

Proteoglycans as potential biomarkers in odontogenic tumors

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Abstract

Proteoglycans (PGs) are essential for normal cellular development; however, alterations of their concentrations can promote tumor growth. To date, a limited number of studies report the presence of PGs in odontogenic tumors (OTs); therefore, the main purpose of this work is to gather the information published on the study of PGs. The search reported 26 articles referring to the presence of different PGs in distinct OTs from 1999 to May 2017. PGs seem to play an important role during OTs' development as they are involved in several tumor processes; however, the number of reports on the study of these molecules is low. Thus, more studies are necessary in order to gain a better understanding of the underlying pathophysiology of OTs.

Keywords: Biglycan, CD44, glypican, odontogenic tumor, perlecan, proteoglycan, syndecan, versican

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Received: 17.07.2017, **Accepted:** 12.02.2018

INTRODUCTION

Odontogenic tumors (OTs) comprise a group of heterogeneous lesions that, from a biological point of view, include hamartomas and nonneoplastic proliferations with distinct differentiation degrees and truly benign and malignant neoplasms with metastatic potential. These lesions are derived from the tooth-forming tissues (epithelial, mesenchymal, or even both), whose remnants stay in the maxillomandibular complex, as well as the adjacent soft tissues.^[1-4]

During odontogenesis, proteoglycans (PGs) play an important role. Several studies report the presence of these molecules during the stages of tooth development (especially during cell differentiation) in human and animal models.

Some of these PGs genes get silenced later and are activated during tumorigenesis of different kinds of neoplasms as they are involved in tumor processes such as growth, invasion and loss of adhesion among others.

The PGs represent a heterogeneous group of high-molecular-weight glycoproteins that share the common feature of a specific protein core covalently bounded to one or more glycosaminoglycan (GAG) chains, such as chondroitin sulfate (CS), dermatan sulfate (DS), keratan sulfate (KS), heparin (He), or heparan sulfate (HS), resulting in a high degree of structural and functional complexity.^[5] GAG chains are linear heteropolysaccharides composed of repeating disaccharides of one uronic acid (or neutral sugar for one of them) and one amino sugar or hexosamine (N-acetyl-galactosamine

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DOI:

10.4103/jomfp.JOMFP_151_17

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How to cite this article: Gómez-Herrera Z, Molina-Frechero N, Damián-Matsumura P, Bologna-Molina R. Proteoglycans as potential biomarkers in odontogenic tumors. *J Oral Maxillofac Pathol* 2018;22:98-103.

or N-acetyl-glucosamine). Covalently-attached chains of GAGs can be sulfated (CS, DS, HS, KS) or those that does not contain any sulfate, such as Hyaluronic acid (HA) which is the GAG with the least net negative charge. HA can be several thousands of monosaccharides long and it is not covalently linked to a protein.^[6]

PGs are major components of extracellular matrix (ECM) of connective tissue and control numerous normal and pathological processes, among which are morphogenesis and tumor development.^[6]

According to Iozzo and Schaefer (2015), there are four major PGs families, based on their cellular and subcellular location, homology at the protein and genomic levels and the presence of unique protein modules: heparan sulfate PGs (HSPGs), chondroitin sulfate PGs (CSPGs), dermatan sulfate PGs and the so-called small leucine-rich proteoglycans (SRLPs).^[7]

Based on their cellular and subcellular localization, PGs can be divided into components of the cell surface of the pericellular matrix, the basement membrane zone and the intracellular and extracellular spaces.^[5,7] PGs that are intimately associated with the plasma membranes of cells can be either directly through a transmembrane protein core (e.g., syndecan, CD44) or through glycosyl-phosphatidyl-inositol (GPI) anchors (glypican). ECM PGs contain the largest class of proteoglycans (SLRPs) that can be structural constituents or signaling molecules (activating several receptors, including tyrosine kinases), especially when tissues are remodeled during tumor formation (e.g., biglycan). Figure 1 indicates the localization of different PGs within cell microenvironment.

During 2016 and 2017, we searched for English-language articles through PubMed database using the keywords OT, PG, *syndecan*, *glypican*, *perlecan*, *CD44*, *versican*, *biglycan* and *decorin* in order to identify the literature available on the study of the PGs in OTs and describe the most important findings. As inclusion criteria, we considered those studies performed in human samples of OTs. Previous reviews on the presence of PGs in OTs were excluded.

FINDINGS

Proteoglycans and odontogenic tumors

OTs derive from the same tissues as teeth, this might be one of the reasons why in the past few years, a series of studies on the presence of PGs in OTs have been reported. These studies include the presence of syndecan-1, glypican-1, perlecan, CD44, versican, decorin and biglycan in the

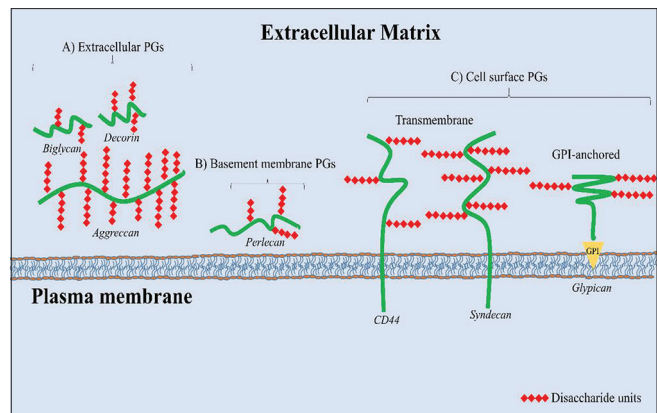


Figure 1: Localization of the proteoglycans. (A) Extracellular proteoglycans, (B) Basement membrane proteoglycans. (C) Cell surface proteoglycans

tumor microenvironment and the importance of their participation in the OTs development.

Syndecan

In mammals, the syndecan family includes four members (syndecan 1–4).^[7-9]

Of all the members that comprise this family, syndecan-1 is the most important and most studied of all^[8] and is mainly expressed in epithelial cells.^[9] The absence of syndecan-1 leads to tissue reparation delay and high neutrophil levels and its overexpression is related to fibrosis and cell proliferation inhibition.^[10] Syndecan-1 attaches to ECM components and modulates the activity of growth factors linked to heparin^[9,11] and is considered a multipotent matrix receptor as it binds diverse ECM molecules, so it is essential for morphology maintenance of epithelial tissues.^[12] Syndecan-1 also participates in odontogenesis.^[12,13]

Most studies have been performed in ameloblastomas (AMs). A decrease of syndecan-1 is related to biological behavior, tumor growth, invasive potential and aggressiveness among AM subtypes and ameloblastic carcinoma.^[12-16] Syndecan-1 has been correlated with cell proliferation proteins. Wnt1-dependent cell proliferation is modulated by certain HSPGs, such as syndecan-1. The presence of syndecan-1 in the ECM and stromal cells correlates with Wnt1 in different subtypes of AMs, suggesting the participation of both proteins in cell proliferation and local invasiveness.^[13] A decrease of syndecan-1 is inversely proportional to Ki-67 increase (when the immunorexpression of syndecan-1 is reduced, the proliferative activity of the cells is elevated), establishing a relation between adhesion loss, tumor growth and progression, which in turn suggesting a possible explanation for the spectrum of differential aggressiveness between AM subtypes.^[12,14,15] Compared to AMs, the

keratocystic OT (KOT) shows higher immunoexpression of syndecan-1, suggesting a more aggressive behavior of the AMs.^[17]

In AMs and cystic lesions, the displacement of syndecan-1 from epithelium to stroma could be related to aggressiveness.^[16,18]

Syndecan-1 could be involved in the development and pathogenesis of some OTs such as the granular cell OT,^[19] the ameloblastic fibro-dentinoma,^[20] and the recently included in the OT classification, the primordial OT.^[21]

The utility of syndecan-1 has been highly studied by our group,^[12,14,15,20,21] establishing this protein as a potential biomarker to distinguish between some aggressive and nonaggressive OTs with epithelial components, especially when the immunoexpression is found in the epithelial or stromal cells. OTs derive from the tissues involved in tooth formation, in our works, the use of tooth germs as controls has helped to study the biological behavior of OTs [Figure 2].

Glypican

Glypicans constitute a family of six members. They are PGs attached to the plasma membrane through GPI anchors and, depending on the biological context, they can either stimulate or inhibit the signaling activity.^[22-24] Due to their HS chain composition and their localization on the cell surface, they can regulate the cellular response to many heparin-binding growth factors, adhesion molecules and ECM components.^[22] Glypicans are present in the cytoplasm and can be secreted to the ECM through the action of notum, a lipase that breaks the GPI anchors releasing the glypicans.^[23] The alterations in this molecule have been identified in different congenital malformations and cancer.^[22]

In AMs, glypican-1 is present in fibroblasts, in epithelial and tumor cells and also in its secreted form in the ECM. The immunoexpression in the fibroblasts is higher in

those nearest to the tumor cells, suggesting that they might participate in the storage of heparin-depending growth factors, which are released by the heparanase at the beginning of infiltration and invasion processes and induce mitogenic stimulation of cancer cells. The intracellular presence of glypican-1 might be related to its capacity to act as a receptor for extracellular ligands such as growth factors.^[22]

The other member of the glypican family that has been studied in OTs is glypican-3, which seems to contribute in OT invasiveness and could be considered as a marker to distinguish aggressive from nonaggressive lesions.^[25]

Perlecan

Perlecan, which was the first HSPG identified in basal membranes, is a modular PG with numerous domains and is one of the main components of the ECM. It participates in cell migration, adhesion, proliferation, lipid metabolism, thrombosis and cell death.^[26-28] In addition, it has both pro- and anti-angiogenic roles depending on its domains' activity.^[7,29] Perlecan is a large PG localized in the basement membrane of vascularized tissues, and it is synthesized by fibroblasts and endothelial and basal cells. Perlecan is also found in stromal spaces and is related to early and late stages of embryogenesis, cancer and diabetes.^[30]

Perlecan is present in AMs and KOTs and could be associated to cell proliferation and tumor growth.^[31-33] The storage of this protein in the ECM of AMs might be related to the myxoid and stellate appearance of the central portion of the tumor, due to the intercellular accumulation of HSPG molecules, synthesized by the tumor cells. Two of the major receptors of perlecan, β 1 integrin and α -dystroglycan, are expressed in different areas of the tumor. α -dystroglycan is present in the intercellular spaces and the basement membrane of stellate cells, while β 1 integrin is in the basal cells area, next to the stromal perlecan, the differential expression between these receptors controls proliferation and differentiation. The central portion of the tumor, which is rich in perlecan, regulates the behavior of the neoplastic cells, but its real function remains unknown.^[31,32] In cystic lesions, the use of perlecan as a diagnosis marker has also been proposed.^[34]

CD44

CD44 is a cell membrane receptor with multiple isoforms, some of these isoforms have GAGs chains, classifying CD44 as a part-time hybrid PG as it has attachment sites for HS and CS.^[35] It interacts with other GAGs (HA) and different proteins such as fibronectin, type I and IV collagens and osteopontin (OPN).^[36] Due to its

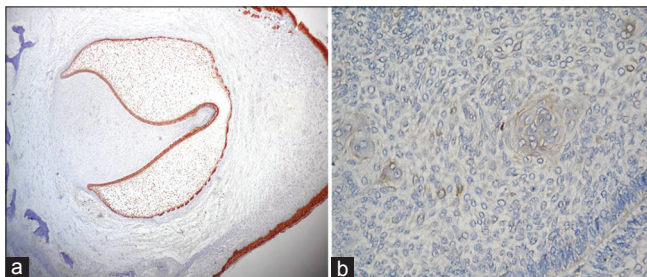


Figure 2: Differential immunoexpression of syndecan-1 in tooth germ, $\times 50$ (a) and ameloblastic carcinoma, $\times 200$ (b) indicates differential behavior between normal and pathological tissues

interactions with multiple molecules, CD44 regulates and participates in cellular processes such as adhesion (cell–cell and cell–ECM), angiogenesis, differentiation, migration, survival and proliferation.^[35]

Among CD44 variants, CD44 v6 is related to tumorigenesis^[35,37] and it has been described in OTs and cystic lesions. An upregulation of CD44 v6 as well as an upregulation of OPN (a protein associated with invasion when it is secreted by tumor cells) has been observed in AMs and KOTs. As CD44 is a receptor for OPN, the bond between both molecules could enhance tumor cell motility, and thus, invasion, migration and spread.^[38,39] This association has also been reported in other cystic lesions, where higher levels of both proteins were observed in the tumors and lesions which were considered more aggressive.^[36]

Versican

Versican belongs to the lecticans' family (also known as hyalectans), a CSPG family with genomic and proteinic similitudes. Their structure and properties allow for lecticans to act as molecular bridges between cell surfaces and the ECM.^[7] Versican is present in the ECM and is the largest member of the lecticans' family and is found in small amounts in most of the soft tissues; however, during inflammation, its levels are upregulated.^[40,41]

The presence of versican has been reported in odontogenic myxoma (OM) and its use as an immunomarker during diagnosis is recommended;^[42] while in other OTs, the presence of versican might be partially implicated in the

morphogenesis of neoplastic epithelium and mesenchymal tissues as well as growth.^[43] In the stroma of the malignant neoplasms, an increase of versican induced by the tumor cells might lead to a decrease in cell–ECM adhesion, promoting migration. The presence of versican was observed in the epithelial growth front supporting the idea that versican is implicated in the epithelial growth, while its presence in the squamous epithelium is correlated with cell differentiation.^[43]

Biglycan and decorin

Biglycan and decorin are both SRLPs. Biglycan participates in cell differentiation, adhesion, proliferation and ECM organization. It promotes the formation of hydroxyapatite crystals and inhibits the growth of pancreatic cancer cells *in vivo*, and the overexpression of its gene has been reported in salivary gland carcinoma, demonstrating its possible role in tumor suppression mechanisms.^[44] There is evidence that during inflammation and tissue damage processes, biglycan, in its soluble state, acts as an alarm signal through the binding of adaptive and innate immune systems.^[45] Decorin was the first PG found to be involved in cell growth control and it is considered to have an anti-oncogenic role. The loss of decorin is correlated with poor prognosis in breast cancer and its downregulation has been described in other malignancies.^[7]

In the OM, the presence of both proteins was related to collagen formation. In addition, they seem to participate in the myxoid appearance, but their exact function remains unknown,^[42] but in odontogenic adenomatoid tumor, the overexpression of biglycan might suggest a host response related to the inhibition of the neoplastic growth. Biglycan

Table 1: Different types of proteoglycans and their role proposed by some authors in distinct odontogenic tumors

Proteoglycan	Type	Odontogenic tumors studied	Participation in tumor behavior	References
<i>Syndecan-1</i>	HSPG	Ameloblastoma, central granular cell odontogenic tumor, keratocystic odontogenic tumor, ameloblastic fibrodentinoma, calcifying cyst odontogenic tumor, primordial odontogenic tumor, dentinogenic ghost cell tumor, ghost cell odontogenic carcinoma and calcifying epithelial odontogenic tumor (clear cell type)	Loss of syndecan-1 and its switch to stroma is associated with tumor growth and invasiveness	[12-21,46-49]
<i>Glypican-1</i>	HSPG	Ameloblastoma	Storage of molecules related to infiltration and invasiveness	[22]
<i>Glypican-3</i>	HSPG	Ameloblastoma, keratocystic odontogenic tumor, adenomatoid odontogenic tumor and calcifying cyst odontogenic tumor	Aggressiveness	[25]
<i>Perlecan</i>	HSPG	Ameloblastoma, keratocystic odontogenic tumor and adenomatoid odontogenic tumor	Proliferation and tumor growth	[31-34,50]
<i>Aggrecan</i>	CSPG	OM	Unknown	[42]
<i>CD44</i>	CSPG/HSPG	Ameloblastomas, keratocystic odontogenic tumor and calcifying cyst odontogenic tumor	Invasion	[36-39]
<i>Versican</i>	CSPG	Ameloblastoma, adenomatoid odontogenic tumor, keratocystic odontogenic tumor, calcifying cystic odontogenic tumor, ameloblastic fibroma, malignant ameloblastoma and OM	Morphogenesis of tumor tissue, loss of adhesion and growth	[42,43]
<i>Biglycan</i>	SRLP	Adenomatoid odontogenic tumor and OM	Inhibition of neoplastic growth	[42,44]
<i>Decorin</i>	SRLP	OM	Unknown	[42]

HSPG: Heparan sulfate proteoglycan, CSPG: Chondroitin sulfate proteoglycan, SRLP: Small leucine-rich proteoglycan, OM: Odontogenic myxoma

interacts with collagens I and IV, which are present in the neoplastic stroma, suggesting a structural role for biglycan.^[44]

The PGs have important roles in OTs' behavior, the most important are mentioned in Table 1.

THE USE OF PROTEOGLYCANS IN ANTITUMOR THERAPY

In addition to their use and application for a better understanding of tumor's pathobiology and their use during diagnosis process, recent studies reported in other non-OTs support the use and modulation of PGs and GAGs as targets in antitumor therapy, representing a novel role for these proteins.

The study of syndecan in antitumor therapy has been reported in a series of neoplasms, either acting directly over the tumor or in an indirect way over the ECM through the use of antibodies, inhibitor enzymes, inhibitor biomolecules and synthetic inhibitors.^[51]

Targeting glypican-3 has also been suggested in antitumor therapy in malignancies such as hepatocellular carcinoma and liver cancer, as this PG is overexpressed in these tumors.^[52]

The downregulation of perlecan has been associated with tumor processes such as cell migration and increases the sensibility of the tumor cells to cisplatin, improving its effect over them.^[53]

The silencing of versican is related to a better efficacy of endostatin, an endogenous inhibitor of angiogenesis.^[54]

CONCLUSIONS AND PERSPECTIVES

In the present work, we described the action of some PGs during the processes involved in OT's development due to their action and effects over the tumor microenvironment and their capability to interact with other molecules that can stimulate tumor growth and invasion. The number of studies reporting the presence and importance of the PGs in OTs is low and some of them are limited to report the presence of these proteins.

Despite being rare neoplasms, OTs are controversial entities due to the methods used for their treatment and since their etiology remains poorly understood. Often these treatments are radical with the purpose of reducing the high recurrence rate; this can compromise patients' quality of life. Due to this, it is necessary to create new therapeutic strategies aimed at decreasing or enhancing the action of the molecular components of OTs.

Studying the presence of PGs in the OTs is important for a better understanding of the biological behavior and pathogenesis of these neoplasms. Furthermore, this study will allow us to consider their use as therapeutic targets. Using certain biomarkers, biomolecules and other medications can regulate PG's expression either directly or through gene suppression, offering alternatives to the use of the invasive and mutilating methods currently used for the treatment of various OTs.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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