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REVIEW

t(11;19) translocation and CRTC1-MAML2 fusion oncogene in mucoepidermoid carcinoma

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Review

Summary Mucoepidermoid carcinoma (MEC) is a relatively uncommon carcinoma of variable histology that can involve many tissue types, most commonly major and minor salivary glands and the tracheo-bronchial tree. In a significant number of cases a recurring t(11;19) translocation with an associated novel fusion oncogene (CRTC1-MAML2) is present. This translocation is also found in Warthin's tumour and clear cell hidradenoma of the skin. The CRTC1-MAML2 oncogene acts as a transcription factor on Notch and CREB regulatory pathways, disrupting normal cell-cycle and differentiation, contributing to tumour development. Data suggest that in MEC, the presence of CRTC1-MAML2 may have some prognostic value. An understanding of these mechanisms extends our knowledge of the role of fusion oncogenes in epithelial malignancy. A review of CRTC1-MAML2 in MEC is presented.

Introduction

Mucoepidermoid carcinoma (MEC) is a relatively uncommon malignancy arising from exocrine glands in the upper aerodigestive tract and tracheo-bronchial tree. Most frequently, they arise in the major and salivary glands where they account for approximately 35% of all malignant salivary gland tumours.[1,2] Of non-salivary sites, MEC is most frequently reported arising within the lung,[3–5] although other tracheal/laryngeal origins have all been documented. Rarely MEC arises at others sites including the thyroid gland, breast, lacrimal gland, and conjunctiva.[6–10]

In the salivary glands, absolute data for the incidence and prevalence of MEC, both overall and by location (i.e. major versus minor glands, specific site, etc.) are uncertain, as is the relative contribution of MEC to the absolute number of all salivary gland malignancy. True estimation is confounded by differing methodology in tumour registration across registries. In the US, reported data from local[11] and National registries[12] suggest an estimated incidence of all salivary gland malignancies of approximately 1–1.2 per 100,000 with similar incidence reported from Sweden.[13] Although retrospective reviews have reported data suggesting that MEC is the most common salivary gland malignancy, accounting for as much as 40–52% of all major and minor salivary gland malignancies,[14,15] other institution's

Abbreviations: MEC, mucoepidermoid carcinoma; WT, Warthin's tumour.

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experience suggests that adenoid cystic carcinoma is more frequent.[16] Nevertheless, it is apparent that MEC represents one of the most common and important forms of salivary gland cancers.

The pathogenesis of MEC is unclear, although data suggest that radiation exposure is a risk factor.[17–19] Recent attention to the presence of a non-random t(11;19) reciprocal translocation as a frequent occurrence in MEC[20] and the identification of the novel fusion oncogene generated, CRTC1-MAML2,[21] suggests that these events are of biological significance in MEC. Recurrent, non-random chromosomal translocations which generate novel chimeric gene fusions with oncogenic activity are well recognised and causally implicated in a range of mesenchymal and haematological malignancies.[22,23] Such 'fusion oncogenes' are typically both derived from and consequently encode for transcription factors, transcriptional regulators and receptor tyrosine kinases that act either alone or in combination with other genetic events to alter gene expression, contributing to tumourigenesis. Increasingly, evidence suggests that such events are also implicated in epithelial malignancy, including papillary and follicular thyroid carcinomas, and prostatic adenocarcinoma.[24]

The presence of such recurrent translocations across different types of salivary gland tumours has also been reported (reviewed in Stenman).[20] Pleomorphic adenomas are associated with two non-random translocations and their variants. Rearrangements involving chromosome 8q12, most frequently t(3;8)(p21;q12), that involves the transcription factor gene, PLAG1, are present in 39% of all pleomorphic adenomas with cytogenetic abnormalities.[20] These rearrangements usually lead to ectopic overexpression of PLAG1, with similar events also implicated in lipoblastoma.[25] A second translocation, involving the 12q14—15 locus, most commonly t(9;12)(p21q13—15), leads to deregulation of the HMGA2 gene, and is found in 8% of pleomorphic adenomas with cytogenetic abnormalities.[20] HMGA2 rearrangements are also present in a number of different benign tumour types, including lipomas and uterine leiomyomas.

In MEC involving the salivary glands and the lung, the presence of a non-random t(11;19) reciprocal translocation has long been recognised, with the same translocation also possibly a feature of certain Warthin's tumours (WTs).[20] Recently, using molecular methods developed following the cloning of its associated CRTC1-MAML2 fusion oncogene,[21,26] a number of key studies have advanced our understanding of this event in both MEC and WT.[27–30] In particular, the significance of CRTC1-MAML2 and certain clinical and pathological features of MEC have been clarified. Moreover, these features provide a basis for novel prognostic and therapeutic strategies in the clinical management of MEC. The aim of this article is to present the available data on the t(11;19) and its associated CRTC1-MAML2 fusion product in MEC with some discussion of the clinical relevance of such features.

Recent key studies of the t(11;19) translocation and related CRTC1-MAML2 fusion oncogene

Four pivotal studies have evaluated CRTC1-MAML2 expression in either various types of salivary gland tumours or MEC involving different sites of origin.[27–30] The majority of data were derived from three independent studies from different patient cohorts.[28–30] All studies were retrospective in nature using archival tumour tissue, although in two of these, analysis was facilitated by the availability of fresh-frozen tumour material. An outline of the key findings from these studies is presented in Table 1.

Table 1 Key studies investigating CRTC1-MAML2 expression in salivary gland tumours

Study	Tumours analysed	Key findings
Martins et al.[27]	10 MEC 7 WT	• 70% MEC fusion +ve • 0% WT fusion +ve
Behboudi et al.[28]	29 MEC 3 WT	• 55% MEC fusion +ve • Fusion expressed in all MEC-cell types • Only low- and intermediate-grade tumours were fusion +ve • Significant correlation between fusion +ve tumours and reduced risk of local recurrence, metastases, or tumour related death ($p = 0.0012$) • One WT fusion +ve
Okabe et al.[29]	71 MEC 26 WT 25 other salivary gland tumours	• 38% MEC fusion +ve • Only low- and intermediate-grade tumours were fusion +ve • Significant correlation between fusion +ve tumours and improved overall survival ($p = 0.002$) • 0% WT fusion +ve • 0% other salivary gland tumours fusion +ve
Tirado et al.[30]	22 MEC 11 WT 22 other salivary gland carcinomas	• 81% MEC fusion +ve • No association between histological grade/clinical stage and fusion status • Significant correlation between fusion −ve tumours and distant metastases ($p = 0.05$) • 36% WT fusion +ve • 0% other salivary gland carcinomas fusion +ve