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Review

Periostin – an unexplored tumor marker of oral squamous cell carcinoma

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Abstract: Cancer is a multi-hit multi-step process that ultimately leads to malignant transformation. Genes encoding for extracellular matrix, proteins of epidermal development, and cell adhesion molecules are mostly altered in oral squamous cell carcinoma. Of late, the paradigm for diagnosis has shifted from clinical status to molecular one. This is because molecular changes occur immediately, whereas clinical changes take a long time to show up. Hence, by evaluating various markers of cancer, its progression, severity, resistance, and prognosis can be predicted way before the clinical signs occur. These markers are present either in the tumors or hosts and help to distinguish between normal and dysplastic tissue. They generally increase during the disease progression or relapse, and decrease when the disease goes into remission. They can also be detected in blood, plasma and saliva apart from tissues. Periostin is one such molecule that gets altered, and hence can be used as a marker. Studies on the expression of periostin in oral cancer are very few; therefore, an attempt is made to throw some light on this novel protein and its role in oral cancer. It can be used in target therapy solely or as an adjunct in treating oral squamous cell carcinoma.

Keywords: periostin protein; oral squamous cell carcinoma; molecular targeted therapy; biomarker; angiogenesis

1. Introduction

Cancer is the second most fatal condition after cardiovascular disease that has affected mankind. Cancer or Neoplasia's literal meaning is "New Growth". Willis defined it as "An abnormal mass of tissue the growth of which exceeds and is uncoordinated with that of the normal tissue and persists in the same excessive manner after the cessation of the stimuli which evoked the change" [1].

Oral cancer accounts for approximately 30% of all cancers with at least 3000 in every 100,000 persons suffering from it. At least five people die of oral cancer every hour every day in India [2]. Indian Council of Medical Research has predicted 17 lakh new cases and around 8 lakh deaths due to cancer by 2020 [3]. World Health Organization has recognized oral cancer as the 6th most common cancer in males and the 10th most common in females [4]. In 2016, the incidence of oral cancer in India was 113,000, whereas it was prevalent in 397,000 patients [5]. Of the cases, around 90–95% of oral cancers in India are Oral Squamous Cell Carcinoma (OSCC) [2]. The prevalence of OSCC is more in India due to increased population getting exposed to cigarettes, alcohol, and smokeless tobacco like gutka, betel nut with tobacco and paan masala. The most recent entrant is exposure to the Human Papilloma Virus. It can also be attributed to poor oral hygiene, lack of dental awareness, as well as mal-nourishment [6].

Oral cancer is a multifactorial disease. In spite of so many advances in diagnosis and treatment modalities, the 5-year survival rate is still low, which can be attributed to late diagnosis, metastasis, and high rate of recurrence. Thus early and prompt diagnosis is the key to success here. The three areas where there is potential to get better results for early diagnosis are- better cytological analysis, easy identification of tumor markers, and better techniques to detect any changes in oral mucosa [7]. The biomarkers play an important role in the diagnosis, prognosis, and risk assessment of the patient even before clinical changes are visible.

NIH'S National Cancer Institute (NCI) has defined biomarker as "A biological molecules found in blood, other body fluids or tissues that is a sign of a normal or abnormal process or of a condition or disease". These molecules are also called molecular markers or signature molecules. Any biologically derived product or process which helps in diagnosing the prognosis, screening, or risk of cancer are considered as cancer markers [8].

These markers are present either in the tumors or hosts and help to distinguish between normal and dysplastic tissue. They generally increase during disease progression or relapse, and decrease when the disease goes into remission [9]. Apart from tissues, they can also be detected in blood, plasma, and saliva [10]. These markers are simple, painless, and can be repeated. Hence, treatment can be started faster, with the chance of stopping the cancer progression. They help in identifying patients at risk, diagnose cancer at an early stage, select the best treatment modality, and help in monitoring the response of treatment [11].

Biomarkers are classified into three categories as based on (1) Disease State as Prediction, Detection, Diagnosis and Prognosis markers, based on (2) Biomolecules as DNA, RNA, Protein and Glyco biomarkers and last category based on (3) other criteria like imaging, pathological and *in-silico* biomarkers [8].

Genes coding for extracellular matrix (ECM), proteins of epidermal development, and cell adhesion molecules are mostly altered in oral squamous cell carcinoma. Periostin is a part of all the above categories, and hence it can also be used as a marker [12]. Due to the scarcity of published literature, available resources were explored to review its role in the development of oral squamous

cell carcinoma and as a possible drug target.

2. Brief introduction to periostin

It was first called osteoblast-specific factor 2 and was isolated from mouse cell lines by Takeshita et al. in 1993 [13]. Later it was renamed as periostin as it was abundantly expressed in the periosteum surrounding the bone. It is encoded by the POSTN gene [13].

Periostin is a homodimeric glycoprotein with around 836 amino acids and has 23 exons [14]. This 93.3 kDa protein shares structural similarity with fasciclin, which is a cell adhesion molecule found in Drosophila insects [15]. It is also a member of Vitamin K dependent Gla- containing protein and belongs to the family of transforming growth factor- β (TGF-β) proteins [16].

TGF-β 1, 2 and 3, bone morphogenetic proteins (BMP) 2 and 4, vascular endothelial growth factor (VEGF), connective tissue growth factor 2, Vitamin K, an angiotensin II antagonist called valsartan, platelet-derived growth factor-bb (PDGF-bb), interleukins (IL) -3,4,6 and 13, all cause induction of Periostin expression in cells [17].

As a matricellular protein periostin is a non-structural ECM protein that manages cell-matrix interaction and cellular functions. It either binds to cell surface receptors or directly to ECM proteins forming a scaffold that can trigger extracellular signalling pathways for increasing inflammatory cytokines [18]. Being a matricellular protein, its interaction with αv integrins, activates the nuclear factor kappa-light-chain-enhancer of activated B-cells/signal transducers and activators of transcription 3 (NF-kappa B/STAT 3), phosphatidylinositol 3-kinase/protein kinase B (PI3K/Akt) and focal adhesion kinase (FAK) signalling pathways. Periostin also manages the expression of collagen, fibronectin, TGF-β1 genes in tissues [17].

This protein is expressed more during embryonic development and becomes latent in normal adult tissues. Increased values are found during wound healing, tissue remodelling, chronic inflammation, and cancers [18]. It acts as an extracellular adhesion molecule helping in communication between cells as well as cells and their microenvironment. It is secreted by stromal cells like cancer-associated fibroblasts, myofibroblasts, osteoblasts, bone marrow-derived mesenchymal stromal cells, and in some instances, by tumor cells, mainly cancer stem cells [19].

3. Structure of periostin

Periostin gene is located on the long arm of chromosome 13, i.e. precisely 13q13.3 [14] and has four parts, namely: N- terminal, EMI domain, four FAS domains, and a C- terminal region [13].

The N-terminal region has a signal peptide (SP) for secretion encoded by exon1. EMI domain is a cysteine-rich region with 75 amino acids that produce multimers encoded as exon 2 & 3 [14]. After SP and EMI domain there are 4 homogenous FAS domains with 150 amino acids encoded as exon 3–14. They act as ligands and attach themselves to integrins on the cell surface, thus helping N-terminal to bind to the cell surface [14]. At the end, is the C- terminal region encoded as exon 15–23, which is hydrophilic in nature. This region can get spliced to form various isoforms of periostin. It helps in cell-matrix organization and interacts with other ECM proteins like collagen V, tenascin C, fibronectin, βigH3, and periostin itself too [20].

Periostin contains all necessary amino acids found in Gla- proteins. They are present on the N-terminus of the 1st FAS domain. All 4 FAS domains are carboxylated by their own carboxylase

recognition sites.

Periostin has nine variants with changes in C- terminal exons 17 to 21 [21]. They are made of 751–836 amino acids with a molecular weight ranging from 83–93 kDa. Only four isoforms are sequenced as below [14]:

Isoform 1 or (OSF-20s) – full-length periostin with all exons
Isoform 2 or (OSF-2p1) – exon 17 & 18 absent
Isoform 3 or (PLF) – exon 17 & 21 absent
Isoform 4 – exon 17, 18 & 21 absent

The other variants are: deletion of only 1 exon (17 or 20 or 21), deletion of 3 exons (17, 18 & 19) and deletion of 4 exons (17, 18, 19 & 21) [22].

It also contains 2 YH motifs composed of tyrosine and histidine residues and is located on FAS1-2 and FAS1-4 domains which bind to integrins [20].

4. Periostin and normal physiological processes

Periostin is overexpressed during embryogenesis and becomes dormant in adult life. It is mostly found in fetal tissues like embryonic periosteum [23], periodontal ligaments of teeth, placenta, lungs, stomach, heart [24], vagina, breast, skin, and kidneys.

It plays a vital role in the formation and maintenance of bone, teeth & heart [15]; helps in fibrillogenesis of collagen, and is increased during healing processes like an injury to skeletal muscles and the response of heart after acute myocardial infarction. It also attaches to ECM proteins like fibronectin [24], tenascin C, collagen V to help in ECM remodelling [14]. Periostin expression is low in tissues having less fibroblast content like the spleen and is more in tissues with high fibroblast content like skin and breast [25].

In immunohistochemical staining, periostin is found in the basal layer and partly in the spinous layer of the normal oral mucosa. Wein-Qun Guan et al. found periostin concentration in serum of the healthy groups to be around 20.64 ± 5.3 ng/ml [23].

Periostin expression in tumor cell lines is low as compared to tumor tissues. This confirms that the biomarker is secreted by stromal cells surrounding the tumor and not the cancer cells themselves [25].

5. Periostin and epithelial-mesenchymal transition (EMT)

A lot of studies have been done on the expression of periostin in pancreatic, breast, and lung carcinoma. The serum periostin level increases in patients suffering from OSCC, and it also correlates with the stage of tumor and lymph node metastasis [26].

EMT is the essential step required for metastasis as it is responsible for the detachment of primary tumor epithelial cells to distant organs. The steps in metastasis are as follows: the proliferation of cells, induction of angiogenesis, detachment of cells, motility, invasion in blood and lymph circulation, aggregation and survival of cells, and finally extravasation into distant organ parenchyma [27].

Here, tumor cells switch from a well-defined epithelial phenotype to an invasive mesenchymal phenotype [18]. There is the loss of epithelial cell markers like E-cadherin and simultaneous overexpression of mesenchymal proteins fibronectin, vimentin, N-cadherin, periostin, etc. as there is

increased activity of MMP 2, 3 & 9.

EMT is started with the activation of PIK (Figure 1), EGFR & c-KIT, which are tyrosine and serine-threonine kinase receptors. This, in turn, activates ras – raf – MEK – MAPK pathway. PI3K and AKT also cause EMT by directly activating TGF-β or by indirect activation of EGF or PDGF [14].

Helix – loop – helix transcription factor called **Twist,** and another Zinc finger protein called **Snail** are also considered as significant regulators of EMT. Periostin is positively correlated with these two regulators according to a study done on lung cancer [28].

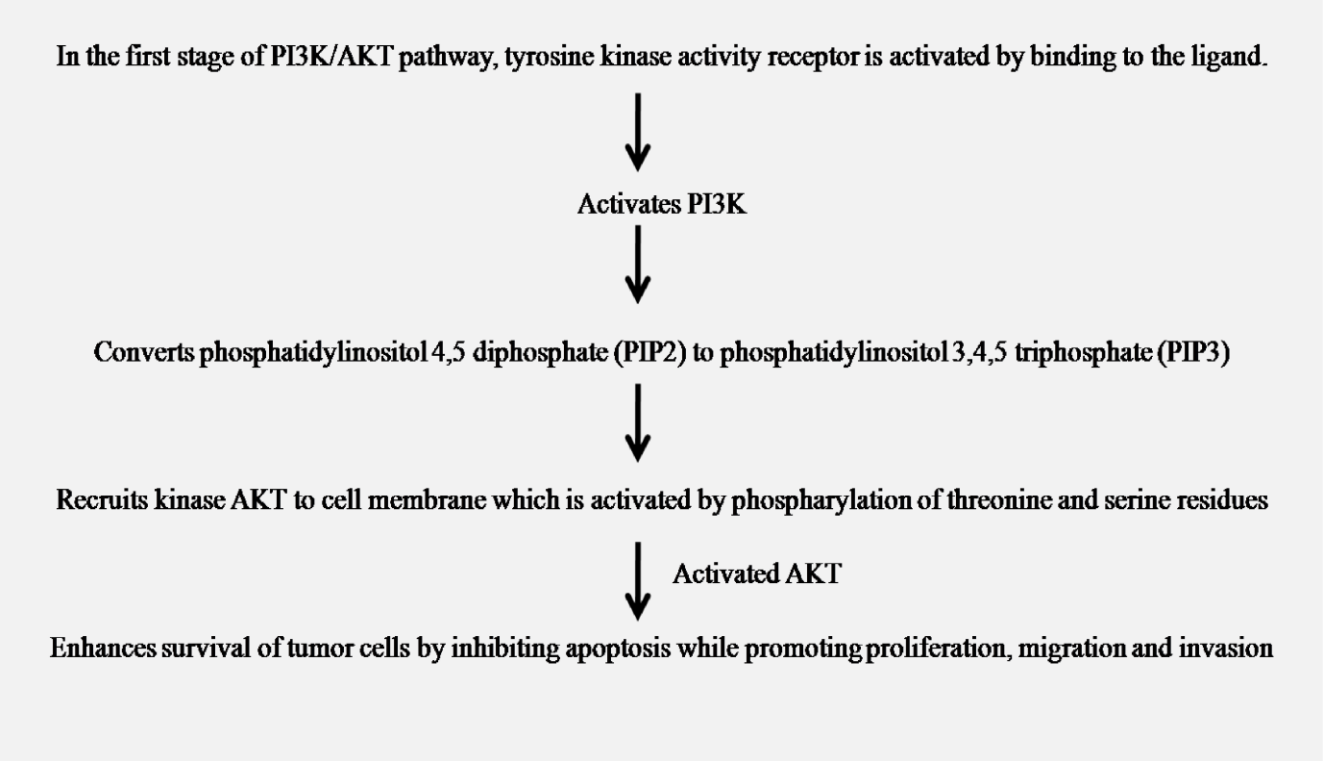

Figure 1. Process of epithelial-mesenchymal transition.

6. Periostin and tumor microenvironment

Like the hypothesis of "seed and soil", tumor survival needs assistance from the surrounding microenvironment. This microenvironment in which a tumor exists is made of tumor cells, surrounding blood vessels, immune cells, cancer-associated fibroblasts (CAFs), ECM, and signalling molecules [21]. There are various tumor microenvironments like cancer stem cell niche, perivascular niche, pre-metastatic niche, immunosuppressive microenvironment and other growth factors supporting microenvironment wherein periostin can act [19].

In regards to the tumor microenvironment, periostin binds to integrins αvβ3 [29], αvβ5, and α6β4 leading to the activation of PI3K/AKT and FAK signalling pathways by recruiting EGFR [26,30,31]. These pathways promote all steps of tumor invasion like cell survival, migration, invasion, and angiogenesis [17,32]. It also acts on Wnt signalling [33] by binding with protein tyrosine kinase and helps in the self-renewal of cancer stem cells and its distant metastasis [34].

Periostin is secreted by tumor stromal cells, especially CAFs as well as from bone marrow

derived mesenchymal stromal cells. This proves the creation of premetastatic niche by bone marrow derived cells in secondary sites occurs before the influx of tumor cells as an essential microenvironment for promoting metastasis [21].

Inflammation can cause local and systemic cytokines and growth factors to be secreted by epithelial cells. These factors and TGF-β cause stromal cells to release periostin which then activates the signalling pathways. Thus, it acts as a scaffold, ligand during inflammation, and tumorigenesis [26]. Hence, chronic inflammation is also one of the factors leading to tumor formation.

7. Periostin influence on invasion pattern and metastasis in oral cancer

Periostin is found in the basement layer or part of the spinous layer of normal cells and premalignant lesions by immunohistochemical staining [35]. In oral squamous cell carcinoma, it is found in scattered interstitial cells present in cancer cells [23]. Expression of periostin is more in metastatic tumors as compared to primary ones [25]. Hence, it is found in Jacobson's stage IV classification of cancer and not stage I and II. The lower the degree of tissue differentiation, the higher is the expression of periostin [23]. Thus, it predicts the invasiveness of a lesion and is identified as an invasion promoting factor.

Periostin causes a pro-tumorigenic effect by releasing MMP 9, 10 & 13, leading to ECM degradation and fibrillogenesis [17]. Hence, it promotes ECM re-organization, required for local spread and invasion of tumor cells. It causes changes in the matrix around the tumor, weakens adhesion between cells, and causes proliferation of epithelial cells. These epithelial cells secrete inflammatory cytokines like TGF-β, TNF-α, FGF which stimulate normal epithelial cells to proliferate and evolve. Thereby it causes cells to detach from their primary lesion site, extravasate, and reach the bloodstream for further dissemination to distant organs [23].

Periostin has FAS1 domains which are similar to ones on βigH3 [36]. They bind with integrins and gylcosaminoglycans especially interacting with αvβ3, αvβ5, and α3β1 leading to endothelial cell adhesion and migration [36]. This suggests that FAS1 domains help periostin to bind with the integrins of endothelial cells along with cancer cells [27].

Once it interacts with the integrins, it inhibits them from binding with the ECM and/or activation of intracellular signals in OSCC cells and promotes angiogenesis in endothelial cells. Both invasion and angiogenesis lead to metastasis (Figure 2) [37].

Periostin works with mutant p53 by activating STAT 1 signalling network seen in epithelial cancer invasion and aggressive tumors. Tumor growth occurs due to resistance to cytotoxic stress cascade caused by increased STAT1 signaling [38].

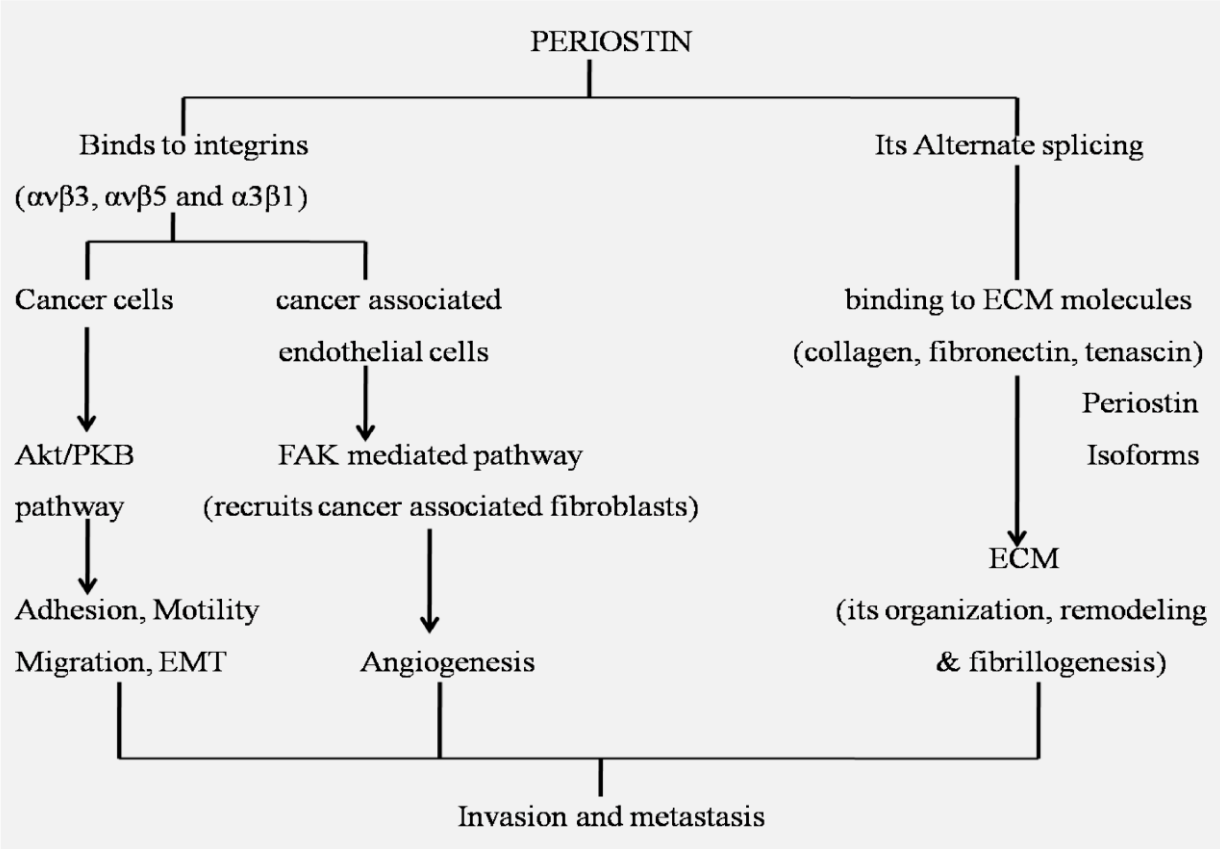

Figure 2. Effect of periostin in invasion and metastasis.

8. Periostin's influence on angiogenesis and lymphangiosis

New capillaries are required to provide nutrients and oxygen to solid tumors when they grow beyond 2–3 mm. This requires proliferation and migration of vascular endothelial cells to form new vessels [29].

Periostin is associated with an increase in blood vessel density in tumors and promotes capillary formation from endothelial cells of existing vessels. Siriwardena et al. also proved that OSCC tumors showed more blood vessel density in periostin positive tumors as compared to periostin negative tumors [27]. It also recruits endothelial progenitor cells from the bloodstream, manages its proliferation, differentiation, and migration to the location of newly formed blood vessels [14].

Periostin performs the above function by interacting with integrin αvβ3. It also interacts with VEGF present on endothelial cells and helps to bind with its receptor VEGFR to form new blood vessels [39]. It increases the expression of VEGFR through an integrin αvβ3 – FAK mediated pathway [37,40] and further influences VEGF-C, which is essential for lymphangiosis by activating tyrosine kinases Src and AKT [35,37].

9. Periostin as a target for therapy

Though biopsy is the GOLD STANDARD for establishing the diagnosis and prognosis of cancer, it becomes excruciating for the patient to perform repeated biopsies. Due to this, many

patients refuse repeated biopsies compromising tracking of the disease progression. Serological tests of tumor markers are relatively simple and less painful.

Target therapies are in the trend now. The US spent $27 billion in 1990 and $90 billion in 2008, which will increase to $157 billion by 2020 on cancer therapy. Of this targeted therapy cost increased from $1.3 billion in 2001 to $13 billion in 2006 [41].

Various studies have proved the accessibility, stability, and specificity of ECM proteins as tumor antigens for targeted therapy [13]. Neutralizing antibody MZ-1 against periostin suppressed metastasis. Modified DNA aptamer, PNDA-3 which binds to periostin inhibits migration and invasion of breast cancer cells [42]. Zhu et al. proved that neutralizing antibodies targeted against periostin decreased the metastasis in ovarian cancer [18].

Kudo et al. found periostin in condition media of OSCC cell lines [43]. Hence, periostin secreted from OSCC cells can be found in the saliva and blood of patients. Elevated levels of periostin in tissues and body fluids of cancer patients, its influence on the process of tumorigenesis, and its association with poor prognosis are the reasons to use periostin as a target for therapy.

10. Periostin: its effect on cancers of various origins

It has also been reported that matricellular proteins like periostin in the tumor microenvironment are involved in proliferation, invasion, matrix remodelling, and dissemination to premetastatic niches in distant organs. Kim GE et al. in 2017 reported a good correlation between epithelial periostin overexpression with poor survival in patients with invasive breast carcinoma [44]. In a review article published by Gonzalez & Alonso in 2018 high POSTN levels were usually associated with aggressiveness of tumors in advanced stages. It is also the cause of poor prognosis in cancers of breast, ovary, lung, prostate, pancreas, liver, bladder, colorectal, and bone [24].

11. Studies related to the expression of periostin in oral squamous cell carcinoma

A lot of studies have been carried out to represent periostin in the pathogenesis of the lung, colon, bladder, oesophageal carcinoma, breast [24,44], but few have been performed to correlate the expression of periostin and OSCC.

Studies that were carried out on human oral squamous cell carcinoma tissues or cell lines proposed periostin to be directly proportional to the invasiveness of the disease [27,43,45]. They also laid emphasis on the effect of periostin on cancer-associated fibroblasts to increase proliferation [21]. Its presence also increased the chances of metastasis [27,43,45–47]. It helped in tumor survival by inducing angiogenesis via up regulation of MMPs and VEGF [46,47] and also helped in the disruption of cell cycle as well as inhibition of apoptosis causing gene alterations in the cell (Figure 3) [48].

There is only one systematic review in literature by Sundar S et al. on the effect of periostin in OSCC [37]. They concluded that periostin is essential for angiogenesis, invasion, and metastasis and therefore, periostin can be considered for molecular target therapy. The summary of all studies carried out to find a correlation between periostin and oral cancer are concised in Table 1.

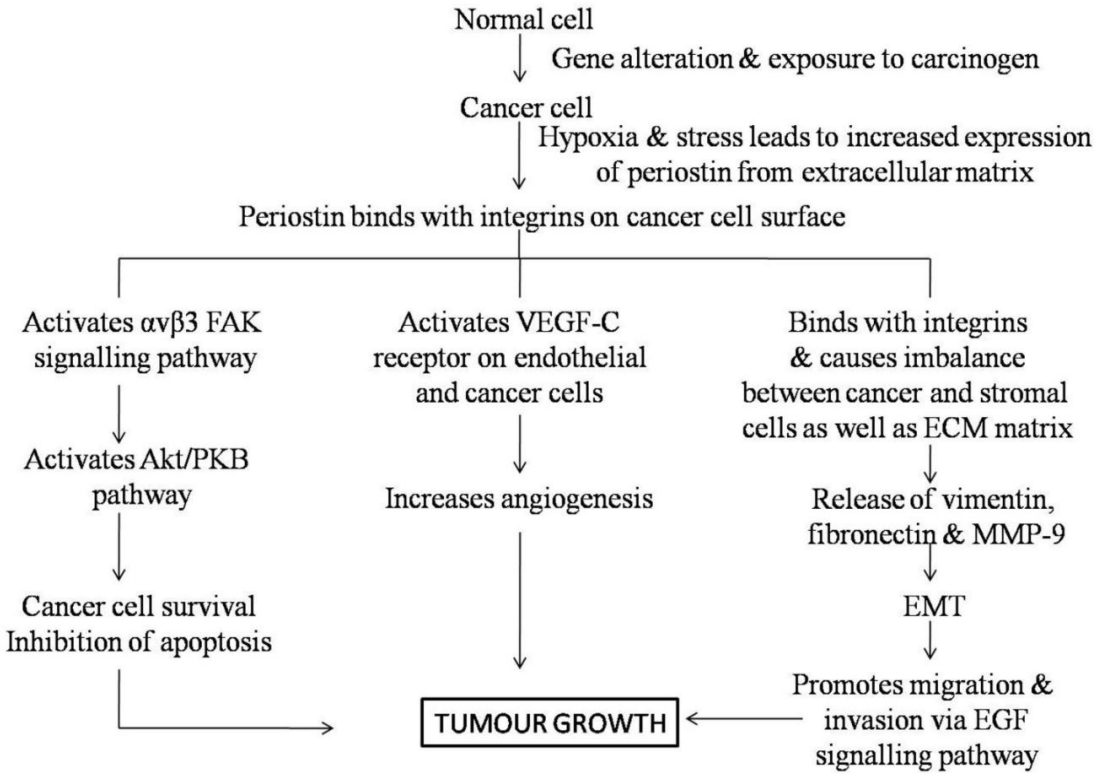

Figure 3. Effect of periostin on cell.

Table 1. Studies carried out on periostin in oral squamous cell carcinoma to date.

Authors	Samples and Methods used	Significance
Siriwardena BSMS et al. [27]	Human oral squamous cell carcinoma tissue OSCC cell lines RT-PCR Immunohistochemistry	Periostin expression was related to the development of tumor. It enhances invasiveness, angiogenesis and it is expressed more in lymph node metastasis.
Kudo Y et al. [43]	Human oral squamous cell carcinoma tissue Immunohistochemistry Microarray analysis RT-PCR Western Blotting	Periostin expression correlated with tumor development. It increased invasion and anchorage-independent growth of OSCC cells. It was expressed more in lymph node metastasis. Periostin expression correlated with the angiolymphatic invasion.
Choi P et al. [45]	Human Oral Squamous cell carcinoma tissue Immunohistochemistry RT-PCR Microarray analysis	Periostin expression correlated with tumor progression. Periostin expression in the epithelium was associated with an aggressive phenotype.

Continued on next page

Authors	Samples and Methods used	Significance
Deraz EM et al. [46]	Cell line study Human Head and Neck Oral Squamous cell carcinoma tissue Immunohistochemistry RT-PCR	MMP 10 helps periostin in its invasive nature.
Kudo Y et al. [47]	Human Oral Squamous cell carcinoma tissue OSCC cell lines Serum of OSCC patients Immunohistochemistry ELISA RT-PCR	Periostin expression correlated with tumor development, lymphatic invasion and metastasis. It induced VEGF-C induced lymphangiogenesis.
Gawish GEH et al. [48]	Cell line study FACS calibre	Periostin causes tumorigenesis by causing disruption in the cell cycle, apoptosis. It enhances gene alterations.
Qin X et al. [21]	Human Oral Squamous cell Carcinoma Tissue Head and neck cancer cell lines RT-PCR Immunohistochemistry ELISA Western blotting	Periostin expression correlated with tumor development. Periostin secreted from cancer associated fibroblasts was essential for tumor progression.
Guan WQ et al. [23]	Human Oral Squamous cell Carcinoma Tissue Serum of patients RT-PCR Immunohistochemistry ELISA	Periostin expression is correlated with tumor progression. Can be used as a tumor marker due to its expression in serum.
Kang Y et al. [35]	Human Oral Squamous cell Carcinoma Tissue OSCC Cell Lines Immunohistochemistry RT-PCR Western Blotting	Periostin expression is correlated with tumor progression. It helps to promote proliferation and invasion of tumor cells.

Notes: OSCC: oral squamous cell carcinoma; RT-PCR: Real Time Polymerase Chain Reaction; ELISA: enzyme-linked immunosorbent assay; MMP: matrix metalloproteinase; VEGF: vascular endothelial growth factor: FACS: Fluorescence-activated cell sorting.

12. Conclusion

As more research is being based on finding molecular solutions and treatments in cancer, periostin can definitely be considered as a potential target for therapy or as a prognostic marker in oral squamous cell carcinoma. However, large scale research studies need to be conducted further to establish periostin as a potential therapeutic target in oral cancer.

Conflict of interest

All authors declare no conflicts of interest in this paper.

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