Roles of Proteoglycans in the Tumourigenesis and Development of Adenoid Cystic Carcinoma and Pleomorphic Adenoma of the Salivary Gland: A Systematic Review

Jie WANG[1], Yan Ning ZHANG[1]

Salivary adenoid cystic carcinoma (ACC) and pleomorphic adenoma (PA) are the most common types of salivary gland tumours; the former is malignant and the latter is benign but with features of a border tumour. Proteoglycans (PGs) produced by neoplastic myoepithelial cells are ubiquitous in both types of tumours. However, normal myoepithelial cells of salivary glands do not have the ability to secrete PGs. When the synthesis of PGs is blocked, the pulmonary metastasis and perineural growth of salivary ACC as well as the implanting growth of salivary PA are inhibited, highlighting the important functions of PGs in the tumourigenesis and development of these two tumours. In this review, we summarise literature from the past 40 years, including more recent findings from our laboratory, to clarify the pivotal roles of PGs produced by neoplastic myoepithelial cells in both the histogenesis and biological behaviours of ACC and PA.

Key words: *adenoid cystic carcinoma, pleomorphic adenoma, proteoglycans, RNA interference, xylosyltransferases*

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Proteoglycans (PGs) are large, complex molecules and the main components of the extracellular matrix (ECM). PGs control numerous normal and pathological processes, including cell adhesion, proliferation, apoptosis, migration, angiogenesis, invasion and metastasis[1-5]. In this review, we summarise the pivotal roles of PGs produced by neoplastic myoepithelial cells in the histogenesis and biological behaviours of adenoid cystic carcinoma (ACC) and pleomorphic adenoma (PA).

1 Department of Oral Pathology, College and Hospital of Stomatology, Hebei Medical University; The Key Laboratory of Stomatology, Shijiazhuang, Hebei Province, P.R. China.

Corresponding author: Dr Jie WANG, Department of Oral Pathology, College and Hospital of Stomatology, Hebei Medical University, Shijiazhuang 050017, Hebei Province, P. R. China. Tel: 86-0311-86266292; Fax: 86-0311-86265748. Email: wangjiephd@163.com

Role of proteoglycans in the histogenesis of adenoid cystic carcinoma and pleomorphic adenoma

Proteoglycans and the histogenesis of adenoid cystic carcinoma

Salivary ACC is a malignant epithelial tumour composed of four major cell types: intercalated duct, myoepithelial, secretory, and pluripotential reserve/stem cells[6,7]. According to the degree of myoepithelial participation, ACC is recognised to be epithelial-myoepithelial (biphasic), mainly consisting of neoplastic epithelial cells and neoplastic myoepithelial cells[8]. However, the main proliferating component exhibits the overall organisation and appearance of modified myoepithelial cells[9].

ACC is classified into three structural subtypes: glandular (cribriform) type, tubular type, and solid type. The glandular (cribriform) type consists of epithelial cell nests permeated by numerous cylindrical spaces, which are occupied by a hyaline stroma that is positive for both periodic acid-Schiff and alcian-blue staining. The tubular type consists of epithelial strands surrounded by a hyaline stroma. The solid type consists

of solid epithelial strands and mass, often with central necrosis[10-12].

Electron microscopy has enabled visualisation of the mucoid material in the characteristic cyst-like space, in which three readily recognisable zones are observed, as follows: a juxtacellular zone of a network of replicated basal lamina, an intermediate zone of stellate granules of mucoid material, and a central core of densely packed, aperiodic filaments or collagen fibrils[13]. Immunoelectron microscopic and electron microscopic histochemical studies have demonstrated that neoplastic myoepithelial cells are positive for the α-smooth muscle actin (SMA), myosin, and S-100 protein and that the glial fibrillary acidic protein (GFAP) lines the cyst-like spaces and surrounds the periphery of epithelial nests. The cribriform spaces are filled with PGs that are positive for ruthenium red stain, which are produced by neoplastic myoepithelial cells. The collagenous fibrillae and elastic fibres are the main components of the hyaline protein cylinder, which are synthesised intracellularly and released into the pseudocysts by neoplastic myoepithelial cells[14-17]. The presence of collagen may be correlated with the pathological type, the tumour, node, metastases (TNM) stage, and metastasis of ACC[18].

The pseudocyst enlargement and replicated basal lamina are associated with neoplastic myoepithelial cells diffusing outward[15,19]. These cells, producing the basement membrane-type heparan sulfate PG (HSPG), known as perlecan, tend to form initial structures of stromal pseudocysts[20,21]. PGs, such as chondroitin 6 sulfate proteoglycans (C6SPGs), chondroitin 4 sulfate proteoglycans (C4SPGs), dermatan sulfate proteoglycans (DSPGs), HSPGs, and keratan sulfate proteoglycans (KSPGs), are distributed in the centre of pseudocysts and peripheral solid and cluster structures of ACC. Additionally, myoepithelial tumour cells are positive for PGs, and the hyaluronan (HA), link protein (LP), and the HA-LP-versican complex have been observed in the pseudocyst space of the cribriform structures in ACC[22,23].

Characteristic cribriform structures similar to ACC could appear in other salivary gland tumours, e.g. basal-cell adenoma[24,25]. In basal cell adenoma, a small amount of neoplastic myoepithelial cells is present surrounding the base of the strand and tubular structures or dispersed among the strand cells. The ruthenium red-positive granules of PGs are visible in the secretory vacuoles and intercellular spaces of neoplastic myoepithelial cells of basal-cell adenoma[26,27].

PGs produced by neoplastic myoepithelial cells mediate the formation of characteristic cribriform structures; thus, this histopathological feature appears in both ACC and basal-cell adenoma. However, in the solid-type ACC, the cuboidal tumour cells are arranged in dark epithelial islands and may sometimes have neoplastic myoepithelial cells in the centre. These structures are not obvious cribriform structures, and the amount of PGs in the centre of the tumour cell nests is insufficient, which may result in necrosis.

Thus, the histological structures and subtype of ACC depend on the PGs content and distribution. PGs are produced by neoplastic myoepithelial cells in the tumour. The ACC has low microvessel density, which suggests that ACC does not depend on neo-angiogenesis[28]. The presence of PGs provides a rich source of nutrition for ACC cell proliferation.

Proteoglycans and histogenesis of pleomorphic adenoma

Salivary PA is considered a ‘mixed tumour’ because the epithelial elements are intermingled with mucoid-, myxoid- and chondroid-type tissues[10,11]. The tumours are characterised microscopically by increased structural pleomorphism; architectural complexity, given by the multitude of cytological differences; and proliferation patterns. Tumours also exhibit diverse stromal components, which consist of neoplastic epithelial cells and neoplastic myoepithelial cells. In the tumour, major myoepithelial cells are the main proliferating components[8,9,29].

Ultrastructural studies have revealed that two cell types, i.e. luminal epithelial and myoepithelial cells, are often identified in compact and highly cellular regions. The main cell type in the myxoid and chondromyxoid regions is a type of structurally modified myoepithelial cell, and a variety of myoepithelial cell modifications, such as squamous and chondroid metaplasia, have been observed[30,31].

Immunoelectron microscopic and immunohistochemical studies have indicated that neoplastic myoepithelial cells show different morphologic features. For example, cells can exhibit spindle, stellate, polygonal, angular and plasmacytoid shapes, and be positive for α-SMA, myosin, S-100 protein, and GFAP. In the myxoid region, some neoplastic myoepithelial cells exhibit early chondroid differentiation[32-34].

Electron microscopic histochemical studies revealed that PGs of the myxochondroid stroma could be visualised as numerous, extracellular, 25 to 50 nm ruthenium red-positive, polygonal matrix granules with fine projecting filaments. Similar positive ruthenium red-stained intracellular granules were observed within

the Golgi-derived vacuoles of neoplastic myoepithelial cells in the myxochondroid region. Some cells located at the periphery of the double-layer ductal structure had the features of neoplastic myoepithelial cells and showed similar positive ruthenium red-stained granules in the intracellular vacuoles and intercellular space. These observations indicated that the neoplastic myoepithelial cells in the myxoid region were probably derived from the periphery of the double-layer ductal structure[35-37]. In addition, neoplastic myoepithelial cells have the ability to synthesise and secrete procollagen and precursors of elastin, thus forming collagenous fibres and elastic fibres, which constitute the trestle and are distributed in myxochondroid areas[38].

Small and large PGs, including decorin, biglycan, PG-M/versican, aggrecan, and HA, were detected in salivary PA. Both aggrecan and biglycan play important roles in chondroid differentiation and morphogenesis, particularly in the myxoid stroma[23,39-41]. Aggrecan also exhibits constant positive reactivity in transition regions from tubular proliferative units to myxoid areas, which were implicated in the trans-differentiation of neoplastic myoepithelial cells from the myxoid zones to the lacuna cells of adjacent chondroid areas, completing the morphology of this salivary gland tumour[42].

Lumican, a keratan sulfate PG, is a small, leucine-rich, repeat PG that has been reported to be associated with cartilage formation. Lumican is predominantly deposited in the hyaline, fibrous, and chondroid areas and is associated with the formation of mesenchyme-like structures in salivary PA[43].

Perlecan is distributed in the myxoid stroma and ductal structures of PA, and the tumour cells are able to invade the capsule and involve blood vessels when they are situated in a perlecan-rich milieu[44].

The myxoid stroma and chondroid areas also exist more or less in benign and malignant myoepithelial tumours of the salivary glands[45-47]. Myoepithelioma cells are capable of secreting PGs and form the myxoid region. Myoepithelioma cells can also synthesise and secrete procollagen and a precursor of elastin, which can form collagenous and elastic fibres in the stroma; thus, the appearance of the myxoid region is similar to that of PA and myoepithelioma[48,49].

However, normal myoepithelial cells of the salivary gland structurally resemble both epithelial cells and smooth muscles, also called basket cells. These cells are flat, stellate and spindle-shaped, and surround the acinus and intercalated duct. They constrict to help the discharge of secretions[50]. After the cells transform into neoplastic myoepithelial cells, they acquire strong secreting functions and can secrete PGs, procollagen and elastin precursors[15,16,27,35-38,48,49]. Neoplastic myoepithelial cells manifest a different morphology and phenotype than the normal myoepithelial cells[51-60] and are thus responsible for the myriad histopathology of salivary gland tumours[61]. Therefore, the different morphological features and histological types of salivary ACC and PA may depend completely on the amount and distribution of PGs produced by the neoplastic myoepithelial cells.

Role of proteoglycans in the biological behaviours of adenoid cystic carcinoma and pleomorphic adenoma

Proteoglycans and the biological behaviours of adenoid cystic carcinoma

Salivary ACC is a rare tumour that accounts for approximately 10% of all salivary gland tumours. ACC is characterised by slow, asymptomatic growth and local invasiveness with frequent recurrence, metastasis and perineural invasion[62-73]. The metastasis sites of ACC cases include the lung, bone, liver, brain, pancreas, sternum, cecum, ileum and colon, among which the lung is the most frequent metastatic site[74-81].

Metastasis of tumours is a complex, multistep biological process involving a multitude of genes and biomolecules[82-91]. Genetic rearrangements, hotspot mutations, oncogene expression and signalling pathways are involved in the carcinogenesis and progression of metastatic ACC of the salivary gland[92-110]. PGs are important components of the ECM and play an active role in tumour growth and progression[111-116]. For example, HA and versican interact to create pericellular coats and open spaces, which facilitate cell sorting, proliferation, migration and survival. Two small, leucine-rich PGs, i.e. biglycan and decorin, play pivotal roles in the regulation of cellular pathways that are intrinsically involved in cancer initiation and progression. In highly metastatic tumours, tumour endothelial cells interact with tumour cells by secreting of a small leucine-rich repeat PG known as biglycan. Biglycan then stimulates the metastasis of tumour cells. Metastatic melanomas show a significant increase (up to 15-fold) in perlecan mRNA levels when compared with normal tissue. Moreover, ACC-M cells of the salivary gland, which exhibit high metastatic activity, also show a higher expression of HSPG than ACC-2 cells, which have low metastatic activity[117-121]. Thus, rich PGs, such as HSPG, C6SPG, C4SPG, DSPG and KSPG, are distributed in three histological regions in the salivary

gland ACC produced by neoplastic myoepithelial cells[20-23,122]. In the clinical setting, distant metastases of ACC also develop in three histological types, i.e. cribriform, tubular and solid[81,123-126]. However, the roles of PGs in the metastasis of ACC are still unclear.

PGs are widely distributed in the human body and participate in diverse interactions vital for physiological and pathological processes[127]. Both the pulmonary and nervous systems are rich in PGs, such as heparan sulfate (HS), chondroitin/dermatan sulfate (CS/DS), HA and chondroitin sulfate proteoglycans (CSPGs)[128-131], whereas small, leucine-rich PGs are molecules that have signalling roles in various biological processes[132]. CSPGs affect neuronal cell adhesion, spread and neurite growth[133]. Pulmonary metastasis and perineural invasion are the most common complications of salivary ACC; indeed, ACC cells migrate long distances to establish tumours in a new, more suitable environment. During progression to distant ACC metastasis, PGs produced by neoplastic myoepithelial cells may provide a crucial source of nutrition and energy for cell adhesion, diffusion, migration, proliferation and infiltration.

Proteoglycan and biological behaviours of pleomorphic adenoma

Salivary PA is the most common benign tumour of the salivary glands and accounts for approximately 45 to 75% of all salivary gland neoplasms. Approximately 80 to 90% of PA occurs in the major salivary glands, preferentially originating in the parotid gland; 10% occurs in minor salivary glands. The onset age ranges from newborns to elderly individuals[134-155]. In the clinical setting, although PA appears to be a slow-growing swelling without symptoms, it is rarely a cause of syncope[156], but frequent implanting growth and recurrence after surgery are observed, and its biological behaviours are actually consistent with those of border tumours[157-167]. The recurrence time of PA after the first operation varies from a few months to more than 10 years, and the overall recurrence rate is approximately 6.7%. Recurrence is the presence of a multifocal tumour that can invade the surrounding organs[168-180]; the tumours are typically accompanied by oncoprotein overexpression, gene mutations and pathway dysregulation[181-184]. Additionally, PA tends to recur and can transform to carcinoma ex PA[185-195]. The rate of malignant transformation in recurrent PA is about 3.3%, and approximately 25% of PA cases exhibit malignant transformation. Multifocal recurrence and carcinoma in PA are observed in 73% and 9% of patients, respectively[196-199]. However, the most important cause of recurrence is enucleation with rupture and incomplete tumour excision at surgery. More accurately, recurrence is thought to occur because of small islands or residual tumour cells left behind at surgery. Most recurrent PA is multinodular[200-202]. Salivary PA tends to exhibit implanting growth once the tumour is ruptured, allowing the tumour cells to leak out and form multiple nodular tumours or develop as a string of beads along the surgical incision during recurrence.

Generally, tumour implanting growth requires two conditions: nutrient-rich gelatinous matrix and seeds of tumour cells. Salivary PA consists of epithelial elements intermingled with tissues of mucoid, myxoid or chondroid appearance, usually with capsular infiltration[203], formerly called mixed tumours. The myxoid stroma contains rich PGs and tumour cells[38-43] and leaks out easily if the capsule is accidentally ruptured during surgery. If the conditions are appropriate, the tumour will grow. During the growth of implanted PA cells, rich PGs in the tumour may provide abundant nutrients for cell adhesion, proliferation and implanted growth. High expression of MUC1/DF3 in the primary lesions is observed more frequently in patients with recurrence[204,205].

Metastases of PA may occur years after the initial disease, in association with local recurrence[206,207]. In most cases, metastases occur due to carcinoma ex PA[208-211]. However, metastasising PA is not rare; it is histologically identical to benign PA and inexplicably metastasises. Clinical, rather than pathologic, evidence seems to justify the inclusion of metastasising PA in the group of low-grade malignant salivary tumours. The most common sites for metastases are the bone, lung, liver and neck lymph nodes, or simultaneous metastasis in both lungs and liver[212-218]. Interestingly, such metastasis can be present in either benign PA or carcinoma ex PA, and gene mutations and abnormal expression are rarely involved in metastasis[219-222]. In studies where the mechanisms of metastasis for benign PA and carcinoma ex PA are compared, their histological structures have both been shown to contain mucoid, myxoid or chondroid areas that are PG-rich[35-44,209-211].

PGs are known to control numerous normal and pathological processes, including morphogenesis, tissue repair, inflammation, vascularisation and tumour metastasis. PGs are also the key molecular effectors of cell surface and pericellular microenvironments; they perform multiple functions in cancer and angiogenesis[1,223,224]. HSPGs and chondroitin sulfate glycosaminoglycans (CS-GAGs) play important roles in the invasion, growth and metastatic properties of cancerous cells[225-231]. The PGs versican, syndecan (SDC) and glypican (GPC-3) are also able to regulate many cellular processes, including cell adhesion, proliferation,

apoptosis, migration, angiogenesis, invasion and metastasis[232-238]. Some small-molecule PGs, such as biglycan, may play an important role in the development and progression of cancer[239], whereas the PG perlecan can degrade basement membranes during the metastasis of cancer[240]. HA has been shown to demonstrate preferential tumour accumulation[241]. In the mucoid, myxoid and chondroid areas of salivary PA, there is a rich distribution of PGs, including HSPGs, CSPGs, HA, decorin and biglycan. The presence of these PGs may provide sufficient nutrition and energy for tumour metastasis in both benign and carcinoma ex PA, thereby providing insights into the apparent metastasis of benign PA.

Synthesis and suppression of proteoglycans

The structure of PGs contains a central core protein with covalently attached glycosaminoglycans (GAGs) and N- or O-linked glycosylation chains. The GAGs include CS, keratan sulfate, DS, HS, HA and some small molecules[242-248].

In the biosynthesis process of PGs, xylosyltransferases I and II (XT-I and XT-II), the chain-initiating enzymes in the biosynthesis of PGs, catalyse the transfer of D-xylose from UDP-D-xylose to specific serine residues of the core protein. Therefore, XT-I and XT-II are the key enzymes in PG biosynthesis and are an important fraction of the ECM. The amino acid sequence of the XT-II isoform shares 55% identity with human XT-I; XT-II is also likely to have crucial regulatory roles in the biosynthesis of PGs[249-255].

Silencing the UDP-galactose-4-epimerase gene with specific siRNAs results in marked inhibition of PG synthesis in human articular chondrocytes[256]. Inhibiting GAG chain polymerisation can decrease the inhibitory activity of astrocyte-derived CSPGs[257].

To investigate the effects of PG downregulation on the proliferation of human salivary ACC, we designed and constructed short hairpin RNA (shRNA) plasmids, i.e. shRNA WJ1–WJ6, silencing the human XT-I gene. shRNA-WJ3 showed the most powerful RNA interference and gene silencing effects, followed by shRNA-WJ4[258,259]. A rabbit polyclonal antibody against human XT-I was successfully prepared[260]. Then, shRNA-WJ7, which silenced XT-II (shRNA-XT-II), was designed and constructed[261]. These constructs were successfully applied to silence the XT-I and XT-II genes by RNA interference (RNAi); the biosynthesis of PGs was effectively suppressed in salivary ACC and PA[261-265].

Owing to similarities between the amino acid sequences of XT-I and XT-II, which are ubiquitously expressed in human tissues, XT-I was silenced using shRNA-WJ3 and shRNA-WJ4, and XT-II was silenced using shRNA-WJ7. The biosynthesis of PGs is inhibited in the same way. In the overproduction of different PGs in tumourigenesis or abnormal deregulation of PGs in tumours[266-269], plasmid vectors used for silencing the human XT-I and XT-II genes can also provide new measures that aim at PG inhibition against other tumours, including benign and malignant myoepithelioma of the salivary glands.

Salivary adenoid cystic carcinoma and pleomorphic adenoma rely on proteoglycans

Proteoglycans contribute to perineural growth and pulmonary metastasis of adenoid cystic carcinoma

Perineural invasion in adenoid cystic carcinoma

Despite acknowledgment of the clinical significance of perineural invasion, the underlying mechanisms remain unclear. Perineural invasion is known to result from a balanced, symbiotic relationship between the tumour and the host microenvironment. The propensity of salivary ACC to invade the nerves depends on various factors, including the properties of cancer cells and the ECM. Current studies on perineural invasion have recently shifted to focus on neurotrophic factors, chemokines, cellular adhesion molecules and the microenvironment; for example, molecules such as C-C motif chemokine ligand 5/C-C motif chemokine receptor 5, Slug, ECM metalloproteinase inducer, E-cadherin, Notch-4, and neural cell adhesion molecules, are involved in this process[270-274].

CSPGs have been found in salivary ACC invasive perineural tissue, which contains multiple PGs, including HSPGs[275,276]. These PGs participate in peripheral nerve terminal differentiation[277-279], provide a support structure and an attachment site for cells, and may play important roles in perineural invasion. PG subtypes, such as SDC-3, GPC-1, and SDC-2[280-282], are involved in neural invasion. Moreover, we found that the downregulation of the XT-I gene in ACC cells by RNAi leads to a reduced secretion of PGs, and the neurotropic invasion behaviours of salivary ACC were obviously inhibited in vivo[263]. These insights indicated that perineural invasion of ACC involved PGs produced by neoplastic myoepithelial cells.

Pulmonary metastasis in adenoid cystic carcinoma

Many factors are involved in the lung metastasis of salivary ACC[95,283,284]. However, PGs, as major components

of the lung ECM, are present throughout the lung[285] and can cause the invasive-tumour phenotype[286]. High expression of these PGs in tumours is also related to lung metastasis[287-296]. Additionally, silencing of the XT-I gene in SACC-M cells (a salivary ACC cell line showing a high frequency of metastasis to the lung) by shRNA-WJ3 and shRNA-WJ4 significantly suppresses the biosynthesis of PGs. Moreover, reduction of PG content can inhibit cell adhesion, invasion and lung metastasis in SACC-M cells. Lung metastasis from salivary ACC has been shown to involve PGs produced by neoplastic myoepithelial cells[264].

In further research, we found that the expression of GPC-5 (a subtype of HSPGs) increased more than threefold in SACC-M cells compared with that in SACC-2 and SACC-83 cells (two cell lines with low lung metastasis potential). In the clinic, the expression of GPC-5 in patients with ACC with lung metastasis was much higher than that in patients without lung metastasis. Lung metastasis of SACC-M cells was obviously decreased after the silencing of GPC-5 in vivo. Moreover, the silencing of the GPC-5 gene could more effectively and accurately suppress lung metastasis of salivary ACC[297]. PGs are necessary and essential for the proliferation, perineural invasion and lung metastasis of salivary ACC. Indeed, strong evidence has shown that salivary ACC relies on PGs. However, these PGs are produced by neoplastic myoepithelial cells, not normal myoepithelial cells.

Proteoglycans are involved in the implanting growth of pleomorphic adenoma

The growth of implanted salivary PA is a unique and rare biological behaviour in salivary gland tumours. Based on histological structure, salivary PA contains rich PGs in mucoid-, myxoid- and chondroid-type tissues. In the clinical setting, salivary PA shows potential malignant tendencies, implanting growth and recurrence.

The connections between PGs and their biological behaviours have not been fully elucidated due to difficulties in obtaining sufficient evidence. In early 2003, we established a method for primary cell culture of salivary PA[298]. Until 2012, we applied acellular dermal matrix, a popular material widely used in the laboratory and the clinic[299-305], as a scaffold, and cultured fibroblasts from the tumour capsule or subcutaneous connective tissue to construct tissue-engineered fibrous tissue from the same patient, constituting a minimally permissive microenvironment[306-313]. We implanted salivary PA cells on this tissue-engineered fibrous tissue and subsequently transferred the tissue/cells subcutaneously into nude mice, establishing a patented living tissue model of human salivary PA through a tissue-engineered method (patent no. ZL 2012 1 0570059.5; National Intellectual Property Office of the People's Republic of China)[261,262]. This model of established salivary PA is a new breakthrough contributing to research methods for investigation of salivary PA and salivary PA implanting growth.

XT-I or XT-II gene silencing in salivary PA using shRNA-WJ4 or shRNA-WJ7 efficiently suppresses the biosynthesis of PGs. Additionally, salivary PA cells completely lose proliferation, invasion, migration and implantation abilities[261,262]. Thus, these findings showed that in salivary PA, the survival and biological behaviours rely on the existence of PGs secreted by neoplastic myoepithelial cells, and that neoplastic myoepithelial cells must produce PGs for salivary PA cells to proliferate, invade, migrate and exhibit implanting growth. Accordingly, factors other than the morphological complexity of the tumour can cause some diagnostic difficulties and pitfalls[314-316].

Future perspectives

Neurotropic growth and pulmonary metastasis in salivary ACC and implanting growth of salivary PA are very difficult to combat during clinical treatment. Clinicians hope to improve the biological safety of vectors to silence the XT-I and XT-II genes for clinical use, enabling suppression and inhibition of salivary ACC and PA, which rely on the presence of PGs. Treatments targeting PGs could improve surgery outcomes to reduce or eliminate lung metastasis and nerve invasion by salivary ACC and to avoid implanting growth of salivary PA.

Furthermore, treatments targeting PGs may be superior to traditional surgery and provide patients with novel treatment options without pain or scarring. Moreover, such treatments could avoid the risk of facial nerve damage in patients with parotid ACC and PA and could improve the quality of life of patients.

Conflicts of interest

The authors declare no conflicts of interest related to this study.

Author contribution

Dr Jie WANG drafted most parts of the manuscript and revised the whole manuscript; Dr. Yan Ning ZHANG helped in drafting part IV of the manuscript.

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