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The Participation of Transponible DNA Elements in the Etiology and Prognosis of Oral Epidermoid Carcinoma

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Amanda Feitoza da Silva*[1], Gabriel Gomes da Silva[2], Ana Paula Gomes e Moura[1], Thaine Oliveira Lima[1], Gilton Vieira Santos Júnior[1], Iago Filipe Correia Dantas[1], Kathleen Michelle de Jesus Santos[3], Lucas Bezerra Santos[1], Fernanda Augusta Barbosa da Silva Monteiro[4], Juliana Campos Pinheiro[1]

1 University Tiradentes, Aracaju, Sergipe, Brazil.
2 Odontology, Natal, Rio Grande do Norte, Brazil.
3 Uniages, Paripiranga, Bahia, Brazil.
4 Potiguar University, Natal, Brazil.

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ABSTRACT

Oral squamous cell carcinoma (OSC) is the most common malignant neoplasm in the oral cavity, with the lower lip and oral tongue being the most common sites. This is a literature review article, developed through a bibliographic survey in the Medline, PubMed and Science Direct databases. Like all malignancies, the OSC has a multifactorial etiology, with a strong association with smoking, alcohol consumption and chronic exposure to solar radiation. Deregulation of transposable DNA elements has been reported in developmental diseases, as well as in different types of human cancers, however, in the literature there are no studies correlating the deregulation of transposable DNA elements to the OSC. The prognosis of the OSC is directly related to the development of local recurrence and metastases, which may depend on several factors, concomitant to these findings, the altered expression of transposable DNA elements and demonstrate to be registered trademarks of cancer and may be responsible for conducting cellular mutations, inducing tumorigenesis, new molecular studies must be carried out in order to investigate the correlation of the transposable elements with the OSC.

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INTRODUCTION

Oral squamous cell carcinoma (OSC) is the most common malignancy in the oral cavity and represents a public health problem in Brazil, according to the latest data from the National Cancer Institute (INCA), for the year 2018, 14,700 new ones were estimated cases, which places this neoplasm as the fifth most incident type in Brazilian men and twelfth in women, representing from 90% to 95% of cases. The OSC has a multifactorial etiology, integrating endogenous factors, such as genetic predisposition, and exogenous environmental and behavioral factors, such as smoking, drinking, excessive sun exposure, inadequate oral hygiene, malnutrition, immunodeficiencies and secondary infections, which may be related to viruses epsten barr (EBV), herpes simplex virus (HSV) and human immunodeficiency virus (HIV)[1].

OSC occurs anywhere in the mouth, with the tongue and vermilion lip as the most frequent locations. It is observed that this neoplasm can present a varied biological behavior, with a greater or lesser aggressiveness, mainly related to the size of the lesion, presence of metastasis, histological gradation and occurrence site[2]. Regarding OSC, lesions diagnosed on the tongue are considered to have an unfavorable prognosis, due to their high potential for developing regional lymph node metastases, which is due, in part, to the rich supply of blood and lymph vessels in this anatomical site[3,4].

The transposable elements are units of DNA that give rise to interspersed repetitions, sequences that make up the majority of our genomes, however, they can move within the genome promoting mutations. Line-1, in turn, is considered a transposable element of self-propagating DNA and protein coding, which can cause genomic instability, mutation and carcinogenesis. The altered expression of transposable elements may be associated with cancer etiopathogenesis and may be responsible for leading to tumorigenesis[5]. Thus, the present study proposes to carry out a literature review to evaluate the role of transposable DNA elements in OSCs.

MATERIAL AND METHODS

It is a literature review article, developed through a bibliographic survey in the Medline, PubMed and Science direct databases. The search strategy used was “Oral Neoplasms”; “Squamous Cell Carcinoma”; “Transposable DNA Elements”. 23 articles published between 2005 and 2019 were selected, included based on the following inclusion criteria: availability of the full text,

publication in Portuguese, English and Spanish and clarity in the methodological details used. In addition, articles cited by more than one author were sought to serve as a more accurate and complete reference for the review. The abstracts were read and evaluated by the authors and categorized as relevant or not to the topic according to the inclusion criteria previously elucidated.

RESULTS

OSC occurs anywhere in the mouth, with the tongue and vermilion lip as the most frequent locations. Among lip cancers, the literature has shown that 90% to 95% of cases affect the lower lip, with OSC carcinoma being the most prevalent. Lower lip squamous cell carcinoma can develop from premalignant lesions, such as actinic cheilitis[6]. Clinically, OSC can be observed as white, erythematous, leuko-erythroplastic plaques or as nodular and ulcerated lesions. When present on the lower lip, it usually presents as a hardened and crusted ulcer often preceded by an actinic cheilitis[7]. In the histopathological aspect, the OSC presents a pattern of invasion of islands, cords and sheets, constituted by malignant epithelial cells inside the connective tissue. Tumor cells, in most cases, present eosinophilic cytoplasm in varying amounts, with nuclear hyperchromatism and loss of the nucleus-cytoplasm relationship, as well as typical and atypical mitosis figures, dyskeratosis and formation of keratin beads in well-differentiated tumors. When the tumor is in its early stages, it can be called microinvasive or superficially invasive. In more advanced stages, malignant cells can extend deeply reaching muscle, nervous, adipose and / or bone tissue and invade blood vessels[8].

The most used staging system is the so-called TNM system for Classifying Malignant Tumors. This system is based on the anatomical extent of the disease. Taking into account the characteristics of the primary tumor (T), the characteristics of the lymph nodes of the lymphatic drainage chains of the organ in which the tumor is located (N), and the presence or absence of distant metastases (M). These parameters receive grades, generally from T0 to T4, from N0 to N3 and from M0 to M1, respectively. In general, studies have shown that the more advanced the clinical stage of the tumor, the worse the patient's prognosis[9,10]. Thus, in order to assist in the correct determination of the tumor stage, histological grading methods were developed. The histopathological malignancy grading system aims to provide information capable of predicting the biological behavior of OSCs[11,12].

The human genome is abundant with repetitive and interspersed sequences from retrotransposons. So far, three categories of retrotransposons have remained unmistakably active: Line-1 (L1), Alu and SVA. The first is autonomous, capable of self-propagation through RNA intermediaries - and the last two are non-autonomous and, therefore, depend on L1 for mobilization. There are approximately 500,000 L1 copies in the human genome, making up 17% of human DNA. However, most L1s lose the ability to retrotranspose due to truncations of inverted rearrangements or point mutations that occur during reverse transcription or subsequent chromosomal replication of the inserted element[13]. An intact LINE-1 sequence measures approximately 6 kilobases in length and encodes two well-recognized proteins, open frame 1 protein (ORF1p) and open frame 2 protein (ORF2p). Line-1 also has antisense promoter (ASP) activity that can initiate fusion transcripts and aberrant coding sequence (ORF0) in the opposite direction field[14,15].

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DISCUSSION

OSC also called squamous cell carcinoma and squamous cell carcinoma is defined as a malignant neoplasm originating from the stratified squamous epithelium[16,17]. Such cancer is the most common malignant neoplasm of the oral cavity, it is responsible for about 90% of malignant lesions, which affect the oral cavity and oropharynx[8]. Being considered a public health problem worldwide. Currently, it is the fifth, in men, and the sixth, in women, the most prevalent type of cancer and despite the progress in research and therapeutics, survival has not improved significantly in recent years, representing a continuous health challenge, representing 90% to 95% of cases[1].

Men have a higher prevalence between the fifth and sixth decade of life, as this group is more exposed, over the years, to risk factors. Recent studies have shown an increase in the number of women affected and in groups of young people, probably due to the social changes and daily activities associated with the modern social profile of women, allowing greater exposure to carcinogenic agents, such as smoking and alcohol consumption and exposure to biological agents, such as high risk to human papillomavirus (HPV) subtypes, which is one of the main factors associated with the increase in the group of young people[1].

Despite the relevance of information related to the clinical and pathological aspects of OSC, over time, the researchers also realized that there were some discrepancies in relation to biological behavior among tumors with similar clinical characteristics[9]. Due to these differences in clinical and histopathological behaviors between OSCs, tumor staging has been established, which can be clinical and pathological. Clinical staging is established based on data from the physical examination and complementary examinations relevant to the case. Pathological staging is based on surgical findings and anatomopathological examination of the surgical specimen. It is established after surgical treatment and determines the extent of the disease with greater precision. Pathological staging may or may not coincide with clinical staging and is not applicable to all tumors[18].

Almangush et al. (2014)[19] developed a new proposal for a histopathological grading system called the BD model ("B" represents the "budding" (small nests) of tumor cells and "D" represents the depth of invasion). Tumor sprouts are defined as the presence of isolated tumor cells or small clusters with less than 5 tumor cells on the invasive forehead. The depth of invasion is measured from the surface of the tumor to the deepest point of invasion. The cut-off point for tumor cell bud count and invasion depth was set at 5 buds and 4 mm, respectively. The result of the analysis of the histopathological patterns of the system established by Almangush et al. (2014) 19 are classified into three groups: (1) Score 0: tumor with depth of invasion <4mm and tumor cell buds absent or <5 on the invasive forehead; (2) Score 1: the tumor must have one of the following characteristics: a - tumor with depth of invasion ≥ 4 mm and <5 cell buds on the invasive forehead or b - superficial tumor (<4 mm), but with high nest activity of invasive forehead cells (≥ 5 buds) and (3) Score 2: tumor with depth of invasion ≥ 4 mm and with high activity of cells nests on the invasive forehead (≥ 5 buds).

Line-1 is considered the transposable element with the highest activity in human DNA, playing an important role in carcinogenesis[18,20]. Line-1 has been linked to the activation of oncogenic factors as well as to the inhibition of tumor suppressor genes. The dysregulation of gene expression, activation of the epithelium-mesenchymal transition contribute to the oncogenic activation mediated by Line-1[21,22]. In addition, genomic instability, including chromosomal breaks and DNA recombination, which can be induced by mobile Line-1 inserts, reinforces mutation rates and carcinogenesis[23].

Deregulation of transposable elements has been reported in developmental diseases, as well as in different types of human cancers. Homologous recombination between transposable elements of DNA can result in gene mutation, such as the BRCA1 and MLL-1 genes involved in the pathogenesis of cancers such as myeloid leukemia and Ewing's Sarcoma. Gene therapy based on the use of transposable elements of DNA has been tested in animal models for the treatment of diseases such as hemophilia A and B, junctional epidermolysis bullae, pulmonary fibrosis and Crigler-Najjar type I syndrome, showing favorable results. Capture of genes based on transposable elements is an efficient approach for the identification of genes involved in diseases other than cancer[18].

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