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Up-regulation of SIBLING proteins and correlation with cognate MMP expression in oral cancer

Kalu U.E. Ogbureke [a,e,*], Nikolaos G. Nikitakis [b,f], Gary Warburton [c], Robert A. Ord [c], John J. Sauk [b], Jennifer L. Waller [d], Larry W. Fisher [e]

[a] *Department of Oral Biology and Maxillofacial Pathology, AD1442, Medical College of Georgia, 1120 Fifteenth Avenue, Augusta, GA 30912, USA*
[b] *Department of Diagnostic Sciences and Pathology, Greenebaum Cancer Center, Room 4-E-28, Dental School, University of Maryland, 666 West Baltimore Street, Baltimore, MD 21201, USA*
[c] *Department of Oral and Maxillofacial Surgery, Suite 3-G-23, University of Maryland, 666 West Baltimore Street, Baltimore, MD 21201, USA*
[d] *Department of Biostatistics, AE3036, School of Graduate Studies, Medical College of Georgia, Augusta, GA 30912, USA*
[e] *Craniofacial and Skeletal Disease Branch, NIDCR, NIH, DHHS, 30 Convent Drive, Building 30, Room 228, Bethesda, MD 20892-4320, USA*
[f] *Department of Oral Pathology and Oral Medicine, School of Dentistry, National and Kapodistrian University of Athens, Greece*

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Summary Various combinations of the SIBLING family of proteins have been found to be up-regulated in many human cancers and have been linked to different stages of tumor progression, including metastasis. Bone sialoprotein (BSP), osteopontin (OPN) and dentin matrix protein 1 (DMP1) specifically bind and activate MMP-2, MMP-3, and MMP-9, respectively. These proteases have also been shown to play important roles in oral squamous cell carcinoma (OSCC) invasion and metastasis. However, with the exception of OPN, there are no reports on the expression of the family of five SIBLING proteins in OSCC. This study examines the expression patterns of the SIBLING family (and MMP partners when known) in OSCC, correlating expression to outcome variables. Archived paraffin sections of 87 cases of primary OSCC were screened by immunohistochemistry for the SIBLINGs and their MMP partners. Three SIBLINGs (BSP, DSPP, and OPN), were expressed in OSCC, while DMP1 and MEPE expression were never observed. Furthermore, BSP and OPN were always expressed with their known MMP partners, MMP-2 and MMP-3,

* Corresponding author. Address: Department of Oral Biology and Maxillofacial Pathology, AD1442, Medical College of Georgia, 1120 Fifteenth Avenue, Augusta, GA 30912, USA. Tel.: +1 706 721 2526; fax: +1 706 721 3392.
E-mail addresses: kogbureke@mail.mcg.edu (K.U.E. Ogbureke), NNikitakis@umaryland.edu (N.G. Nikitakis), thewarburtons@verizon.net (G. Warburton), rord@umaryland.edu (R.A. Ord), jsauk@umaryland.edu (J.J. Sauk), jwaller@mail.mcg.edu (J.L. Waller), lfisher@dir.nidcr.nih.gov (L.W. Fisher).

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respectively. Poorly differentiated tumors exhibited reduced or no immunoreactivity for BSP and OPN but increased immunoreactivity for DSPP. Seventy eight (90%) cases were positive for BSP and DSPP, while 79 cases (91%) were positive for OPN. Overall, 91% of the cases were positive for at least one SIBLING. There were no correlations between SIBLING expression and tumor size (''T''; of the Union Internationale Contre le Cancer [UICC]-TNM classification for OSCC), and between SIBLING expression and lymph node spread for the T1/T2 tumors. The levels of DSPP expression for floor of mouth and retromolar region tumors were higher than for tongue tumors. Statistically significant correlations were, however, found between the expression levels of BSP and MMP-2 ($p < 0.0001$), BSP and MMP-3 ($p < 0.0001$), and OPN and MMP-3 ($p < 0.0024$). We conclude that BSP, DSPP, and OPN are highly up-regulated in OSCC. While the production of these SIBLINGs is independent of T, they correlate with oral location of tumor, cognate MMP expression, and for DSPP, the degree of tumor differentiation.
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Introduction

Oral cancer is the sixth most common cancer in the world and the incidence of new cases indicates a continuing rise in developing countries.[1,2] About 30,000 new cases of oral and oropharyngeal cancers are diagnosed annually in the United States with about 7,500 resultant deaths.[3,4] For the last four decades, the mortality rate from oral cancer has remained high (~50%), in spite of new treatment modalities.[2] Over 90% of oral malignancies are histologically characterized as oral squamous cell carcinomas (OSCC).[3] Most OSCC patients die as a result of local and regional spread of the disease and not of distant organ metastasis.[2]

On the basis of their common genetic and structural features as well as interactions with other acknowledged family groups such as integrins and matrix metalloproteinases (MMPs), bone sialoprotein (BSP), osteopontin (OPN), dentin sialophosphoprotein (DSPP), dentin matrix protein 1 (DMP-1), and matrix extracellular phosphoglycoprotein (MEPE) have been proposed to constitute a gene family called the SIBLINGs (Small Integrin-Binding LIgand, N-linked Glycoproteins).[5,6] The SIBLINGs are encoded by a tandem cluster of genes within a ~375,000 basepair region of human chromosome 4.[5] The four acidic SIBLING proteins, BSP, OPN, DMP1, DSPP, were discovered many years ago embedded in the mineralized matrices of bone and teeth by many laboratories.[6,7] The basic protein, MEPE, was discovered more recently in association with tumors that cause phosphate wasting, but is also expressed in the skeleton.[8] With the exception of OPN (previously reported to be expressed in non-mineralizing tissues such as the kidney, lactating mammary gland, and certain immune cells,[9–11]) the SIBLINGs were generally thought to be limited to bones and teeth in normal adult tissues. Results of recent studies however indicate that all five members of the SIBLING family are expressed in the ductal epithelial cells of normal adult salivary glands[12] and kidney.[13]

Over the last few years, the up-regulation of the SIBLING family members has been reported for a number of cancers.[14–28] For example, OPN and BSP have been linked with different stages of tumor progression: cell growth; adhesion; migration and/or metastasis,[28] and published reports indicate that various combinations of SIBLINGs are up-regulated in breast,[14,15] prostate,[16,17] lung,[18,19] and colon cancers.[26] High BSP and OPN expression in breast and prostate primary tumors are significantly associated with poor prognosis and the development of bone metastases in these diseases.[17,21–25] More recently, Chaplet and colleagues found that DSPP is up-regulated in prostate cancer.[27] Cancers of these organs however differ from oral cancer in two significant respects. First, cancers of the breast, prostate, lung, and colon are essentially adenocarcinomas while oral cancer is predominantly squamous cell carcinoma. Second, cancers of the breast, prostate, lung, and colon are characterized by their high tendency to metastasize to distant sites early in the course of the disease, while in OSCC distant metastasis beyond regional cervical lymph nodes, if it occurs at all, remains a late event.

Recent reports also document the specific partnering and co-localization of MMP-2, MMP-3, and MMP-9 with three members of the SIBLING family: BSP; OPN; and DMP1, respectively, both *in vitro* and *in vivo*.[12,13,29] There are also numerous reports documenting the expression of MMP-2, MMP-3, and MMP-9 in OSCC tissues and cell lines, but except for OPN,[30–32] there are no reports on the expression of the other SIBLINGs in human OSCC. Sasaguri et al. demonstrated the presence of BSP mRNA and protein in the chemically-induced hamster buccal-pouch OSCC model system.[33]

We have screened archived paraffin sections of surgical resections from 87 patients with primary OSCC for the presence of all five SIBLINGs and the three known MMP partners,[12,13,29] using immunohistochemistry. Our objectives were to determine which of the SIBLINGs and their MMP partners are expressed in OSCC, and the extent to which each expression is related to tumor size (T). In addition, we sought to examine the extent to which SIBLING-MMP expression in the T1/T2 OSCC relate to histologic differentiation, presence or absence of regional lymph node spread, and to other notable variables associated with outcome and prognosis in oral cancer. This is with a view to examining whether such expression provides new opportunities for predicting OSCC aggressiveness and prognosis.

We have limited our analysis of the relationship between SIBLING/MMP expression and prognostic outcomes in OSCC to the small (T1/T2) tumors because of their unpredictable course and outcome. While the large (T3 and T4) tumors, often presenting with preoperative N-positive neck disease, create no controversy as to the treatment approach required, considerable doubt and debate on the best management approach to the T1/T2 OSCC linger. For example, although OSCC patients with T1/T2 lesions often present with clinically negative (N0) nodes, these patients also have

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