UDC 575
DOI: 10.2298/GENSR1402601D
Original scientific paper

INCIDENCE AND CLINICAL RELEVANCE OF T(11;19) TRANSLOCATION IN SALIVARY GLAND MUCOEPIDERMOID CARCINOMA

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Mucoepidermoid carcinoma (MEC) harbors a recurring *t(11;19)* translocation with an associated novel fusion oncogene-*MECT1-MAML2*. The *CRTC1-MAML2*oncogene disrupts normal cell-cycle and differentiation, contributing to tumor development. The objectives of this study were to establish the incidence of *CRTC1-MAML2* fusion in Serbian patients and estimate its relevance as a genetic marker of MEC behavior. In this retrospective study, 20 cases of MEC of salivary glands were tested for the presence of *CRTC1-MAML2* fusion using reverse transcriptase-polymerase chain reaction. Clinicopathological parameters and survival data were examined in relation to fusion status. The *CRTC1-MAML2* fusion was detected in 40% of MECs and its presence was associated exclusively with low-intermediate grade tumor histology *(P = 0.02)* and favorable clinical outcome, with 100 % overall survival rate *(P=0.046)*. The study has shown that the presence of the CRTC1-MAML2 fusion can serve as an additional diagnostic and prognostic marker for mucoepidermoid carcinomas.

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Key words: Salivary gland, Mucoepidermoid carcinoma, Chromosomal translocation (11,19), MECT1-MAML2, RT-PCR diagnostic

INTRODUCTION

The World Health Organization recognized twenty-four types of benign and malignant salivary gland tumors (EVESON *et al.,* 2005). Mucoepidermoid carcinoma (MEC) represents 5% of all salivary gland tumors and 20% of salivary gland malignancies (GOODE *et al.,* 2005). Clinical monitoring of this tumor and its outcome prediction are complicated due to biological diversity and clinical heterogeneity (BELL *et al.,* 2005). Seventy years after the first identification of MEC, a unique, standardized grading system does not exist (LUNA, 2006). Hence, "failure to diagnose" or "erroneous diagnosis" are not uncommon, leading to delayed or missed therapy or treatment and wrong prognosis. In other words, MEC remains a considerable challenge for pathologists, and additional molecular markers that could contribute to better diagnosis and predict the natural history of these tumors are needed.

Genetic research of mucoepidermoid carcinomas was mainly focused on a non-random *t (11;19) (q21;p13)* reciprocal translocation which appeared as a possible hallmark of MEC. This translocation generates *CRTC1-MAML2* fusion in which the *CREB*-binding domain of the *CREB* coactivator *CRTC1* (also known as *MECT1, TORC1 or WAMTP1*) is fused to the transactivation domain of the *Notch* coactivator *MAML2* (MITELMAN, 2000). It seems that *MECT1–MAML2* fusion induced activation of *CREB* is critical for cell transformation (TONON *et al*., 2003; WU *et al*., 2005). A *CRTC3-MAML2* fusion gene resulting in the same MEC phenotype as *CRTC1-MAML2* has been described as well (FEHR *et al.,* 2008).

The incidence of *CRTC1–MAML2* fusion in salivary gland MEC reported in different studies varied considerably (between 38%–and 81%) (OKABE *et al.,* 2006; MIYABE *et al.,* 2009, JEE *et al*., 2013) and it was assumed that the *t (11; 19)* gene fusion product was present only in low- and intermediate-grade MECs (OKABE *et al.,* 2006; SEETHALA *et al.* 2010). Conversely, other studies have shown that the fusion gene could be found in high grade (HG) MEC as well, which sparked a debate on its prevalence and relevance (TIRADO *et al.,* 2007; CHENEVERT *et al*., 2011, NAKANO *et al*., 2013). The aim of this research was to assess the relevance of *CRTC1-MAML2* fusion as a potential genetic marker of tumor behavior in MECs in Serbian population.

MATERIALS AND METHODS

Patients and specimens

Formalin-fixed, paraffin-embedded specimens of 52 mucoepidermoid carcinomas of salivary glands resected in the period 2001-2010 at the Clinic of Maxillofacial Surgery, School of Dental Medicine, University of Belgrade were available for the analysis. Prior to molecular genetics analyses, the cases were once more carefully reviewed in 2012 by two independent pathologists (Z.T. and T.L.) according to the criteria of the WHO Classification for Pathology and Genetics of Head and Neck Tumors (EVESON *et al*., 2005). Upon revision, 15 cases of alleged high grade (HG) MEC were excluded from further analysis. After RNA extraction additional 17 cases had to be excluded because of insufficient RNA quantity or quality. Evaluable PCR-results were obtained for 20 cases of MEC. The study was approved by the Ethical Committee of the School of Dental Medicine, University of Belgrade (IRB: 36/10) and written informed consent was obtained from each patient in accordance with the Declaration of Helsinki.

Clinicopathological data

The following parameters were recorded for every patient: age, sex, primary tumor site, tumor size, metastases to regional lymph nodes, clinical stage, histological grade, and follow-up and the tumor specimens were histologically classified according to a 3-grade system described by BRANDWEIN *et al.* (2001). The tumor grade was determined from the sum of the point values assigned to each of the following histologic elements: cystic component, neural invasion, necrosis, mitosis, and anaplasia.

CRTC1-MAML2 fusion detection

The *CRTC1-MAML2* fusion transcript was detected using one step reverse transcription-polymerase chain reaction (RT-PCR). To this end, microtome sections were prepared from paraffin-embedded tissue blocks and one of the sections was stained with hematoxylin/eosin (HE) for microscopic inspection by a pathologist. Tumor containing tissue was then microdissected, deparaffinized and RNA was extracted, using the RNeasy FFPE Kit (Qiagen, Hilden, Germany). The *CRTC1-MAML2* specific RT-PCR was performed, using the Qiagen OneStep RT-PCR kit according to the manufacturer instructions (Qiagen, Hilden Germany). Primers used for detecting the *CRTC1-MAML2* fusion transcript were the following:

MECT1 For 5'-GCCTTCGAGGAGGTCATGA-3'
MAML2 Rev 5'-CTTGCTGTTGGCAGGAGA-3'.
As a positive control for each sample wild type MAML2 was also amplified using the primers:
MAML2 For 5'-GTAGCAATAATGGTGGCAGT-3'
MAML2 Rev 5'-CTTGCTGTTGGCAGGAGA-3'.

PCR reactions were performed in an ABI 2720 Thermal Cycler (Applied Biosystems, Foster City, USA) using the following amplification conditions: after an initial denaturation step at 94°C for 3 min, 35 cycles of 94°C for 45 sec, 55 °C for 30 sec, and 72° C for 30 sec were run followed by a final extension step of 10 min at 72°C. PCR products were run and analyzed using the ABI 3130 Genetic Analyzer and the Gene Mapper v. 4.0 Software (Applied Biosystems, Foster City, USA).

Statistical analysis

For general information about the sample usual descriptive statistic tests were used. The survival rate was calculated with the Kaplan–Meier method. All analyses were performed with the statistical package SPSS, version 18 (IMB statistics software).

RESULTS

Clinicopathological characteristics of MECs and association with CRTC1-MAML2 fusion

The study sample included 12 male and 8 female patients diagnosed with MEC, with the age ranging from 15 to 81 years (mean 55.5 years). Primary MEC localization were major salivary glands in all 20 cases (parotid gland, submandibular and sublingual). Out of the 20 confirmed MECs 7 had more than 2 cm in diameter and they were classified as clinical stages III and IV. Only 3 showed metastases to the regional cervical lymph nodes. Histologically, 9 cases

were classified as low grade, 5 as intermediate grade and 6 as high grade. The *CRTC1-MAML2* fusion transcript was detected in 8 (40%) of the 20 MEC cases. Correlation of *CRTC1-MAML2* fusion with clinicopathological features of MEC is given in Table 1. The fusion positive cases were associated with low-intermediate histological grade *(P = 0.02)*. Of the five factors constituting the histological grade, two correlated significantly with the presence of the fusion transcript- absence of necrosis *(P= 0.024)* and a lesser degree of anaplasia *(P= 0.024).*

Table 1. Distribution of epidemiological, clinical and histological characteristics of 20 MEC patients in relation to the presence/abscence of CRTC1-MAML2fusion

Variable		MECT1 – MAML2 fusion		P
		Positive (n=8)	Negative (n=12)	
Age (years)	Mean	50,25	59	NS
Sex	Male	3	9	NS
	Female	5	3	
Tumour site	Major	8	12	NS
	Minor	0	0	
Tumour size	>20 mm	7	7	NS
	<20 mm	1	5	
Nodal status	Positive	0	3	NS
	Negative	8	9	
Clinical stage	I, II	7	8	NS
	III, IV	1	4	
Histological findings Histological grade	Low	7	2	0.02
	Intermediate	1	4	
	High	0	6	
Cystic component	>20%	4	6	NS
	<20%	4	6	
Neural invasion	Positive	0	2	NS
	Negative	8	10	
Necrosis	Positive	0	6	0.024
	Negative	8	6	
Mitoses	>4/10 HPF	2	7	NS
	<3/10HPF	6	5	
Anaplasia	Positive	0	6	0.024
	Negative	8	6	

Abbreviations: NS, not significant; HPF, high-powered field

Factors affecting disease-free and overall survival

The follow-up was 138 months. At the last medical visit 10 patients were alive with no evidence of disease and 4 were alive with the disease. Among patients who died, 4 died from disease and 2 from other cause. None of the patients with *CRTC1-MAML2* fusion-positive MEC died of the tumor.

Kaplan-Meier analysis for disease-free survival, showed that MEC patients with positive *CRTC1-MAML2* fusion transcript had 100 % survival rate *(P= 0.002)* (Table 2). Cases negative for the fusion had the following survival rates: 89% in histological grade I, 60% in grade II and 17% in grade III. As expected, patients with advanced tumor size *(P=0,001)* and clinical stage III/IV *(P=0.003)* showed low rate of disease-free survival. Low rate of disease-free survival was also observed in cases with tumor necrosis *(P=0.001)*, neural invasion *(P=0,006)*, anaplasia *(P=0.003)* and increased mitotic index *(P=0,003)*. The Kaplan-Meier analysis showed a statistically significant association between several variables and survival rates (Table 2), including the fusion status (Fig. 1).

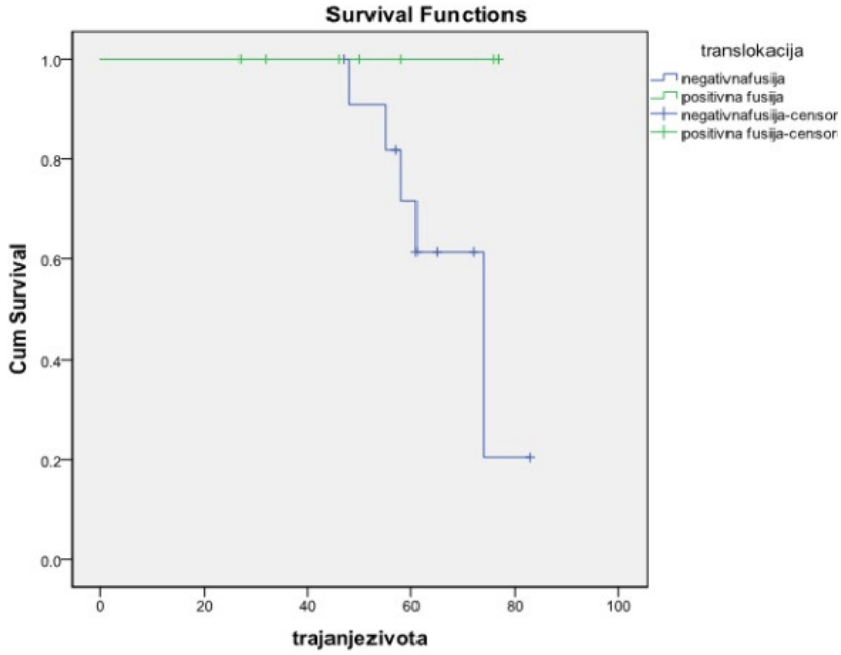

Figure 1. Kaplan Meier representation of MEC patients overall survival in relation to the presence/absence of CRTC1-MAML2 fusion ranscript.

Table 2. Survival analysis in MEC patients in relation to clinical, histological and genetic data

Variable	Variable's value	Disease free survival (P)	Overall survival (P)
		MEC (n=20)	MEC (n=20)
Tumor size	>20 mm <20 mm	0.001	0.008
Nodal status	Positive Negative	NS	NS
Clinical stage	I, II III, IV	0.003	0.031
Histological grade	Low Intermediate High	0.006	NS
Cystic component	>20% <20%	NS	NS
Neural invasion	Positive Negative	0.006	NS
Necrosis	Positive Negative	0.001	0.002
Mitoses	>4/10 HPF† <3/10HPF	0.003	0.004
Anaplasia	Positive Negative	0.003	NS
MECT1-MAML2	Positive Negative	0.002	0.046

Abbreviations: *NS, not significant; †HPF, high-powered field

DISCUSSION

Specific chromosomal translocations are commonly observed in hematopoietic and mesenchymal stromal tumors and define distinct clinicopathological entities. Interestingly, translocations are rather an exception than a rule in epithelial tumors, and mucoepidermoid carcinomas fall into less than 1% of all epithelial cancers with a recurrent, pathogenic chromosomal aberration (MITELMAN, 2000). According to STENMAN (2005), FEHR *et al.,* (2009) and BHAIJEE *et al* (2011) *CRTC1-MAML2* fusion might define a distinct clinicopathological subset of mucoepidermoid carcinomas. This opinion is corroborated by the present study which showed that the *CRTC1-MAML2* fusion is associated with low-intermediate grade histology and favorable clinical outcome.

The *CRTC1-MAML2* fusion transcript was detected in 40% of Serbian patients with MEC which is in agreement with the study of OKABE *et al.* (2006) who found 34% of fusion positive cases in their MEC sample, but it is a significantly lower percentage than reported by TIRADO *et al.* (2007), SCHWARZ *et al.* (2011), JEE *et al*. (2013). Our results demonstrated that the *MECT1–MAML2* fusion was associated with low-intermediate grade tumor histology and a good prognosis which is also in agreement with other studies (OKABE *et al.,* 2006*;* MIYABE *et al.,* 2009). Similarly to our results, other groups have also shown that the fusion-positive cases had smaller tumor size, lower frequency of nodal metastasis and less advanced clinical stage (OKABE *et al.,* 2006; OKUMARA *et al.,* 2011). In addition, OKABE found that patients with fusion-positive tumors had significantly greater overall survival compared to fusion-negative patients. In this study patients with fusion-positive MECs also showed 100% overall survival. All high grade MECs were negative for the fusion transcript and all the patients with HG MEC died within the first five years after the diagnosis.

Yet, some authors found a relatively high prevalence of fusion transcripts in high grade MECs (TIRADO *et al.,* 2007*;* MIYABE *et al.,* 2009). One of the possible reasons for this discrepancy is the absence of a uniform classification system and frequent misdiagnosis of various tumors (such as squamous cell carcinoma or adenosquamous carcinoma), as "high-grade" MECs (BRANDWEIN *et al*., 2000; CHENEVERT *et al.,* 2011). Two-tiered and three-tiered systems of MEC grading are in use (BAI *et al.* 2013), which may lead to confusion. BEHBOUDI *et al.* (2006) and OKUMURA (2011) among others suggested the introduction of molecular classification of MECs in which *MECT1–MAML2* fusion status would serve as an additional diagnostic tool for distinguishing molecular subtypes of this tumor.

The results of a recent study using high-resolution array-based comparative genomic hybridization revealed that low-grade MECs had significantly fewer copy number alterations compared to high grade MECs and regardless of their histological grade, fusion -positve MECs had a much more stable genome then fusion-negative MECs (JEE *et al.,* 2013).

The great majority of MECs are treated by surgical resection with radiation as an adjunct therapy (SPIRO, 1998). Determination of *CRTC1-MAML2* fusion could have clinical benefits. Preoperative RT-PCR analysis using tumor material obtained by fine-needle aspiration (JAYARAM et al., 1994) could be clinically useful and improve therapeutic strategies. A new protocol should be approved indicating that radical surgical resection with a postoperative radiotherapy is required for aggressive tumors such as fusion negative HG MECs. On the other hand, fusion positive MECs should undergo a less radical surgical resection with preservation of the facial nerve and without postoperative radiotherapy. It has been shown that expression of *CRTC1-MAML2* fusion is essential for tumor growth in fusion positive carcinomas (KOMIYA *et al.* 2006), making the fusion a potential therapeutic target.

There is a limited number of publications on the *CRTC1-MAML2* fusion and its possible role as a diagnostic and prognostic tool obtained on European populations. This is the first report on the prevalence of *CRTC1-MAML2* fusion in Serbian patients with mucoepidermoid carcinomas and it represents a significant contribution to the extremely scarce genetics of salivary gland tumors in Serbian population (MILAŠIN *et al.* 1993, NIKOLIĆ *et al*. 2013).

In summary, the fusion may be considered as a molecular marker in this heterogeneous group of salivary gland tumors, i.e. fusion positive and fusion negative MECs should be viewed as distinct clinicopathological entities and treated with apposite therapies.

ACKNOWLEDGEMENT

This research was financed with the Grant No 175075 of the Ministry of Education, Science and Technological Development of Serbia and supported by the Institute of Haematopathology Hamburg, Hamburg, Germany. There is no conflict of interest. The authors would like to thank Cora Hallas, Sonja Shuhle, Verica Petrović, Nađa Nikolić and Boško Toljić for their technical help.

Received May 20th, 2014
Accepted July 22th, 2014

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INCIDENCA I KLINIČKI ZNAČAJ TRANSLOKACIJE T(11;19) U MUKOEPIDERMOIDNOM KARCINOMU PLJUVAČNIH ŽLEZDA

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Izvod

Kod velikog broja mukoepidermoidnih karcinoma (MEK) pljuvačnih žlezda detektovana je *t(11;19)* hromozomska translokacija koja vodi nastanku *CRTC1-MAML2* fuzionog produkta sa onkogenom aktivnošću koji remeti ćelijski ciklus i diferencijaciju dovodeći do razvoja tumora. Ciljevi ove studije bili su da se ispita učestalost *CRTC1-MAML2* fuzije kod naših pacijenata obolelih od MEK-a i da se proceni značaj fuzije kao potencijalnog markera biološkog ponašanja ovih maligniteta. U ovoj retrospektivnoj studiji 20 slučajeva MEK-a bilo je testirano na prisustvo *CRTC1-MAML2* fuzionog transkripta koristeći reverznu transkriptazu- lančanu reakciju polimeraze (RT-PCR). Ispitivana je korelacija *CRTC1-MAML2* fuzionog statusa sa kliničko-patološkim karakteristikama tumora kao i vreme preživljavanja pacijenata sa MEK-om. *CRTC1-MAML2* fuzija je detektovana u 40% slučajeva i pokazana je njena povezanost sa niskim odnosno srednjim histološkim gradusom karcinoma *(P = 0.02),* kao i sa 100%-nom stopom preživljavanja *(P=0.046)*. CRTC1-MAML2 fuzioni status u mukoepidermoidnom karcinomu pljuvačnih žlezda pokazao se kao koristan dopunski parameter za pouzdaniju dijagnozu i prognozu.

Primljeno 20.V.2014.
Odobreno 22. VII.. 2014.