# **ORIGINAL ARTICLE**



# Expression of amine oxidase-related proteins in breast phyllodes tumor

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**Summary.** Background. Breast phyllodes tumors (BPTs) are difficult to differentiate from other tumor types. Indepth research is needed due to the insufficient description of the amine oxidase protein family, particularly in BPTs.

Objective. This study investigated the expression and clinical implications of amine oxidase-related proteins in BPTs. METHODS: Tissue microarrays were constructed (n=181), and amine oxidase-related proteins of monoamine oxidase (MAO) A, MAOB, lysyl oxidase (LOX), and primary-amine oxidase 3 (AOC3) were assessed using immunohistochemical staining. Staining patterns of these proteins were compared and analyzed with clinicopathologic parameters.

Results. In all, 149, 27, and 5 cases were classified as benign, borderline, and malignant, respectively. A higher grade of BPT was associated with increased MAOB (P<0.001), LOX (P=0.035), and AOC3 (P<0.001) expression. BPT cases with tumor recurrence and distant metastasis had higher proportions of MAOB positivity in stromal components (P=0.002 and 0.018, respectively). During follow-up, there was a significant association between MAOB positivity in the stromal component and shorter disease-free survival (DFS) (P=0.001) as well as overall survival (P=0.003). Moreover, MAOB positivity emerged as an independent factor for shorter DFS (hazard ratio: 4.253, 95% confidence interval: 1.034–17.49, P=0.045).

Conclusions. Higher MAÓB, LOX, and AOC3 expression were observed in higher-grade BPTs, and MAOB expression was identified as a significant prognostic factor.

**Key words:** Amine oxidase, Breast, Phyllodes tumor, Monoamine oxidase B

## Introduction

Breast phyllodes tumors (BPTs) are rare tumors that account for less than 1% of all breast tumors. As a fibroepithelial tumor, it exhibits an overlapping pathologic feature with fibroadenomas and shows heterogenous histologic features within the tumor, which makes it difficult to differentiate it from other tumor types (Tavassoli and Devilee, 2003; Anderson et al., 2004). According to the WHO classification, various histologic classifications have been suggested for BPTs, categorizing them as benign, borderline, and malignant (Tavassoli and Devilee, 2003). The majority of BPTs have a benign feature, and the local recurrence rate ranges between 17 and 27% according to histologic grading, whereas distant metastasis can be present in approximately 22% of cases of malignant BPTs (World Health Organization. and International Agency for Research on Cancer, 2020). The histologic grading of BPTs is comprehensively assessed using the indices of stromal cellularity, stromal atypia, mitosis, stromal overgrowth, and tumor margin. These grading systems appear to be correlated with clinical outcomes, however, they present limitations in that they may not be sufficient in predicting patient outcomes when considering variable clinical features (Lenhard et al., 2008; Karim et al., 2009; Tan et al., 2012). Consequently, researchers have endeavored to examine the expression of diverse immunohistochemical markers in BPTs, aiming to determine their potential as prognostic indicators of patient outcomes (Shubham et al., 2019; Chaudhary et al., 2020; Kim and Koo, 2020; Chen et al., 2021; Jahangir et al., 2021).

Amine oxidase is an oxidative enzyme that cleaves alkylamine aldehydes and ammonia. Amine oxidases can be categorized into two groups, according to their cofactors: (i) as a cofactor of copper: lysyl oxidase (LOX), diamine oxidase (AOC1), and primary-amine oxidase (AOC2 and AOC3) and (ii) as a cofactor of flavin: monoamine oxidase (MAO) A and B (Mondovi and Finazzi Agrò, 1982). Amine oxidases play a role in multiple metabolic pathways that govern cell differentiation, cell signaling, cell growth, detoxification, and wound healing (Kumar et al., 1996). Accumulating



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evidence indicates that amine oxidases also play an important role in carcinogenesis. LOX plays a crucial role in the regulation of tumor cell proliferation, migration, invasion, and metastasis in various human cancers (Ye et al., 2020). The expression of AOC3 is now thought to be related to the prognosis of various cancers (Sun et al., 2017; Lai et al., 2018; Chang et al., 2021). Moreover, aberrant expression of MAOA has been documented to correlate with unfavorable prognoses in various cancer types (Liu et al., 2018; Chen et al., 2020), thereby affecting tumorigenesis and metastasis in prostate cancer (Wu et al., 2014). Finally, high levels of MAOB expression have been reported in human gliomas (Sharpe and Baskin, 2016) and are related to poor prognosis in colorectal cancers (Yang et al., 2020). It could, therefore, be hypothesized that amine oxidases influence cancer biology. However, there is a lack of a comprehensive description regarding the expression of amine oxidase family proteins, particularly in BPTs, within the existing literature, emphasizing the need for further investigation. In the present study, we

Table 1. Source, clone, and dilution of the antibodies used.

Antibody Company Clana Dily	tion	
Antibody Company Cione Dilu	Dilution	
Monoamine oxidase A Abcam, Cambridge, UK EPR7101 1:11 Monoamine oxidase B Abcam, Cambridge, UK Polyclonal 1:11 Lysyl oxidase (LOX) Abcam, Cambridge, UK Polyclonal 1:11 Amine oxidase (AOC3) Abcam, Cambridge, UK Polyclonal 1:11	00 00 00 00	

Table 2. Clinicopathological characteristics of patients with breast phyllodes tumor.

aimed to examine the expression of these proteins in BPTs and the clinical implications.

#### Materials and methods

#### Patient selection

Tissue samples were collected from BPT patients who underwent surgery between 2000 and 2010 at the Department of Pathology of the Severance Hospital. The study received approval from the Institutional Review Board of Yonsei University Severance Hospital. Following fixation in 10% buffered formalin, all surgical specimens were embedded in paraffin. Two pathologists (JS Koo and HM Kim) independently reviewed all archival hematoxylin and eosin (H&E)-stained slides of each case. The histologic grade of BPT was evaluated according to the WHO classification (Tavassoli and Devilee, 2003). Additionally, clinical factors such as age, tumor recurrence, metastasis, and survival were obtained alongside histologic grading, using the H&Estained slides.

#### Tissue microarray

From the H&E-stained slide of the tumor, a specific region was chosen to represent the tumor, and a corresponding spot was identified on the surface of the paraffin block. The selected area was extracted using a biopsy needle, resulting in a 3-mm tissue core, which was then inserted into a  $5 \times 6$  recipient block. To

Parameters	Total n=181 (%)	PT, Benign n=149 (%)	PT, Borderline n=27 (%)	PT, Malignant n=5 (%)	P-value
Age (years, mean±SD)	39.5±12.1	38.9±12.2	42.3±11.5	43.8±7.2	0.297
Tumor size (cm, mean±SD)	3.9±2.5	3.6±2.2	4.3±2.5	9.5±5.0	<0.001
Stromal cellularity					<0.001
Mild	117 (64.6)	116 (77.9)	1 (3.7)	0 (0.0)	
Moderate	56 (30.9)	33 (22.1)	23 (85.2)	0 (0.0)	
Marked	8 (4.4)	0 (0.0)	3 (11.1)	5 (100.0)	
Stromal atypia					<0.001
Mild	152 (84.0)	147 (98.7)	5 (18.5)	0 (0.0)	
Moderate	23 (12.7)	2 (1.3)	20 (74.1)	1 (20.0)	
Marked	6 (3.3)	0 (0.0)	2 (7.4)	4 (80.0)	
Stromal mitosis					<0.001
0–4 / 10 HPFs	150 (82.9)	149 (100.0)	1 (3.7)	0 (0.0)	
5–9 / 10 HPFs	26 (14.4)	0 (0.0)	26 (96.3)	0 (0.0)	
≥10 / 10 HPFs	5 (2.8)	0 (0.0)	0 (0.0)	5 (100.0)	
Stromal overgrowth					<0.001
Absent	173 (95.6)	149 (100.0)	24 (88.9)	0 (0.0)	
Present	8 (4.4)	0 (0.0)	3 (11.1)	5 (100.0)	
Tumor margin					<0.001
Circumscribed	167 (92.3)	146 (98.0)	20 (74.1)	1 (20.0)	
Infiltrative	14 (7.7)	3 (2.0)	7 (25.9)	4 (80.0)	
Tumor recurrence	13 (7.2)	5 (3.4)	6 (22.2)	2 (40.0)	<0.001
Distant metastasis	3 (1.7)	0 (0.0)	1 (3.7)	2 (40.0)	<0.001

PT, phyllodes tumor; HPFs, high-power fields.

minimize extraction bias, two tissue cores were obtained. Each individual tissue core was assigned a distinct location number within the tissue microarray, which was linked to a database containing additional clinical and pathological information.

## Immunohistochemistry

Table 1 provides a list of the antibodies utilized for immunohistochemistry in this study. Immunostaining procedures were conducted on formalin-fixed, paraffinembedded tissue sections using an automated immunohistochemistry staining device (Benchmark XT, Ventana Medical System, Tucson, AZ, USA). In summary, tissue sections with a thickness of 3  $\mu$ m were prepared from paraffin blocks, followed by deparaffinization and rehydration using a xylene and alcohol solution. Antigen retrieval was performed with cell conditioning 1 (CC1) buffer (citrate buffer, pH 6.0; Ventana Medical System). For the negative control, the



**Fig. 1.** Expression of amine oxidase-related proteins according to breast phyllodes tumor (BPT) grade. Following an increase in BPT grade, higher expression of monoamine oxidase B (MAOB), lysyl oxidase (LOX), and primary-amine oxidase 3 (AOC3) was observed in stromal components. Scale bar: 300 μm.

Parameters n=181(%)	Total Benign n=149 (%)	PT, Benign Borderline n=27 (%)	PT, Malignant n=5 (%)	PT,	P-value
MAOA (E)* Negative Positive	84 (48.6) 89 (51.4)	69 (46.6) 79 (53.4)	13 (56.5) 10 (43.5)	2 (100.0) 0 (0.0)	0.232
MAOA (S) Negative Positive	179 (98.9) 2 (1.1)	147 (98.7) 2 (1.3)	27 (100.0) 0 (0.0)	5 (100.0) 0 (0.0)	0.805
MAOB (E)* Negative Positive	53 (30.6) 120 (69.4)	44 (29.7) 104 (70.3)	7 (30.4) 16 (69.6)	2 (100.0) 0 (0.0)	0.101
MAOB (S) Negative Positive	166 (91.7) 15 (8.3)	142 (95.3) 7 (4.7)	21 (77.8) 6 (22.2)	3 (60.0) 2 (40.0)	<0.001
LOX (E)* Negative Positive	16 (9.2) 157 (90.8)	13 (8.8) 135 (91.2)	2 (8.7) 21 (91.3)	1 (50.0) 1 (50.0)	0.135
LOX (S) Negative Positive	43 (23.8) 138 (76.2)	41 (27.5) 108 (72.5)	2 (7.4) 25 (92.6)	0 (0.0) 5 (100.0)	0.035
AOC3 (E)* Negative Positive	136 (78.6) 37 (21.4)	118 (79.7) 30 (20.3)	17 (73.9) 6 (26.1)	1 (50.0) 1 (50.0)	0.500
AOC3 (S) Negative Positive	151 (83.4) 30 (16.6)	130 (87.2) 19 (12.8)	20 (74.1) 7 (25.9)	1 (20.0) 4 (80.0)	<0.001

**Table 3.** Expression of amine oxidase-related proteins according to breast phyllodes tumor grade.

\*Eight tumors without an epithelial component were excluded. E, epithelial; S, stromal.

primary antibody incubation step was omitted, while a positive control tissue was included as recommended by the manufacturer. Harris hematoxylin was used for counterstaining on the slides. The evaluation of all immunohistochemical markers was conducted under light microscopy, and the staining intensity was graded as follows: 0 for negative, 1 for weak, 2 for moderate, and 3 for strong. Cases with a grading of 2 and 3 were considered positive, while those with 0 or 1 were deemed negative.

#### Statistical analysis

Data analysis was performed using IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, NY, USA). To determine statistical significance, the Student's t-test and Fisher's exact test were utilized for continuous and categorical variables, respectively. A significance level of P<0.05 was considered statistically significant. Kaplan-Meier survival curves and log-rank statistics were employed to assess the time to tumor recurrence. Multivariate regression analysis was conducted using a Cox proportional hazards model.

#### Results

#### Basal characteristics of BPTs

The basal characteristics of 181 patients with BPTs



**Fig. 2.** Correlation between clinicopathological parameters and the expression of amine oxidase-related proteins. The positive expression rate of stromal monoamine oxidase B (MAOB), stromal lysyl oxidase (LOX), and stromal primary-amine oxidase (AOC) is higher in the group with moderate or marked stromal atypia than in the group with mild stromal atypia. The group with stromal mitosis  $\geq$ 5/10 high-power fields (HPFs) had higher expression of stromal MAOB and AOC compared with the <5/10 HPF group. Stromal MAOB expression has a higher positivity rate in the group with tumor recurrence and distant metastasis than in those without.

are presented in Table 2. A total of 149, 27, and 5 cases were classified as benign, borderline, and malignant BPTs, respectively. The tumor size increased significantly when the BPT grade was higher (P=0.001), and tumor recurrence and distant metastasis were more frequently found following an increase in BPT grading (P<0.001). In three cases showing distant metastasis, the metastasized organ was identified as the lung.

# Expression of amine oxidase-related proteins according to BPT grade

When assessing the status of amine oxidase-related proteins according to BPT grade, a significant difference was observed in MAOB (P<0.001), LOX (P=0.035), and AOC3 (P<0.001) expression in the stromal component; the expression increased in higher grade BPTs (Table 3). MAOA, MAOB, and AOC3 showed a cytoplasmic staining pattern, whereas LOX showed a nuclear staining pattern (Fig. 1).

## Relationship between clinicopathologic parameters and the expression of amine oxidase-related proteins

The expression of amine oxidase-related proteins based on clinicopathologic parameters indicated that stromal atypia was significantly associated with stromal MAOB (P<0.001), stromal LOX (P=0.004), and stromal AOC3 expression; stromal mitosis differed according to the expression of stromal MAOB (P=0.001) and stromal AOC3 (P=0.006). BPTs with moderate or marked stromal atypia had higher stromal MAOB, stromal LOX, and stromal AOC expression compared with the mild group, and stromal MAOB and stromal AOC expression was higher in the stromal mitosis  $\geq$ 5/10 high-power field (HPF) groups than in those without. Stromal MAOB positivity was more frequent in groups with tumor recurrence (P=0.002) and distant metastasis (P=0.018) (Fig. 2).

# Effect of the expression of amine oxidase-related proteins on disease prognosis

Univariate analysis revealed that the factor associated with shorter disease-free survival (DFS) and overall survival (OS) in patients with BPTs was MAOB positivity in the stromal component (P=0.001 and 0.003, respectively) (Fig. 3 and Table 4). Multivariate Cox analysis demonstrated that the factors associated with a shorter DFS were stromal overgrowth (hazard ratio [HR]: 13.31, 95% confidence interval [CI]: 1.855-95.52, P=0.010) and MAOB positivity in the stromal component (HR: 4.253, 95% CI: 1.034-17.49, P=0.045). Stromal overgrowth also predicted a shorter OS (HR:

Table 4. Univariate analysis of the expression of amine oxidase-related proteins for disease prognosis, using the log-rank test.

Parameters	No. of patients	Disease-free survival		Overall survival		
	Total/recurrence/metastasis	Median survival (95% CI) months	P -value	Median survival (95% CI) months	P-value	
MAOA (E)*			0.299		n/a	
Negative	84/7/2	146 (137-155)		n/a		
Positive	89/4/0	174 (166-182)		n/a		
MAOA (S)			n/a		n/a	
Negative	179/13/5	n/a		n/a		
Positive	2/0/0	n/a		n/a		
MAOB (E)*			0.298		n/a	
Negative	53/5/1	162 (149-176)		n/a		
Positive	120/6/1	173 (166-180)		n/a		
MAOB (S)			0.001		0.003	
Negative	166/9/3	173 (166-179)		179 (176-183)		
Positive	15/4/2	86 (61-111)		101 (83-120)		
LOX (E)*			0.982		0.074	
Negative	16/1/1	166 (145-186)		166 (147-186)		
Positive	157/10/1	171 (164-178)		181 (178-184)		
LOX (S)			0.147		n/a	
Negative	43/1/0	172 (164-180)		n/a		
Positive	138/12/5	167 (158-175)		n/a		
AOC3 (E)*			0.694		0.403	
Negative	136/9/1	170 (162-178)		181 (178-184)		
Positive	37/2/1	147 (136-157)		151 (143-158)		
AOC3 (S)			0.934		0.810	
Negative	151/11/4	169 (162-177)		178 (173-182)		
Positive	30/2/1	146 (130-163)		154 (144-163)		

\*Eight tumors without an epithelial component were excluded. E, epithelial; S, stromal.

#### 97.70, 95% CI: 9.910-963.2, p<0.001) (Table 5).

#### Discussion

In this study, we assessed the expression of four amine oxidase-related proteins (MAOA, MAOB, LOX, and AOC3) in surgically removed BPTs. Our key finding is that as BPT grading increased, so did MAOB, LOX, and AOC3 expression in the stromal component. While there is no previous research specifically focused on amine oxidase-related proteins in BPTs for direct comparison, our results align with studies reporting increased expression of MAOB (Sharpe and Baskin, 2016; Yang et al., 2020), LOX (Liu et al., 2017; Lai et al., 2018; Boufragech et al., 2019; Zhu et al., 2021), and AOC3 (Kostoro et al., 2016; Sun et al., 2017) in various cancers. This suggests that the expression of these proteins may correlate with higher BPT histologic grades. Notably, MAOB expression has been linked to a shift toward mesenchymal gene expression in colorectal cancer (Yang et al., 2020), while AOC3 is associated with myofibroblasts (Hsia et al., 2016; Marttila-Ichihara et al., 2017). LOX, known for its role in collagen and elastin cross-linking, is also highly expressed in myofibroblasts within the tumor microenvironment (Peyrol et al., 1997), supporting our findings of increased expression in BPT stromal components.

The association between MAOB, LÓX, and AOC3 expression in higher-grade BPTs, along with the potential implications for patient outcomes, may be explained by their roles in carcinogenesis. MAO-dependent reactive oxygen species (ROS) production has been implicated in tumorigenesis (Resta et al., 2022), affecting ROS homeostasis and promoting cancer cell antioxidant ability, facilitating the evasion of cell death (Qin et al., 2017; Kirtonia et al., 2020). ROS also activates pathways involved in tumor initiation and progression, such as the NRF2, MAPK, HIF-1 $\alpha$ , and PI3K/Akt pathways (Liu et al., 2020). LOX family proteins catalyze the cross-linking of collagen and elastin, playing essential roles in tissue remodeling. Dysregulation of LOX family proteins is associated with

Table 5. Multivariate analysis of disease-free survival and overall survival in patients with breast phyllodes tumors.

Included factor	Disease-free survival			Overall survival		
	Hazard ratio	95% CI	P-value	Hazard ratio	95% CI	P-value
Stromal cellularity Mild vs.			0.976			
moderate or marked	1.033	0.123-8.683				
Stromal atypia Mild vs.			0.397			
moderate or marked	0.367	0.036-3.738				
Stromal mitosis 0-4/10 HPFs vs.			0.095			
>4/10 HPFs	9.761	0.675-141-1				
Stromal overgrowth			0.010			<0.001
Absent vs. Present	13.31	1.855-95.52		97.70	9.910-963.2	
Tumor margin			0.157			
Circumscribed vs. Infiltrative	0.261	0.041-1.681				
MAOB (S)			0.045			0.331
Negative vs. Positive	4.253	1.034-17.49		2.710	0.363-20.21	



various diseases, including cancer, where they regulate invasion, migration, metastasis, and progression (Bondareva et al., 2009; Baker et al., 2011; Gong et al., 2016; De Donato et al., 2017; Han et al., 2019; Umezaki et al., 2019). AOC3, also known as vascular adhesion protein-1, is involved in leukocyte extravasation, and aberrant leukocyte migration can induce diseases, including cancer (Salmi and Jalkanen, 2019). Tumor infiltrating leukocytes utilize AOC3 to bind to tumor vessels (Yoong et al., 1998; Irjala et al., 2001), and AOC3 gene amplification has been identified in human gastric cancer patients (Varis et al., 2002). Overall, the increased expression of these amine oxidase-related proteins in more aggressive BPT phenotypes suggests their association with carcinogenesis.

The study found that MAOB positivity in the stromal component is associated with adverse patient outcomes, including tumor recurrence and distant metastasis. This aligns with previous research showing that MAOB expression correlates with poor prognosis in colorectal cancer (Yang et al., 2020; Zhang et al., 2022), urinary bladder (Li et al., 2021), and lung adenocarcinoma (Zhang et al., 2020). MAOB expression has also been incorporated into prognostic nomograms for these cancers (Zhang et al., 2020; Li et al., 2021; Zhang et al., 2022). Considering the existence of prognostic nomograms for BPTs (Tan et al., 2012; Zhou et al., 2018; Ma et al., 2021), investigating whether adding MAOB expression improves their predictive value is warranted.

Our findings suggest that targeting MAOB, LOX, and AOC3, which are highly expressed in higher-grade BPTs, could benefit BPT management. MAOB inhibitors, originally used for Parkinson's disease (Fernandez and Chen, 2007; Alborghetti and Nicoletti, 2019), are being investigated for cancer treatment (Sharif Siam et al., 2021). LOX inhibitors, like  $\beta$ aminopropionitrile (Bondareva et al., 2009; Yang et al., 2013; Boufraqech et al., 2015; Natarajan et al., 2019) and dextran sulfate (Xu et al., 2018), show promise in inhibiting cancer cell metastasis and invasion across various cancer types. In addition, the orally bioavailable LOX inhibitor CCT365623 suppresses lung metastasis in an animal model (Leung et al., 2019). AOC3 inhibitors, known for their anti-inflammatory properties and used for the treatment of diabetic retinopathy (Boyer et al., 2021), have potential implications in cancer biology due to the close association between cancer and inflammation (Coussens and Werb, 2002; Singh et al., 2019). Further pre-clinical and clinical studies are needed to evaluate the impact of inhibiting MAOB, LOX, and AOC3 in BPTs.

In conclusion, we found that higher-grade BPTs were associated with the increased expression of the amine oxidase-related proteins MAOB, LOX, and AOC3 in the stromal component. As the expression of MAOB was found to be a significant prognostic factor of BPTs, it can be used as a potential therapeutic target.

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*Declaration of interest.* The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript.

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