P120 catenin expression and its correlation with E-cadherin in salivary gland neoplasms

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ABSTRACT

Objectives: Altered P120 catenin expression has been associated with E-cadherin loss and poor prognosis in several cancers. The objectives of this study were to examine the P120 catenin expression in salivary gland neoplasms in correlation with E-cadherin and assess the relationships between their expression levels and pathologic characteristics.

Methods: Fifty-two cases of salivary gland neoplasms, i.e. 25 mucoepidermoid carcinomas (MEC), 13 adenoid cystic carcinomas (ACC), 12 pleomorphic adenomas (PA) and 2 polymorphous adenocarcinomas (PAC) were included. The expression of P120 catenin and E-cadherin was investigated immunohistochemically.

Results: Both P120 catenin and E-cadherin were overexpressed in salivary gland neoplasms, compared to normal tissue. P120 catenin was primarily detected on the membrane of neoplastic cells in most cases. A significant correlation between levels of expression of both proteins was noted in MECs. In ACCs and PA, ductal cells showed positive immunoreactivity, whereas myoepithelial cells variably expressed both proteins. Increased P120 catenin expression was significantly associated with the solid subtype of ACCs.

Conclusions: The cadherin-catenin complex is preserved in the heterogeneous tumor cell population in salivary gland neoplasms. Overexpression of P120 catenin may be involved in the progression to solid ACCs.

1. Introduction

Epithelial tissues are characterized by their ability to form cell-to-cell adhesion via several types of junctional units. These structures serve as both physical barriers and regulators of substance transport.¹ This process utilizes a myriad of adhesion molecules and is fundamental to the morphogenesis, differentiation, function as well as the integrity of tissues. The altered expression of several epithelial adhesion molecules has been shown to play a role in the transformation and progression into cancer cells.²

Cadherin and catenin family proteins are vital to the integrity of epithelial tissues through the formation of adherens junctions on the basolateral membrane. E-cadherin is the founding member and key component of cadherin family.³ It is extensively studied and well-recognized as a crucial molecule involved in the cancer suppression. The dysfunction or loss of E-cadherin leads to the enhanced epithelial cell migration and invasion. This is crucial in the process of epithelial-mesenchymal transition commonly found in epithelial cancers.^{4–7} Several

studies reported the association between the depleted E-cadherin expression and the development or advanced progression in many cancers, including breast, gastric, lung, colon, skin, renal, hepatocellular and esophageal carcinomas.⁸

P120 catenin is one of the armadillo catenins, specifically interacting with the highly conserved cytoplasmic domain of E-cadherin. It acts to stabilize the adherens junctional complex.⁹ In addition, it also serves other cellular processes, such as the cytoskeletal arrangement, cellular signaling and transcription.¹⁰ The role of P120 catenin in cancer development and progression has been established in several studies. Its function can be varied depending on cancer types. The reduced P120 catenin expression was associated with poor prognosis in patients with pancreatic, colorectal, head and neck and esophageal cancers.¹¹ In contrast, it was shown in breast cancers that P120 overexpression induced cancer cell invasion and metastasis.^{12,13}

In addition, several studies demonstrated that the altered localization of P120 catenin from the plasma membrane to cytoplasm was associated with the E-cadherin inactivation in breast, bladder, lung,

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Table 1
Characteristics of 52 patients with neoplasms of salivary gland.

Characteristics	MEC (25)	ACC (13)	PA (12)	PAC (2)
Sex				
Male	10	3	3	1
Female	15	10	9	1
Male:Female ratio	1:1.5	1:3.3	1:3	1:1
Age (years)				
Mean $\pm$ SD	43 $\pm$ 18.9	39.5 $\pm$ 14.7	36.8 $\pm$ 11.4	60.5
Range	16–81	16–65	21–62	56–65
Sites				
Palate	18	9	8	1
Alveolar mucosa	4	1	0	1
Buccal mucosa	0	1	1	0
Retromolar mucosa	2	0	0	0
Floor of mouth	1	2	1	0
Upper lip	0	0	2	0

pancreatic, prostate and gastric cancers.¹¹ In E-cadherin-negative breast and colon cancers, the cytoplasmic localization of P120 catenin is associated with the aggressive cancer phenotypes and poor patient survival.^{14,15}

E-cadherin has been shown to be differentially expressed in various salivary gland neoplasms.^{16–18} The expression of P120 catenin in salivary gland neoplasms has not been previously reported in the literature. A study in normal mouse salivary gland showed that conditional inactivation of P120 catenin resulted in the abrogation of acinar development, reduction of E-cadherin and transformation to high-grade intraepithelial neoplasia.¹⁹ This suggested that the altered expression or localization of P120 catenin may potentially take part in salivary gland tumorigenesis.

Therefore, the objectives of this study were to examine the expression of P120 catenin in 4 types of salivary gland neoplasms in correlation with the E-cadherin expression, and to determine the relationship between the levels of expression of both proteins with the pathologic characteristics of these neoplasms.

2. Materials and methods

2.1. Tissue samples

Paraffin-embedded tissues of 4 types of salivary gland neoplasms, i.e. mucoepidermoid carcinoma (MEC), adenoid cystic carcinoma (ACC), pleomorphic adenoma (PA), and polymorphous adenocarcinoma (PAC), were obtained from the collection of Department of Oral Pathology from 1997 to 2017. Cases with adequate demographic/clinical data and sufficient tissue specimens were included.

All tissues were reassessed histopathologically. Prognostically

relevant microscopic attributes of MECs were documented. These features include the intracystic components < 25%, perineural, vascular or bone invasion, tumor necrosis, increased mitotic activity > 4/10 HPFs, nuclear atypia and tumor front invasion in small nests. MEC was graded based on the histopathologic criteria from Brandwein et al.²⁰ ACCs were separated into the cribriform, tubular or solid subtypes, depending on the principal microscopic pattern. This research protocol was authorized by the Human Research Ethics Committee of the Faculty of Dentistry, Chulalongkorn University (HREC-DCU 2017-024).

2.2. Immunohistochemical methods

The Bond Polymer Refine Detection kit (Leica Biosystems, Bannockburn, IL) was used for all immunohistochemical staining with Leica Bond-Max Autostainer. Five μ m-thick sections were deparaffinized with the Bond Dewax Solution and incubating with the Bond Epitope Retrieval Solution 2 for 30 min at 100 °C. Slides were then applied with 3% hydrogen peroxide for 5 min. This was followed by 40-min incubation with either the anti-P120 catenin antibody (Dilution 1:200, clone MRQ-5, Cell Marque, Rocklin, CA, USA) or anti-E-cadherin antibody (Dilution 1:600, clone EP700Y, Cell Marque, Rocklin, CA, USA) at room temperature. The 8-min incubation each with Post Primary Polymer and Polymer Poly-HRP IgG were then performed, respectively. The Bond Wash Solution was used to rinse slides between steps. Afterwards, diaminobenzidine was applied for 4 min. Slides were then rinsed deionized water and counterstained with hematoxylin. Breast cancer tissues were utilized as positive controls for both P120 catenin and E-cadherin expression. The isotype-matched mouse IgG1 was used in place of both antibodies for negative controls.

2.3. Immunohistochemical evaluation

Authors were blinded from the subject clinical or pathological data during the examination of immunohistochemical slides. The percentage of positive tumor cells was semi-quantitatively evaluated and classified into 1–4 staining levels, i.e. 0 = no positive cells; 1+ = percent tumor positivity < 10%; 2+ = percent tumor positivity between 10 and 50%; 3+ = percent tumor positivity between 50 and 80% and 4+ = percent tumor positivity > 80%. The expression of both P120 catenin and E-cadherin was later divided into low expression (groups 0 and 1) and high expression (groups 2, 3 and 4).

Statistical analyses were performed using the IBM SPSS Statistics version 21 (IBM Corporation, NY) for Windows. The means $\pm$ standard deviation (SD) was used to present the continuous variables. The Pearson's chi-square test or the Fisher's exact test was used to evaluate the correlation between the clinical-pathologic parameters and the P120 catenin or E-cadherin expression. Statistical significance was recognized when *P*-value was less than 0.05.

Table 2
P120 catenin and E-cadherin expression in neoplasms of salivary gland and normal salivary gland tissues.

Tissues (n)	Proteins	Levels of immunoreactivity, n (%)					Spearman's rho	
		0	1+	2+	3+	4+	r	P value
SG (17)	P120 catenin	0 (0)	16 (94.1)	1 (5.9)	0 (0)	0 (0)	0.685	0.002
	E-cadherin	0 (0)	15 (88.2)	2 (11.8)	0 (0)	0 (0)		
MEC (25)	P120 catenin	8 (32.0)	5 (20.0)	9 (36.0)	1 (4.0)	2 (8.0)	0.594	0.002
	E-cadherin	1 (4.0)	4 (16.0)	9 (36.0)	4 (16.0)	7 (28.0)		
ACC (13)	P120 catenin	3 (23.1)	7 (53.8)	0 (0)	3 (23.1)	0 (0)	0.534	0.06
	E-cadherin	0 (0)	2 (15.4)	6 (46.2)	4 (30.8)	1 (7.7)		
PA (12)	P120 catenin	0 (0)	9 (75.0)	2 (16.7)	1 (8.3)	0 (0)	0.465	0.127
	E-cadherin	0 (0)	0 (0)	6 (50.0)	3 (25.0)	3 (25.0)		
PAC (2)	P120 catenin	0 (0)	1 (50.0)	0 (0)	1 (50.0)	0 (0)	1.0	NA
	E-cadherin	0 (0)	0 (0)	1 (50.0)	1 (50.0)	0 (0)

Fig. 1. P120 catenin (A) and E-cadherin (B) expression in normal salivary gland tissue. Both proteins were primarily detected on ductal cells and some myoepithelial cells.

Fig. 2. P120 catenin (A) and E-cadherin (B) expression in MECs. Strong immunoreactivity of both proteins was detected regardless of tumor grades.

3. Results

3.1. Clinical and demographic data of subjects

Overall, 52 patients with neoplasms of salivary gland were included. There were 25 MECs, 13 ACCs, 12 PAs and 2 PACs. The average age of subjects was 43 ± 18.9 years for MECs, 39.5 ± 14.7 years for ACCs, 36.8 ± 11.4 years for PAs and 60.5 years for PACs. The ratios of male-to-female were 1:1.5, 1:3.3, 1:3 and 1:1 for MECs, ACCs, PAs and PACs, respectively. Most lesions occurred on the palate (Table 1).

3.2. P120 catenin and E-cadherin expression in neoplasms of salivary gland

Levels of P120 catenin and E-cadherin expression were shown in Table 2. Four types of salivary gland neoplasms examined showed apparent but variable expression of both P120 catenin and E-cadherin. In MEC, the immunoreactivity was noted primarily on the plasma membrane and less frequently in the cytoplasm of the neoplastic cells for both proteins. In ACCs, PAs and PACs, their expression was limited to the cell membrane.

Normal salivary gland tissue showed minimal P120 catenin and E-cadherin expression. Most specimens stained P120 catenin (94.1%) and E-cadherin (88.2%) in less than 10% of the cells. Their expression was primarily localized to the glandular epithelial cells of salivary ducts and some myoepithelial cells. No expression of both proteins was detected in the salivary acinar cells (Fig. 1).

In salivary gland neoplasms, the expression of E-cadherin appeared to be greater than that of P120 catenin in most cases. MECs showed markedly diverse expression of P120 catenin and E-cadherin, varying from negative immunoreactivity to positive tumor staining in more than 80%. ACCs demonstrated moderately diverse expression of P120 catenin and E-cadherin. In contrast, the staining pattern of PAs was relatively uniform. The levels of P120 catenin and E-cadherin expression were significantly correlated in both MECs ($P = 0.002$) and normal salivary gland tissue ($P = 0.002$).

3.2.1. Expression in MEC

P120 catenin expression was noted in 68% of MECs. Most MECs (36%) expressed P120 catenin between 10 and 50% of the tumor cells (level 2+). This was followed by no immunoreactivity (level 0, 32% of the cases) and between 0 and 10% of tumor cells (level 1+), 20% of the cases, respectively. The pattern of staining was varied among cases. The positive staining was noted primarily on the membrane of squamous cells, non-specific ductal cells and some intermediate cells. Mucous-secreting cells and clear cells were primarily negative (Fig. 2A). Only one case (4%) showed P120 catenin expression in both cell membrane and cytoplasm.

All but one MEC cases expressed E-cadherin. Most cases (36%) expressed E-cadherin between 10 and 50% of the tumor cells (level 2+), followed by more than 80% of the tumor cells (level 4+, 28% of the cases). Similar to that of P120 catenin, E-cadherin expression was primarily detected on the membrane of epidermoid cells, intermediate cells and non-specific ductal cells. In addition, the membrane of some

clear cells was also immunoreactive (Fig. 2B). Seven cases (28%) showed E-cadherin staining in both cell membrane and cytoplasm of the tumor cells.

Follow-up data were available in 13 MEC cases (52%) with follow-up period ranging from 1 to 15 years. No recurrence was observed. The associations between P120 catenin or E-cadherin expression and various pathologic features of MEC were examined. No statistically significant association was observed between the levels or the localization of expression of both proteins and pathologic characteristics of MECs (Table 3).

3.2.2. Expression in ACC

Most ACCs (53.8%) showed expression of P120 catenin in between 0 and 10% of the tumor cells (level 1+), equally followed by between 50 and 80% of the tumor cells (level 3+) and no immunoreactivity (level 0), constituting 23.1% of the cases in each group. E-cadherin expression was detected in between 10 and 50% of the tumor cells (level 2+) in the majority of cases (46.2%), followed by between 50 and 80% (level 3+, 30.8% of the cases) and between 0 and 10% of tumor cells (level 1+, 15.4% of cases), respectively (Fig. 3).

The immunoreactivity was noted mainly on the cell membrane for both proteins. Regarding the expression of P120 catenin and E-cadherin in different histopathologic patterns of ACCs. For both proteins, only ductal cells showed positive staining in the cribriform and tubular subtypes. However, in the solid histopathologic pattern, both ductal and myoepithelial cell demonstrated strong immunoreactivity. The low P120 catenin expression was significantly associated with ACCs showing cribriform/tubular histopathologic patterns, whereas solid-typed ACCs expressed high P120 catenin ($P = 0.04$). The correlation between the expression levels of E-cadherin and histopathologic patterns of ACCs was not of statistical significance (Table 3).

Table 3

Correlation between P120 catenin and E-cadherin expression and pathologic characteristics of MEC and ACC.

Pathologic features	P120 catenin			E-cadherin		
	Low	High	P-value	Low	High	P-value
MEC						
Cystic component < 25%						
Present	6	4	0.69	2	8	1.00
Absent	7	8		3	12	
Tumor fronts invading in small nests						
Present	6	8	0.43	1	13	0.133
Absent	7	4		4	7	
Anaplasia						
Present	3	4	0.67	0	7	0.27
Absent	10	8		5	13	
Necrosis						
Present	0	2	0.22	0	2	1.00
Absent	13	10		5	18	
Mitosis > 4/HPFs						
Present	0	1	0.48	0	1	1.00
Absent	13	11		5	19	
Bone invasion						
Present	0	2	0.22	0	2	1.00
Absent	13	10		6	18	
Vascular invasion						
Present	0	2	0.22	0	2	1.00
Absent	13	10		5	18	
Pathologic grade						
Low/Intermediate grade	9	7	0.69	5	11	0.12
High grade	4	5		0	9	
ACC						
Pathologic subtypes						
Cribriform/Tubular	10	1	0.04	2	9	1.00
Solid	0	2		0	2	

A.

C.

B.

D.

Fig. 3. P120 catenin and E-cadherin expression in ACCs. Mild P120 catenin immunoreactivity was detected primarily on ductal cells of the cribriform/tubular subtype of ACCs(A), whereas solid subtype (B) showed strong expression. E-cadherin showed strong expression of both cribriform/tubular (C) and solid (D) subtypes.

A.

B

Fig. 4. P120 catenin (A) and E-cadherin (B) expression in PAs. Ductal cells uniformly showed positive immunoreactivity to both proteins, whereas the staining was varied in myoepithelial cells among cases.

3.2.3. Expression in PA

All PAs expressed both P120 catenin and E-cadherin. Most cases (75.0%) showed P120 catenin expression between 0 and 10% of the tumor cells (level 1+), followed by between 10 and 50% of the tumor cells (level 2+, 16.7% of cases) (Fig. 4A). Half of the PA cases expressed E-cadherin between 10 and 50% of the tumor cells (level 2+). The remaining cases showed expression between 50 and 80% (level 3+, 25% of the cases) and more than 80% of the tumor cells (level 4+, 25% of cases). The expression of both proteins was noted mainly on the membrane of ductal cells and some myoepithelial cells (Fig. 4B).

3.2.4. Expression in PAC

Two PAC cases expressed both P120 catenin and E-cadherin on the cell membrane. One case showed expression of both proteins between 50 and 80% of tumor cells. The other case expressed P120 catenin between 0 and 10% of tumor cells and E-cadherin between 10 and 50% of the tumor cells (Fig. 5).

4. Discussion

In this study, we reported the differential expression of P120 catenin in correlation with E-cadherin in 4 distinct types of salivary gland neoplasms. The expression of both proteins was increased in neoplasms compared to normal salivary tissue, with P120 catenin and E-cadherin being expressed in 78.9% and 98.1% of the cases, respectively. The

A.

B

Fig. 5. P120 catenin (A) and E-cadherin (B) expression in PACs. Neoplastic cells in PACs showed positive immunoreactivity to both proteins.

level of P120 catenin expression was generally lower compared to that of E-cadherin. In normal salivary gland tissue, P120 catenin and E-cadherin expression was limited and primarily localized in the membrane of ductal cells and a few myoepithelial cells. Correspondingly in neoplasms, the glandular epithelial cells in MECs, PAs and ACCs remained largely positive for both proteins. Other neoplastic cell populations demonstrated variation in staining pattern. The disparity in expression among neoplasms partly depends on the different amount of each distinct type of tumor cells present in individual cases.

In MECs, the squamous cells and intermediate cells showed variation in number and intensity of positive staining among cases, whereas the mucous-secreting cells and clear cells were primarily negative. Our data supported the findings from previous studies that the strong E-cadherin expression was noted in neoplasms of salivary glands.^{16,18,21} Its level of expression was not correlated with the prognostically related pathologic characteristics of MECs.¹⁷ In addition, we did not find correlations between the pathologic characteristics of MECs and the P120 catenin expression. Significantly, we found the positive correlation between the levels of P120 catenin and E-cadherin in MECs, suggesting that both proteins tend to co-localize in this neoplasm.

Regarding PAs and ACCs, P120 catenin expression was present in most cases albeit at a relatively low level. This could be that the staining was primarily limited to the neoplastic ductal cells, which represented a smaller amount in the mixed population of neoplastic cells in both neoplasms. The differential expression was in part depended on the

number of ductal cells present and the variation in immunoreactivity of myoepithelial cells among cases. The expression of E-cadherin was present in all PA, ACC and PAC cases. We substantiated the data from Cavalcante et al., which observed the decreased expression of E-cadherin in ACCs, compared to PAs.²² It would be of interest to further elucidate whether the loss of E-cadherin is associated with the malignant potential of ACCs.

The loss of E-cadherin was shown to be associated with the cytoplasmic localization of P120 catenin in several cancers.^{14,15,23,24} In this study, we found that in the 4 salivary gland neoplasms examined, the expression of P120 catenin is principally membranous of varying intensity. The cytoplasmic localization of P120 catenin is infrequent and only noted in a portion of neoplastic cells in one case of MEC. Together with the preserved membranous E-cadherin expression, our data suggested that the cadherin-catenin complex is maintained on the neoplastic cell surface in these neoplasms. These results also correspond to the study on genetic level, showing that E-cadherin gene (CDH1)-160C/A polymorphism is uncommon and not related to the E-cadherin expression in PAs and ACCs.²²

In ACCs, it is well-characterized that the solid histopathologic pattern is associated with the worse patient prognosis than either the cribriform or tubular subtype. Significantly, we found the higher P120 catenin expression in solid-subtyped ACCs than those with cribriform/tubular subtype. This finding is of interest in that P120 catenin has been shown to exert the pro-tumorigenic activity in cancers. In breast cancer cell lines, P120 catenin could mediate the ErbB2-induced migration and invasion, via the Rac1 and Cdc42 activation, without the change in E-cadherin expression. In addition, the overexpression of P120 catenin in the ErbB2-positive cancer cell increased its ability to metastasize *in vivo*.¹² In inflammatory breast cancers, the P120 catenin/E-cadherin complex overexpression is associated with the increased invasion and the formation of tumor emboli in response to eIF4G1 overexpression.¹³ Therefore, it could be valuable to examine in future studies whether the P120 overexpression in solid ACCs is associated with the enhanced invasion and overall aggressiveness of this subtype.

The potential therapeutic interventions for cancers with altered or loss of P120 catenin/E-cadherin expression have been implicated. However, any regimens will likely need to customize to specific tumor type.¹ Soto et al. suggested that targeting Rac and MAPK signaling might be beneficial in treating E-cadherin-silenced breast cancers from hypermethylation. Alternatively, those with mutant E-cadherin and cytoplasmic localization of P120 catenin might benefit from ROCK inhibitors.²⁵ In E-cadherin-deficient renal cell carcinomas, Yanagisawa et al. suggested that the N-terminal domain of P120 catenin could be a therapeutic target.²⁶ In addition, a recent study in lung adenocarcinoma showed that the abnormal P120 catenin expression was associated with the increased resistance to EGFR tyrosine kinase inhibitors. This suggested that P120 catenin might also be useful as a predictive marker of therapeutic outcome.²⁷

In conclusion, we provide evidence that both P120 catenin and E-cadherin are overexpressed in salivary gland neoplasms. The levels of P120 catenin and E-cadherin expression are significantly correlated in MECs. The differential expression of both proteins partly corresponds to the varying population of neoplastic cells present in salivary gland neoplasms. The cytoplasmic localization of P120 catenin is a rare event in these neoplasms. P120 catenin may play a role in the progression to the more aggressive solid histopathologic subtype of ACC.

Disclosures

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Appendix A. Supplementary data

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