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Review Article

Dentistry Section

Maspin as a Tumour Suppressor in Salivary Gland Tumour

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ABSTRACT

Maspin is a protein that belongs to serin protease inhibitor (serpin) superfamily. The purpose of this study was to review the literature concerning the expression of maspin in salivary gland tumours. A literature search was done using MEDLINE, accessed via the National Library of Medicine PubMed interface. Statistical analysis was not done because only seven studies were available in literature, the collected data were different and the results could not be compared. Expression of maspin was down regulated in more aggressive salivary gland tumours. Maspin may function as a tumour suppressor in salivary gland tumours.

Keywords: Maspin, Salivary gland tumour, Tumour suppressor gene

INTRODUCTION

The current WHO histological classification of salivary gland tumours includes 24 malignant epithelial tumours, 10 benign epithelial tumours, one soft tissue tumour (haemangioma), 3 haematolymphoid tumours and secondary tumours. Of all the salivary gland tumours, prevalence of benign tumours is about 54-79% and the prevalence of malignant tumours is about 21-46%. Salivary gland carcinomas are rare, accounting for 0.5% of all cancers and less than 5% of head and neck cancers. Malignant tumours comprise 15-32% of parotid tumours, 41-45% of submandibular tumours, 70-90% of sublingual tumours, and 50% of minor gland tumours [1,2].

Histopathology and immunohistochemistry are critical in the diagnosis of salivary gland carcinoma. Significant advancement has taken place in the field of immunohistochemistry and molecular genetics. Immunohistochemistry can be used to differentiate between luminal and abluminal cells, which can help in understanding the complex architecture of salivary gland tumours and aid in diagnosis and evaluation of prognosis. Molecules which are highlighted in luminal cells include low-molecular-weight cytokeratin, carcinoembryonic antigen, epithelial membrane antigen (EMA) or CD117. Molecules which are highlighted in the abluminal cells are high molecular weight cytokeratins (34β E12 or CK 14), p53 or maspin [3].

Maspin (Mammary serin protease inhibitor) is a protein that belongs to serin protease inhibitor (serpin) superfamily [4]. Serpins (serin protease inhibitors) are single chain proteins containing a conserved domain structure of 37-390 residues usually flanked by amino or carboxy terminal extensions [5]. Maspin has been grouped with ov-serpin subfamily, which includes plasminogen activator inhibitor and squamous cell carcinoma antigens 1 and 2 (SCCA1 and SCCA2). All human ov-serpins are known functional protease inhibitors except maspin. Protease inhibition occurs by serpin reactive site loup (RSL), which is the primary functional domain of serpin family. The maspin RSL is not conserved and shorter than most RSL of the serpin superfamily [6,7].

Maspin was first described in breast myoepithelium, and has since been detected in various normal glandular tissues, such as the prostate, pancreas, ovary and salivary glands, as well as in several benign and malignant types of epithelial neoplasms [8]. Maspin expression is down-regulated in breast, prostate, gastric, melanoma and oral squamous carcinomas but over-expressed in pancreatic, gallbladder, gastrointestinal, colorectal, ovarian and thyroid cancers suggesting that maspin may play different activity in different cells. These conflicting observations might be explained by distinct subcellular localization of maspin in cancer cells (cytoplasmic, nuclear or both cytoplasmicnuclear expression); by interactions with extracellular matrix and its structure and epigenetic modifications [4,9-11]. Maspin suppresses tumour growth and metastasis by inhibiting tumour cell invasion and motility [4,12,13].

MASPIN IN SALIVARY GLAND TUMOURS

Maspin has been detected in a series of salivary gland tumours [14-20]. We have done a review of literature concerning the expression of maspin in salivary gland tumours.

A literature search was done using MEDLINE, accessed via the National Library of Medicine PubMed interface (http://www.ncbi.nlm.nih.gov/pubmed), searching for articles relating to the expression of maspin in different types of salivary gland carcinomas written in English. We used the following search string: maspin and salivary gland tumours from 1980-2013. We also used the "Related Articles" featured of PubMed to identify further references of interest within the primary search. These references were obtained, and from their bibliographies, pertinent secondary references were also identified and acquired. The process was repeated until no further new articles could be identified. The abstracted literature was reviewed. Studies describing case series and miscellaneous clinical reports were retrieved. Seven studies were taken into consideration, which involved the expression of maspin in the salivary gland tumours. These were evaluated by two pathologists to determine their agreement with the suggested criteria.

Statistical analysis was not done as there were only seven studies in the literature and there were differences among these studies in the collected data and the method of assessment. So the results of these studies could not be compared. These studies are summarized in [Table/Fig-1].

Animmunohistochemical analysis was done by Navarro et al., [14], on eight cases of pleomorphic adenoma, two cases of epithelial-myoepithelial carcinoma, seven cases of adenoid cystic tumour (two of the tubular type, three cribriform and two solid) and three cases of normal salivary glands to evaluate the presence of maspin. Three patterns of immunostaining were seen: cytoplasmic, nuclear or both. It was observed that normal salivary gland cells had low levels of maspin compared to the tumour cells. Pleomorphic adenoma had a high expression of maspin in non-luminal cells and a low expression in spindle cells and occasional luminal cells. Epithelial myoepithelial carcinoma showed intense cytoplasmic and nuclear reactivity in all cells. In adenoid cystic carcinoma, tubular type had a strong positive expression in luminal and myoepithelial

Authors	Year	Type of study	Number of patients
Navarro et al., [14]	2004	Case series	8 Pleomorphic adenoma (PA) 2 Epithelial myoepithelial carcinoma 7Adenoid cystic carcinoma 3Normal salivary gland
Martins et al., [15]	2005	Case series	16 Carcinoma ex pleomorphic adenoma (CXPA)
Prasad et al., [16]	2008	Case series	23 adenoid cystic tumours 24 polymorphous low grade adenocarcinoma
Schwarz et al., [17]	2008	Case series	25 Adenoid cystic carcinoma 15 Mucoepidermoid carcinoma 13 Carcinomas ex pleomorphic adenoma 12 Salivary duct carcinoma 11 Acinic cell carcinoma
Jun et al., [18]	2008	Case series	58 mucoepidermoid carcinoma
Vered et al., [19]	2010	Case series	7 Low grade variant of mucoepidermoid carcinoma (LGMEC)
Yang et al., [20]	2010	Case series	7 Myoepithelial carcinomas of minor salivary glands
Ghazy et al., [21]	2011	Case series	15 mucoepidermoid carcinoma 14 Adenoid cystic carcinoma (12cribriform and 2 solid pattern) 3 Epi-myoepithelial carcinoma 5 Salivary duct carcinoma 5 Malignant pleomorphic adenoma 6 Low grade adenocarcinoma 5 Acinic cell carcinoma

[Table/Fig-1]: Maspin in salivary gland tumour

cells, cribriform adenoid cystic carcinoma had only few positive cells of luminal type and solid type showed rare positive cells in the core region of nest. Another major finding in this study was maspin was totally negative in areas of anaplasia in all three variants of adenoid cystic carcinoma. Myoepithelial cells lining acini periphery showed a strong nuclear and cytoplasmic immunoreactivity for maspinin normal salivary glands.

Martins et al., [15] investigated the presence and distribution of carcinoma ex pleomorphic adenoma (CXPA) in 16 cases. It was observed that non-luminal cells in the duct-like structures of the remnant pleomorphic adenoma were strongly positive for maspin, whereas only a few luminal cells were immunopositive. A few positive cells were seen in the frequent hypocellular and hyalinised areas. Maspin was abundantly expressed, mainly in non-luminal cells, in transitional areas of CXPA with only epithelial differentiation. In carcinomatous areas, there was a gradual decrease in maspin expression. Almost all cells were maspin positive in CXPA with a myoepithelial component.

An immunohistochemical study was done by Prasad et al., [16] to distinguish adenoid cystic carcinoma from polymorphous low grade adenoid cystic carcinoma. This study was done on 23 adenoid cystic carcinoma and 24 polymorphous low grade adenocarcinoma cases. Maspin was expressed in all the adenoid cystic carcinoma cases (23/23) and in 92% of polymorphous low grade adenoid cystic carcinoma cases (22/24).Maspin was expressed in the nucleus and cytoplasm of abluminal cells, intermediate cells and in some luminal cells and its expression was diminished in adenoid cystic tumour with solid areas.

In a study done by Schwarz et al., [17], they concluded that loss of maspin could be considered as a negative prognostic factor in common salivary gland tumours. Immunohistochemical analysis was done on paraffin embedded specimens of 76 patients who underwent treatment at the University of Regensburg between 1990 and 2006. Clinical data and follow up information were collected. Nuclear and cytoplasmic staining of maspin were considered separately and combined and was valued positive if more than 10% of tumour cells were stained. Staining intensity was graded in a semi quantitative way (0 negative staining, 1+ week staining, 2+ moderate staining, 3+ strong staining). Grade 0 and 1+ were considered negative and grade 2+and 3+ were considered positive. Maspin was not expressed in acinic cell carcinomas. A high proportion of maspin was expressed in adenoid cystic tumour (72% cases showing nuclear and 24% cases showing cytoplasmic staining), mucoepidermoid carcinomas (73% nuclear and 60% cytoplasmic) and carcinomas expleomorphic adenoma (67% nuclear and 67% cytoplasmic) and it was expressed in low proportion in salivary duct carcinomas (20% cytoplasmic staining). It was also seen that loss of maspin and presence of residual tumour correlated with poor prognosis. They also observed that, negative maspin expression was mainly localized to the nucleus and was associated with lymph node metastasis and residual tumour.

An immunohistochemical analysis was done by Jun et al., [18] to evaluate the expression of maspin in mucoepidermoid carcinomas and non-malignant normal salivary glands. A significant higher expression of maspin was observed in mucoepidermoid carcinoma when compared to non-malignant salivary gland tumour. The authors found a negative correlation between maspin expression in mucoepidermoid carcinoma and lymph node metastases and also between maspin expression and postoperative metastasis, but a positive correlation was observed between maspin expression and patient's survival rate. The authors concluded that maspin might be useful as a potential prognostic marker for mucoepidermoid carcinoma

Verad et al., [19] used maspin immunolocalization to differentiate between low grade mucoepidermoid carcinoma (LGMEC) and glandular odontogenic cyst (GOC), both of which shared a lot of histological similarities. Six cases of LGMEC and eight cases of GOC were evaluated immunohistichemically. Maspin expression was seen in all the cases of LGMEC and the volume of maspin-immunopositive epithelial-mucous cytoplasm and nuclei present in LGMEC was significantly higher than in GOC. They concluded that, high levels of maspin in the epithelial mucous cells (in both cytoplasm and nucleus) in LGMEC serve as a tool to distinguish it from GOC.

Yang et al., [20] conducted a clinicopathological and immunohistopathological analysis of seven cases of myoepithelial carcinoma [five women and two men]. Three cases were seen in the hard palate, two in retromolar region and one each in tongue and floor of mouth. Immunohistochemically, maspin showed a strong positivity (+++) in all the seven cases along with p63, SMA, Vimentin, S100, CK AE1/AE3. In this study, presence of maspin was not correlated with clinical features.

Ghazy et al., [21] conducted a study to examine the cellular distribution of maspin in salivary gland carcinomas and their values to predict lymph node metastasis. Immunohistochemical analysis was done on 53 different cases of salivary gland carcinomas which included 15 mucoepidermoid carcinoma (MEC), 14 adenoid cystic carcinoma(ADCC), 3 epi-myoepithelial carcinoma, 5 salivary duct carcinoma, 5 malignant pleomorphic adenoma, 6 polymorphous low grade adenocarcinoma(PLGA) and 5 acinic cell carcinoma (ACC). They observed that all salivary gland carcinomas expressed maspin with variable cellular localization. ADCC with solid pattern were maspin immunonegative (absent in 2 cases) suggestive of its aggressive behaviour, whereas ADCC with cribriform pattern had a high expression of maspin (12/12).Myoepithelial cells in ADCC were maspin immunonegative, which may indicate the role of myoepithelial cells in malignant transformation. Myoepithelial carcinoma showed the smallest value of maspin expression and malignant pleomorphic adenoma showed the highest value of maspin expression (5/5). Maspin expression was high in PLGA and ACC, which reflected the

low grade nature of these tumours with a low metastatic potential and a high survival rate. Salivary duct carcinoma had a low level of maspin expression which can be correlated with the aggressive behaviour of this tumour. High grade MEC was characterized by decreased by maspin expression. In this study, no significant correlation was seen between maspin expression and lymph node metastasis, which was in contrast to the study done by Schwarz et al., and Jun et al., [17, 18].

DISCUSSION

Immunohistochemistry has become an indispensable tool in the diagnosis and evaluation of tumour prognosis. There are several markers associated with diagnosis and prognosis of salivary gland tumours. Maspin is a member of serpin superfamily of protease inhibitors. Previously, the role of maspin in various tumours involving breast, prostate, gastric, colorectal, lung, ovarian and head and neck have been reviewed [9]. To the best of our knowledge, this is the first time a review of literature is being done on expression of maspin in salivary gland tumours. Review of literature suggests that maspin may function as a tumour suppressor in salivary gland tumours [14,17,18,20,21].

Maspin suppresses tumour growth and metastasis by inhibiting tumour cell invasion and motility [4,12]. For tumour suppressor activity, maspin has to be localized to the nucleus. Nuclear localized maspin binds to chromatin and prevents cell metastasis. Nuclear expression of maspin is considered as a positive prognostic factor rather than just cytoplasmic location [22]. There is evidence that maspin interacts with the p53 tumour suppressor pathway and may function as a inhibitor to cell motility, invasion, metastasis and angiogenesis in vitro and in vivo [23]. Maspin has an inhibitory effect over angiogenesis through endothelial cell motility inhibition and causes reduction in the density of microvessels associated with tumour [24]. Maspin sensitizes the breast carcinoma cells to staurosporine induced apoptosis in vitro which implies that it can indirectly induce apoptosis in tumour cells [25]. Maspin was also seen to bind to collagen type 1 and 3 which can restore cell adhesion [14,26]. All these biologic functions of maspin attribute to its role as a tumour suppressor in salivary gland tumours.

CONCLUSION

On reviewing the literature, it was seen that Maspin is consistently present in most of the salivary gland tumours. Presence of maspin can be considered as a positive prognostic factor. Further studies with a larger sample size are required to confirm the role of maspin as a tumour suppressor in salivary gland tumours.

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