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Role of podoplanin in foci of infection pertaining to head and neck region of adult and paediatric population – A systematic review.

(Papel de la podoplanina en focos de infección de cabeza y cuello en población adulta y pediátrica: Una revisión sistemática.)

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Abstract (english)

Head and neck squamous cell carcinoma (HNSCC) stands as a significant global cancer, contributing to increased illness and death rates. It ranks sixth among cancers worldwide, with over 550,000 new cases each year. Major databases such as Medline were explored detailed literature search in resulting in a systematic review pertaining to podoplanin. Fourteen scientific articles dated between 2020 – 2024 pertaining to podoplanin were highlighted. Podoplanin (PDPN) has emerged as a pivotal player in tumor behavior and progression across various carcinomas. Structurally unique, PDPN lacks recognizable functional domains but exerts profound effects on cell behavior through interactions with various proteins, orchestrating processes such as tumor cell migration, invasion, and metastasis. Detailed information regarding podoplanin and its vital role in the field of oral and maxillofacial pathology is discussed in this systematic review.

Keywords(english)

Podoplanin, oral cancer, adult, paediatric, pathology.

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Resumen(español)

El carcinoma escamocelular de cabeza y cuello (CCECC) se considera un cáncer importante a nivel mundial, contribuyendo al aumento de la enfermedad y la mortalidad. Ocupa el sexto lugar entre los cánceres a nivel mundial, con más de 550.000 casos nuevos cada año. Material y métodos: Se exploraron importantes bases de datos como Medline mediante una búsqueda bibliográfica exhaustiva, lo que resultó en una revisión sistemática sobre la podoplanina. Resultados: Se identificaron catorce artículos científicos sobre podoplanina, fechados entre 2020 y 2024. Conclusiones: La podoplanina (PDPN) se ha convertido en un factor clave en el comportamiento y la progresión tumoral de diversos carcinomas. Estructuralmente única, la PDPN carece de dominios funcionales reconocibles, pero ejerce profundos efectos en el comportamiento celular a través de interacciones con diversas proteínas, orquestando procesos como la migración, la invasión y la metástasis de células tumorales. En esta revisión sistemática se analiza información detallada sobre la podoplanina y su papel vital en el campo de la patología oral y maxilofacial.

Palabras clave(español)

Podoplanina, cáncer oral, adulto, pediátrico, patología.

Introduction

Primarily originating in the epithelial lining of the oral cavity, oropharynx, larynx, and hypopharynx, it particularly affects men in India, where oral squamous cell carcinoma (OSCC) leads to a substantial portion of cancer-related fatalities, reaching up to 22.9%. (1,2) Lifestyle choices, habits, demographics, and genetic factors influence its occurrence. Despite advancements in treatment, patient survival rates have not seen substantial improvement. (3) The spread of tumors to nearby lymph nodes greatly impacts disease progression and prognosis, as malignant cells tend to metastasize to approximately 400 lymph nodes in the neck region. (4,5). However, predicting cervical lymph node metastasis reliably remains a challenge. Consequently, current research is directed towards identifying markers indicative of tumor progression to aid in treatment decisions. (1) While numerous molecules and clinical studies have highlighted the significance of hematogenous dissemination, the mechanisms through which tumor cells invade the lymphatic system remain poorly understood. Molecular-level investigations began approximately a decade ago, with podoplanin emerging as one of the initial markers discovered in lymphatic endothelial cells. As a result, podoplanin has been instrumental in elucidating tumor behaviour and progression across various carcinomas over the past few decades. (3,6).

Materials and methods

"Podoplanin" AND "oral cancer" AND "adult'' were the words used in MEDLINE database using advance search strategy targeting different article categories between 2020 to 2024. The result was 51articles, out of which we selected 14 articles based in the inclusion criteria. Inclusion criteria was of scientific literature between 2020-2024. Exclusion criteria was of scientific literature devoid of scientific literature irrelevant to the specific search 'Podoplanin'. This systematic review was conducted to determine importance of podoplanin following the guidelines of the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses). PubMed, Lilacs, Embase, Scopus, and Web of Science were the source of electronic databases. The search strategy used Boolean operators (AND and OR): [ALL ("Podoplanin") AND (pathology OR head OR neck OR adult OR paediatric OR cancer) AND (oral)]. The following data were collected: first author, year, country of study, type of study and outcome. The quality of studies was assessed using the STROBE (Strengthening the Reporting of Observational Studies) checklist

Results

Fourteen articles were included in this systematic review based on the selection criteria and PRISMA flow chart. We analyzed and mentioned in the fourteen articles reviewed. This included only relevant research articles and excluded articles pertaining to non specific search terms.

Discussion

Podoplanin (PDPN) is a distinct transmembrane glycoprot Podoplanin (PDPN) has emerged as a pivotal player in tumor behavior and progression across various carcinomas. Structurally

Table. 1. An overview.

S.No.	Author	Year	Journal	Outcome
1	Sudo, H.; Tsuji, A.B.; Sugyo, A.; Kaneko, M.K.; Kato, Y.; Nagatsu, K.; Suzuki, H.; Higashi, T.	2021	Cells	Therapeutic potential
2	Kobayashi, H.; Furusawa, A.; Rosenberg, A.; Choyke, P.L.	2021	Int.Immunol.	Hybrid cancer therapy
3	Maekawa, N.; Konnai, S.; Nishimura, M.; Kagawa, Y.; Takagi, S.; Hosoya, K.; Ohta, H.; Kim, S.; Okagawa, T.; Izumi, Y.; et al.	2021	NPJ Precis Oncol.	Therapy
4	Kato, Y.; Ito, Y.; Ohishi, T.; Kawada, M.; Nakamura, T.; Sayama, Y.; Sano, M.; Asano, T.; Yanaka, M.; Okamoto, S.; et al.	2020	Monoclon. Antib. Immunodiagn. Immunother.	Antibody therapy
5	Miyashita, T.; Neri, S.; Hashimoto, H.; Akutsu, A.; Sugano, M.; Fujii, S.; Ochiai, A.; Ishii, G.	2020	J. Cell Physiol.	Higher invasion activity
6	De Winde, C.M.; George, S.L.; Crosas-Molist, E.; Hari-Gupta, Y.; Arp, A.B.; Benjamin, A.C.; Millward, L.J.; Makris, S.; Carver, A.; Imperatore, V.; et al.	2021	iScience	Functional biomarker
7	Kanayama, M.; Oyama, R.; Mori, M.; Taira, A.; Shinohara, S.; Kuwata, T.; Takenaka, M.; Yoneda, K.; Kuroda, K.; Ohnaga, T.; et al.	2021	Oncol.lett.	Circulating tumour cells
8	Nishinaga, Y.; Sato, K.; Yasui, H.; Taki, S.; Takahashi, K.; Shimizu, M.; Endo, R.; Koike, C.; Kuramoto, N.; Nakamura, S.; et al.	2020	Cells	photoimmunotherapy
9	Kuwata, T.; Yoneda, K.; Mori, M.; Kanayama, M.; Kuroda, K.; Kaneko, M.K.; Kato, Y.; Tanaka, F.	2020	Cells	Anti podoplanin antibody
10	Suzuki, J.; Aokage, K.; Neri, S.; Sakai, T.; Hashimoto, H.; Su, Y.; Yamazaki, S.; Nakamura, H.; Tane, K.; Miyoshi, T.; et al. Lung Cancer 2021	2021	Lung cancer	Cancer-associated fibroblasts (CAFs) expressing podoplanin (PDPN)
11	Kato, Y.; Sano, M.; Asano, T.; Sayama, Y.; Kaneko, M.K.	2020	Monoclon. Antib. Immunodiagn. Immunother.	PDPN targeted cancer therapy
12	Sayama, Y.; Sano, M.; Asano, T.; Furusawa, Y.; Takei, J.; Nakamura, T.; Yanaka, M.; Okamoto, S.; Handa, S.; Komatsu, Y.; et al..	2020	Monoclon. Antib. Immunodiagn. Immunother	chimeric antigen receptor T technologies.
13	Sayama, Y.; Sano, M.; Kaneko, M.K.; Kato, Y.	2020	Monoclon. Antib. Immunodiagn. Immunother	platelet aggregation-stimulating (PLAG) domains
14	Suzuki H, Kaneko MK, Kato Y.	2022	Cells	PDPN-targeted cancer therapy,

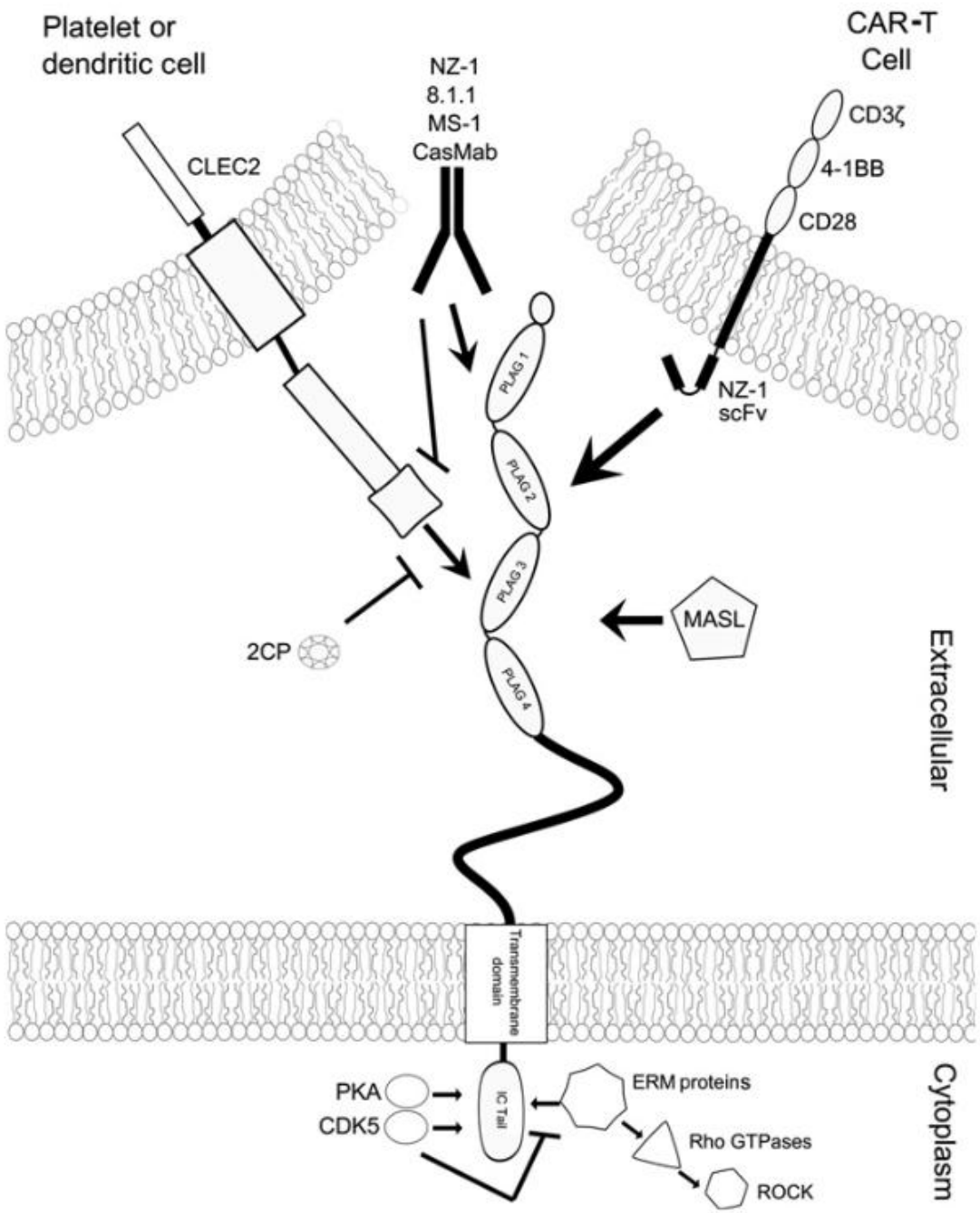


Figure 1. Podoplanin (PDPN) possesses a structural arrangement comprising an extracellular domain, a transmembrane segment, and an intracellular tail. Interaction between CLEC-2 and the PLAG domains within the extracellular region triggers inflammation and promotes tumor advancement. This interaction is susceptible to blockade by various antibodies, including 8.1.1, NZ-1, MS-1, cancer-specific PDPN antibodies (CasMabs), as well as compounds like the synthetic molecule 2CP. Antibodies can directly impede transformed cell growth and mobility by targeting PDPN or can be integrated into CAR-T cells. Additionally, lectins such as MASL demonstrate an ability to target PDPN, thereby impeding tumor progression and inflammation. Phosphorylation of serine residues on the intracellular tail by protein kinase A (PKA) and cyclin-dependent kinase 5 (CDK5) inhibits cell migration, potentially by obstructing the binding of ERM proteins, which typically activate Rho GTPases and Rho-associated coiled-coil kinase (ROCK).

interactions with various proteins, orchestrating processes such as tumor cell migration, invasion, and metastasis.ein receptor with notable characteristics. Structurally, it features a heavily glycosylated amino terminal extracellular domain spanning around 130 amino acids, followed by a single transmembrane domain of about 25 amino acids, and a concise intracellular domain of roughly 10 amino acids. Notably, PDPN lacks recognizable functional domains or enzymatic activities. However, it exerts its effects on cell behavior through interactions with various proteins, including C-type lectin-like receptor-2 (CLEC-2), heat shock protein A9 (HSPA9), CD44, galectin 8, chemokine (C-C motif) ligand 21 (CCL21), ezrin, moesin, protein kinase A (PKA), and cyclin-dependent kinase 5 (CDK5). These ligands and binding partners engage with PDPN, orchestrating processes such as tumor cell migration, invasion, and metastasis. The intricate network of interactions is illustrated schematically in Figure 1, highlighting the multifaceted role of PDPN in influencing cellular behaviour. (7–10)

Podoplanin (PDPN) expression is triggered by various tumor-promoting agents such as TPA, RAS, and Src. (11–13) For instance, Src tyrosine kinase utilizes the focal adhesion adaptor protein Cas/BCAR1 to induce PDPN expression, thereby promoting tumor cell motility. Src, a nonreceptor protein kinase, facilitates nonanchored tumor cell growth and migration crucial for invasion and metastasis across multiple cancer types, including colon, breast, pancreas, brain, and skin tumors.(10,14). Cells transformed by diverse chemicals, viruses, and oncogenes, including Src tyrosine kinase, can be normalized upon contact with non-transformed cells, a phenomenon known as "contact normalization." This process coerces transformed cells to adopt a normal morphology and reside in various organs for extended periods. Comparisons between non-transformed cells, transformed cells, and those undergoing contact normalization offer a sensitive approach to identifying genes governing malignant and metastatic growth. Despite Src kinase activity affecting the expression of around 3000 genes, only a fraction, including PDPN, are influenced by contact normalization. PDPN, induced by numerous tumor promoters, is prevalent in various cancer types.(11,15) High clonal expansion capacity characterizes tumor-initiating cells (TIC), with PDPN serving as a marker for human squamous cell carcinoma. Live single-cell imaging using the Fucci system revealed that PDPN-expressing A431 human squamous cell carcinoma cells more frequently formed large colonies compared to PDPN-negative cells. (7,15,16) While no significant differences in cell cycling were noted, cell death was markedly lower in progenies derived from PDPN-positive single cells. RNA interference studies showed that PDPN suppression increased cell death in single A431 cells, hindering the formation of larger colonies. (7,17).Podoplanin (PDPN) emerges as a significant marker in various cancer types,(7,15,16) with oral cancer serving as a pertinent example of its diagnostic relevance. Elevated PDPN expression correlates with enhanced migration of oral squamous cell carcinoma cells, potentially fostering increased metastatic potential. Consequently, higher levels of PDPN expression align with decreased 5-year survival rates among patients afflicted with these cancers. (18–20) Notably, in precancerous oral lesions such as oral leukoplakias, the presence of PDPN correlates with a threefold increase in the likelihood of malignant transformation compared to lesions devoid of PDPN expression.(21) Beyond cancer cells themselves, PDPN expression is also detected in cancer-associated fibroblasts (CAF), underscoring its multifaceted involvement in the tumor microenvironment. For instance, immunohistochemical analysis revealed PDPN expression in tumor cells from a substantial proportion of melanoma patients, with a concomitant presence in CAF. Notably, patients with PDPN-positive CAF exhibited a higher incidence of sentinel lymph node metastasis and lower disease-free survival rates compared to those with PDPN-negative CAF.(22) Innovative approaches are underway to exploit PDPN as a blood-based biomarker for cancer detection. The development of a circulating tumor cell (CTC) chip coated with PDPN antibodies shows promise in capturing and identifying metastatic cancer cells from peripheral blood samples. This technology has demonstrated efficacy in preclinical models, notably detecting malignant pleural mesothelioma cells. (10) Moreover, PDPN expression in peritumoral basal keratinocytes correlates with aggressive behaviour in extramammary Paget's disease (EMPD) patients. Immunohistochemical analysis revealed a significant association between PDPN expression in peritumoral keratinocytes and tumor invasiveness, thickness, and downregulation of E-cadherin, a crucial adhesion molecule. Model systems are being developed to elucidate the intricate interplay between PDPN and cadherins in controlling tumor invasion and cell motility. Downregulation of PDPN expression inhibits the migration of normal human epidermal keratinocytes, highlighting its role in keratinocyte motility and wound healing. Interestingly, PDPN

downregulation coincides with increased E-cadherin expression, suggesting a complex regulatory relationship between PDPN, CLEC-2, and E-cadherin in modulating keratinocyte migration during wound healing.(23) Transfection experiments conducted on cultured normal and cancer cells aimed to explore podoplanin's role in vitro. Both human keratinocytes and MCF7 breast cancer cells exhibited significant morphological changes upon podoplanin overexpression, characterized by reduced cellular stress fibers and the emergence of filopodia-like membrane protrusions, even in the presence of E-cadherin. (9,18) Moreover, podoplanin expression enhanced cell adhesion and spreading on fibronectin, which was attenuated by neutralizing antibodies against β1-integrin. (24) The interaction between tumor cells and the extracellular matrix (ECM) is crucial for migration and invasion. Podoplanin increased the migration of MCF7 cells and HaCaT keratinocytes, along with enhancing their invasion through matrigel, a process dependent on matrix metalloproteases (MMPs), as evidenced by repression with TIMP2, an MMP inhibitor. These findings suggest that podoplanin promotes cancer cell migration and invasion in human cancers, even in the absence of a cadherin switch and epithelial-mesenchymal transition (EMT). (24) However, recent research with MDCK cells indicates that podoplanin expression enhances single-cell migration following the loss of E-cadherin expression. (25) Thus, podoplanin likely induces invasion in both collective and single-cell migration scenarios. The precise molecular mechanisms governing this phenomenon remain unclear and are likely contingent on cellular context, underscoring the need for further investigation.(24) The presence of podoplanin in various human cancers suggests its potential utility as an immunohistochemical marker for both diagnosis and prognosis. Notably, podoplanin expression is predominantly observed in squamous cell carcinomas, CNS tumors, and germinal neoplasms. These cancers, often maintaining E-cadherin expression even in advanced stages, tend to exhibit collective, cone-like migration patterns. Conversely, the expression of podoplanin is notably absent in the majority of adenocarcinomas, such as those affecting the lung, colon, and prostate.(24) CNS tumors exhibit widespread podoplanin expression, including ependymal tumors, choroid plexus papillomas, meningeomas, pilocytic astrocytomas, and glioblastomas. Higher podoplanin expression in malignant astrocytic tumors correlates with increased histological malignancy. However, due to its prevalence in normal tissue, the diagnostic utility of podoplanin in CNS tumors is limited. (26,27) In cervix tumors, podoplanin expression is detected in a significant proportion of samples, particularly at the invading front. Focal expression of podoplanin correlates with lymphatic invasion, metastasis, and shorter recurrence-free survival, suggesting its potential as a prognostic marker for cervical cancer. (28) In germinal tumors, podoplanin is found expressed in dysgerminomas of the ovary and granulosa cell tumors. It is uniformly expressed in seminomas, with varying expression levels in embryonal carcinomas, teratomas, and yolk sac tumors, although the diagnostic and prognostic significance of these findings remains unexplored.(29). In squamous cell carcinoma of the skin and lung, podoplanin expression varies with tumor differentiation status. Well-differentiated carcinomas typically lack podoplanin expression, while moderately differentiated ones express it exclusively at the invading front. Undifferentiated squamous cell carcinomas exhibit podoplanin expression beyond the basal cell layer, often with cytoplasmic staining. (24) Furthermore, podoplanin is upregulated in mesothelioma and squamous cell carcinomas but not adenocarcinomas of the lung, highlighting its potential as a diagnostic marker in these malignancies. (30) Immunohistochemical analysis was undertaken by Vicente et al to evaluate podoplanin expression in a cohort of 58 oral mucosal dysplasias, with sections containing normal epithelia serving as internal controls. As anticipated, podoplanin expression was consistently detected in the endothelial cells of lymphatic vessels, consistent with its established role as a lymphatic marker. Conversely, in normal oral epithelium, podoplanin expression was either minimal or confined to small clusters of cells within the basal layer, predominantly exhibiting membranous and cytoplasmic staining. (31) Within dysplastic oral epithelium, podoplanin expression exhibited notable variability, predominantly presenting as a membranous pattern at the basal layer, In some instances, expression extended to the suprabasal layer or beyond in one or multiple areas.(31) Studies have indicated that podoplanin serves as an indicator of malignant progression in conditions like oral leukoplakia and other oral precursor lesions such as lichen planus (32–34) In the context of podoplanin expression, heightened cell motility is implicated in the increased rate of malignant transformation observed. Cells expressing elevated levels of podoplanin demonstrate enhanced capability to migrate into the surrounding tissue, potentially contributing to tumor progression(37-51). This association finds support in findings indicating that podoplanin-positive tumor cells often exhibit increased expression of matrix metalloproteinases, facilitating

invasion into the surrounding microenvironment (24). Additionally, podoplanin's influence extends to collective cell migration through the formation of filopodia, achieved by the downregulation of Rho family GTPases, notably RhoA (9). Moreover, podoplanin appears to facilitate single-cell invasion by inducing epithelial-mesenchymal transition (EMT), a process characterized by the downregulation of E-cadherin expression responsible for cell-cell adhesion in epithelial tissue (24,35,36)

CONCLUSION

In conclusion, head and neck squamous cell carcinoma (HNSCC) represents a formidable global health challenge, ranking sixth among cancers worldwide and affecting various regions of the upper aerodigestive tract. Despite advancements in treatment modalities, patient survival rates have not seen significant improvement, necessitating a deeper understanding of its pathogenesis and progression. Podoplanin (PDPN) has emerged as a pivotal player in tumor behavior and progression across various carcinomas. Structurally unique, PDPN lacks recognizable functional domains but exerts profound effects on cell behavior through interactions with various proteins, orchestrating processes such as tumor cell migration, invasion, and metastasis. Its expression is influenced by tumor-promoting agents, and it serves as a significant marker in various cancer types, including oral cancer. Furthermore, PDPN's multifaceted involvement extends beyond cancer cells themselves to include cancer-associated fibroblasts (CAF) and peritumoral basal keratinocytes, emphasizing its crucial role in the tumor microenvironment. Innovative approaches are underway to exploit PDPN as a diagnostic and therapeutic asset in cancer, including its potential utility as a blood-based biomarker and its role in facilitating tumor cell spreading, migration, and invasion. Immunohistochemical studies have provided valuable insights into PDPN expression patterns in various cancers, indicating its potential as a prognostic marker and its association with aggressive tumor behavior. Additionally, mechanistic studies have shed light on the molecular pathways through which PDPN influences tumor progression, including its impact on cell motility, collective migration, and epithelial-mesenchymal transition (EMT). Overall, the comprehensive understanding of PDPN's role in cancer pathogenesis and its potential clinical applications underscore its significance as a promising target for further research and therapeutic interventions in the management of head and neck squamous cell carcinoma and other malignancies..

Conflicts of interest

None to declare

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