. Intense PDGFRβ staining in 29(57%) cases among fifty-one cases of OSCC was analyzed (Table 1).

Table 1: Degree of Distribution PDGFRβ Expression

Degree of Staining	Frequency (n%)
Mild	2 (3.9%)
Moderate	20 (39.2%)
Intense	29 (56.9%)
Total	51 (100%)
Degree of PDGFRβ Staining	
Low Degree	23 (45.1%)
High Degree	28 (54.9%)
Total	51 (100%)

DOI: https://doi.org/10.54393/pjhs.v5i11.1927

A strong membranous expression of PDGFβ was seen in moderately- differentiated squamous cell carcinoma while moderate expression was observed in well-differentiated squamous cell carcinoma(Grade 1)(10X)(Figure 1).

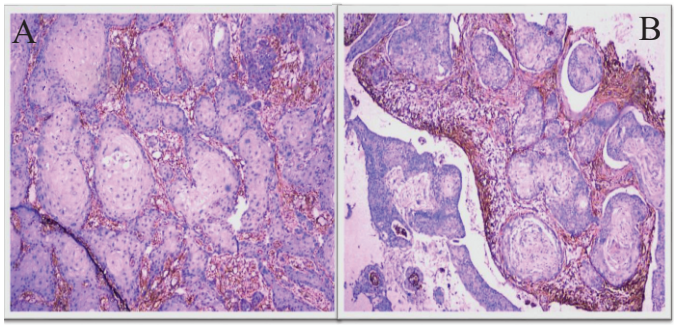

Figure 1: (A) Strong membranous expression in moderately- differentiated squamous cell carcinoma. (B) Moderate membranous expression in well-differentiated squamous cell carcinoma(Grade 1)(10X)

A statistically significant positive correlation was noted between PDGFβ expression and tumor grade(Table 2).

Table 2: PDGFRβ Expression in Different Grades of Tumor

Variable	Grade of Tumor (n=51)					
	Intensity	Low Grade n(%)	Intermediate Grade n(%)	High Grade n(%)	Total n(%)	p-value
PDGFRβ Expression	Mild	2 (100%)	0(0%)	0(0%)	2 (100%)	<0.005
	Moderate	2 (10%)	17(85%)	1(5%)	20 (100%)	
	Intense	0(0%)	17(58.62%)	12 (41.38%)	29 (100%)	

Chi-Square was applied to determine the p-value

Likewise, PDGFRβ expression showed a signification association in different grades of tumors(Table 3).

Table 3: Signification Association in Different Grades of Tumor

Variable	Grade of Tumor (n=51)					
	Intensity	Low n(%)	Intermediate n(%)	High n(%)	Total n(%)	p-value
PDGFRβ Expression	Low Degree	4 (17.4%)	18 (78.26%)	1 (4.35%)	23 (100%)	<0.005
	High Degree	0(0%)	16(58.6%)	12(41.4%)	28 (100%)	

Chi-Square was applied to determine the p-value

Weak, moderate, and strong positive results showed varied and non-significant distribution among male and female (Table 4).

Table 4: Association of PDGFRβ Expression with Gender

Variables	PDGFRβ Expression in Both Genders				
Gender	Mild n(%)	Moderate n(%)	Intense n(%)	Total n(%)	p-value
Male	2(6.7%)	13(43.3%)	15(50%)	30(100%)	0.314
	-	16(53.3%)	14(46.7%)	30(100%)	0.158
Female	0(0%)	7(33.3%)	14(66.7%)	21(100%)	0.314
	-	7(33.3%)	14(66.7%)	21(100%)	0.158

Chi-Square was applied to determine the p-value

DISCUSSION

The tumor microenvironment, composed of stromal cells and extracellular matrix components, plays a crucial role in cancer cell growth, invasion, and metastasis. Cancer-associated fibroblasts (CAFs), an important part of tumor microenvironment, facilitate tumor growth and invasion through elevated matrix metalloproteinase (MMPs), CCL-2 and Il-6, and activate the STAT-3 pathway [12]. Additionally, CAFs induce angiogenesis directly through vascular endothelial growth factor (VEGF) and indirectly by PDGF receptors, recruiting more CAFs that further increase VEGF levels [13]. In cancer treatment, PDGF and other tyrosine kinase molecules contribute to drug resistance by elevating intracellular pressure, and hindering drug penetration [14]. Notably, PDGFRβ serves as a reliable marker for detecting CAFs, identified through various techniques like immunoassays and immunohistochemistry. Early identification and targeting of these interactions are essential for effective cancer management [15]. Little research has focused on the immune-histochemical expression of PDGFRβ and the relation of expression on different grades of squamous cell carcinoma of the head and neck area. In the present study, Byrne's grading system was used to grade the tumor as a low, intermediate, and high-grade tumor. Most of the patients were diagnosed with an intermediate grade of squamous cell carcinoma found in 34 of the patients. High-grade tumors were seen in 13 patients. Only 4 patients had low-grade tumors. For the expression of PDGFRβ, two scoring systems were used. We labelled tumors as low and high degrees by multiplying the intensity score with percent area that was positively stained as indicated by Shinohara *et al.*, [12]. We also categorized the PDGFRβ expression as weak, moderate, and strong positive by calculating intensity and proportion score as done by Kwon *et al.*,[11]. There was no case of negative staining in our study. We found the intensity of staining was maximum in patients with an intermediate grade of tumor according to Shinohara *et al.*, system [12]. Intermediate grades had more low-degree cases (52.9%) compared to high-degree cases(47.1%). High-grade tumors had 92.3% cases of high-degree cases compared to only 7.7% of low-degree cases. Low-grade tumors showed only a low degree of staining in all cases while there was no case of a high degree in low-grade tumors. The results showed a significant association between the degree of PDGFRβ expression in different grades of tumor (p-value=0.001). As the grade increases, the expression of PDGFRβ also increases. This approach can be applied in reverse to identify the grade of the tumor. We found that the staining intensity was maximum in patients with intermediate grade of tumor. Intermediate

DOI: https://doi.org/10.54393/pjhs.v5i11.1927

grade had the same number of severe and moderate staining 17 (50.0%). While high-grade tumors showed 12 (92.3%) strong positive results compared to only 1 (7.7%) moderate positive case. Mild staining was seen in only 2 (100%) cases, and both were of low grade. We found some significant results according to this grading system (p-value=0.000). The current study did not find a significant association between PDGFRβ expression and different age groups and gender distribution. Our results were consistent with Zhang *et al.*, 2016, who concluded that the expression of PDGF-D and PDGFRβ levels are upregulated in tongue squamous cell carcinoma and correlate positively with the grade of the tumor [7]. Cierpikowski, Lis-Nawara, and Bar 2023 observed that the expression of PDGFRβ was upregulated in 70% of cases of OSCC, and this high expression was associated with shorter overall survival [7]. Lin *et al.*, in 2020 observed the upregulated expression of PDGFRβ in OSCC in association with metastatic lymph nodes and poor overall survival [16]. Wang *et al.*,also reported a significant association of PDGFRβ with the clinical stage (p=0.036), lymph node metastasis (p=0.013) and tumor histological grade (p=0.037)[17]. A 5-year follow-up showed a shorter overall survival of the patients with high expression of PDGFRβ[4]. Kartha *et al.*, in 2016 found high expression of PDGFRβ in oral squamous cell carcinoma in only 12 cases, and they found that this marker was present in the perivascular stroma and is absent in tumor epithelium.They concluded that PDGFRβ expression is high in the case of OSCC [18]. Our findings were in contrast to the findings of Valle *et al.*, in 2023,who reported that the advanced-stage tumors showed a low expression of PDGFRβ (p=0.020). According to their findings,a low expression of PDGFRβ was associated with a shorter disease-free survival (p=0.036). They also concurred that a reduction in expression is associated with a 209.874-fold increase in recurrence (p=0.006) [7]. Different studies have been conducted on the expression of PDGFRβ in different body cancers. Paulsson *et al.*, in 2009, determined PDGFRβ expression in different tumors. They found that 80% of colon carcinoma showed PDGFRβ in the perivascular region, while only 31% of prostate cancer were positive for this marker. They also noted a significant correlation between the expression of PDGFR and the grade of breast tumor in which they found PDGFRβ only in the perivascular area in pericytes and is not present in the tumor itself [19]. However, some studies negate this concept. Shinohara *et al.*, published their study on PDGFRβ expression in small cell lung carcinoma. They found that there is no significant difference in marker staining in different age groups, gender, or tumor grade. They also mentioned that the degree of marker staining does not affect the 5-year survival rate [12]. Following a tissue injury, as in the case of cancer, platelets get activated, which not only activates the coagulation cascade but also results in the release of PDGF. PDGF attaches to its specific receptors present on CAFs, pericytes, and other cells, leading to their stimulation. In the same way, binding of these molecules on their specific receptors on different cells causes an increase in endothelial growth factor (EGF), resulting in fibroblast migration, proliferation, and remodeling. PDGF not only influences the levels of tumor growth factor (TGF) and fibroblast growth factor (FGF) but also contributes to the chemotaxis of inflammatory cells and mitogenesis of mesenchymal stem cells. PDFG also influences the levels of VEGF and connective tissue growth factor (CTGF), both of which are responsible for angiogenesis and an increase in the levels of collagen [20]. By blocking the PDGFRβ on CAF cells, the respective pathways can be blocked, thus inhibiting tumor growth, invasion, and metastasis. PDGFR pathway antagonists like Ezetimibe work by inducing G1 blockade in tumor cells thus inhibiting cancer cell proliferation [21]. Agents or antibodies that block PDGF receptors have more specific targets. Imatinib, Sorafenib, Nilotinib, Sunitinib and Pazopanib are some of the PDGFR kinase inhibitors [22]. The present study shows that PDGFRβ is also found in OSCC and increases by increased tumor grade and can be a potential therapeutic target. No study has been conducted regarding the therapeutic role of targeting PDGF/PDGFR in OSCC. The current study did not determine the effect of the expression of PDGFRβ on local invasion, distant metastasis of tumor, prognosis, and patient survival. Further studies are suggested to check the effect of the expression of tumor markers on overall patient management. Furthermore, studies should be done to check the therapeutic role of PDGFRβ.

CONCLUSIONS

It was concluded that head and neck cancer is one of the leading causes of morbidity and mortality around the globe. Early diagnosis and prompt treatment may reduce the morbid effects of this devastating condition. Identification of specific tumor markers may prove a milestone in achieving this goal. Platelet-derived growth factor receptor β is a promising tumor marker. Based on this study, it is concluded that PDGFRβ increases proportionately to the increasing grade of tumor. PDGFRβ may prove a beneficial target for not just the early diagnosis but also for the treatment of OSCC.68196.

Authors Contribution

Conceptualization: SR
Methodology: SR, SC
Formal analysis: SR, AUR, RA, SC
Writing review and editing: AUR, RA, NRK, SC

All authors have read and agreed to the published version of

DOI: https://doi.org/10.54393/pjhs.v5i11.1927

the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The author received no financial support for the research, authorship and/or publication of this article.

REFERENCES

[1] Kawaharada M, Yamazaki M, Maruyama S, Abé T, Chan NN, Kitano T *et al*. Novel Cytological Model for the Identification of Early Oral Cancer Diagnostic Markers: The Carcinoma Sequence Model. Oncology Letters. 2022 Mar; 23(3): 1-9. doi: 10.3892/ol.2022.13196.

[2] Mummudi N, Agarwal JP, Chatterjee S, Mallick I, Ghosh-Laskar S. Oral Cavity Cancer in the Indian Subcontinent-Challenges and Opportunities. Clinical Oncology. 2019 Aug; 31(8): 520-8. doi: 10.1016/j.clon.2019.05.013.

[3] Xie L and Shang Z. Burden of Oral Cancer in Asia from 1990 to 2019: Estimates from the Global Burden of Disease 2019 study. PLoS One.2022 Mar; 17(3): e0265950. doi: 10.1371/journal.pone.0265950.

[4] Capote-Moreno A, Brabyn P, Muñoz-Guerra MF, Sastre-Pérez J, Escorial-Hernandez V, Rodríguez-Campo FJ *et al*. Oral Squamous Cell Carcinoma: Epidemiological Study and Risk Factor Assessment Based on A 39-Year Series. International Journal of Oral and Maxillofacial Surgery. 2020 Dec; 49(12):1525-34. doi: 10.1016/j.ijom.2020.03.009.

[5] Carvallo SL. Prognostic Value of Immuno-expression of CCR4, CCR5, CCR7 and CXCR4 in Squamous Cell Carcinoma of Tongue and Floor of the Mouth. Medicina Oral, Patologia Oral, Cirugia Bucal. 2019 May; 24(3): e354-63. doi: 10.4317/medoral.22904.

[6] Kilvaer TK, Rakaee M, Hellevik T, Vik J, Petris LD, Donnem T *et al.* Differential Prognostic Impact of Platelet-Derived Growth Factor Receptor Expression in NSCLC. Scientific Reports. 2019 Jul; 9(1): 10163. doi: 10.1038/s41598-019-46510-3.

[7] Zhang H, Sun JD, Yan LJ, Zhao XP. PDGF-D/PDGFRβ Promotes Tongue Squamous Carcinoma Cell (TSCC) Progression Via Activating p38/AKT/ERK/EMT Signal Pathway. Biochemical and Biophysical Research Communications.2016 Sep;478(2):845-51.doi: 10.1016/j.bbrc.2016.08.035.

[8] Do Valle IB, Oliveira SR, Da Silva JM, Peterle GT, Có AC, Sousa-Neto SS et al. The Participation of Tumor residing pericytes in oral squamous cell carcinoma. Scientific Reports. 2023 Apr; 13(1): 5460. doi: 10.1038/s41598-023-32528-1.

[9] Tsioumpekou M, Cunha SI, Ma H, Åhgren A, Cedervall J, Olsson AK et al. Specific Targeting of PDGFRβ in the Stroma Inhibits Growth and Angiogenesis in Tumors with High PDGF-BB Expression. Theranostics.2020; 10(3): 1122. doi: 10.7150/thno.37851.

[10] Thamilselvan S, Pandiar D, Krishnan RP, Ramalingam K, Pavithran P. Comparison of Broder's and Bryne's Grading System for Oral Squamous Cell Carcinoma with Lymph Node Metastases and Prognosis:A Scoping Review.Cureus. 2024 Jan; 16(1). doi: 10.7759/cureus.51713.

[11] Kwon KY, Ro JY, Singhal N, Killen DE, Sienko A, Allen TC *et al*. MUC4 Expression in Non–Small Cell Lung Carcinomas: Relationship to Tumor Histology and Patient Survival. Archives of Pathology and Laboratory Medicine.2007 Apr; 131(4): 593-8. doi: 10.5858/2007-131-593-MEINCL.

[12] Shinohara ET, Gonzalez A, Massion PP, Olson SJ, Albert JM, Shyr Y *et al*. PDGFR-B Expression in Small Cell Lung Cancer Patients. International Journal of Radiation Oncology* Biology* Physics.2007 Feb; 67(2): 431-7. doi: 10.1016/j.ijrobp.2006.08.060.

[13] Coursier D, Calvo F. CAFs vs. TECs: When Blood Feuds Fuel Cancer Progression, Dissemination and Therapeutic Resistance. Cellular Oncology.2024 Mar; 47: 1-22. doi: 10.1007/s13402-024-00931-z.

[14] Ebrahimi N, Fardi E, Ghaderi H, Palizdar S, Khorram R, Vafadar R et al. Receptor Tyrosine Kinase Inhibitors in Cancer. Cellular and Molecular Life Sciences. 2023 Apr; 80(4): 104. doi: 10.1007/s00018-023-04729-4.

[15] Nurmik M, Ullmann P, Rodriguez F, Haan S, Letellier E. In Search of Definitions: Cancer-Associated Fibroblasts and Their Markers. International Journal of Cancer. 2020 Feb; 146(4): 895-905. doi: 10.1002/ijc.32193.

[16] Lin LH, Lin JS, Yang CC, Cheng HW, Chang KW, Liu CJ.Overexpression of Platelet-Derived Growth Factor and Its Receptor Are Correlated with Oral Tumorigenesis and Poor Prognosis in Oral Squamous Cell Carcinoma. International Journal of Molecular Sciences.2020 Mar; 21(7): 2360. doi: 10.3390/ijms21072360.

[17] Wang L, Song H, Yang S. The Expression Tendency and Prognostic Value of PDGFRB in Oral Cancer. doi: 10.21203/rs.3.rs-53698/v1.

[18] Kartha VK, Stawski L, Han R, Haines P, Gallagher G, Noonan V *et al*. PDGFRβ is a Novel Marker of Stromal Activation in Oral Squamous Cell Carcinomas.PLoS One. 2016 Apr; 11(4): e0154645.doi:10.1371/journal.pone.0154645.

[19] Paulsson J, Sjöblom T, Micke P, Pontén F, Landberg G, Heldin CH *et al*. Prognostic Significance of Stromal Platelet-Derived Growth Factor B-Receptor Expression in Human Breast Cancer. The American Journal of Pathology.2009 Jul; 175(1): 334-41. doi: 10.2353/ajpath.2009.081030.

DOI: https://doi.org/10.54393/pjhs.v5i11.1927

[20] Piccin A, Di Pierro AM, Canzian L, Primerano M, Corvetta D, Negri G *et al*.Platelet Gel:A New Therapeutic Tool with Great Potential.Blood Transfusion. 2017 Jul;15(4):333.doi: 10.2450/2016.0038-16.

[21] He Q, Kong L, Shi W, Ma D, Liu K, Yang S *et al*. Ezetimibe Inhibits Triple-Negative Breast Cancer Proliferation and Promotes Cell Cycle Arrest by Targeting the PDGFR/AKT Pathway.Heliyon.2023 Nov ; 9(11). doi: 10.1016/j.heliyon.2023.e21343.

[22] Roskoski Jr R. The Role of Small Molecule Platelet-Derived Growth Factor Receptor(PDGFR)Inhibitors in the Treatment of Neoplastic Disorders. Pharmacological Research. 2018 Mar; 129: 65-83. doi: 10.1016/j.phrs.2018.01.021.