Literature Review

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Biological role and potential significance of salivary IL6, IL8, IL1-RA and TNFα in oral squamous cell carcinoma and potentially malignant disorders

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Abstract

Oral squamous cell carcinoma (OSCC) and oral potentially malignant disorders (OPMD) are significant health problems. Early diagnosis and screening for these diseases is a major clinical goal. Examination of signaling molecules in saliva as indicators in the diagnostic and screening processes is a new strategy, which is still developing and seeking its confirmation. Changes in salivary composition and expression of signaling molecules and other cytokines have been reported in cases of OSCC and OPMD. To define signaling molecules as potential diagnostic, prognostic or predictive factors detailed knowledge of their biological functions is required. There is accumulated data for the basic physiological and biochemical effects of some cytokines and influence of signaling pathways such as JAK/STAT, MAPK and PI3/Akt on apoptosis, cell survival and proliferation. There are reports of relationships between salivary cytokine expression and some clinical and pathohistological features of the OSCC. The importance of some cytokines in oncological cases is still debatable. Some molecules have not been studied in oral carcinoma cases yet.

Keywords: oral squamous cell carcinoma, oral potentially malignant disorders, cytokines, saliva.

Introduction

Oral squamous cell carcinoma remains a major health problem worldwide. Data from the Global Cancer Observatory (GCO) and the World Health Organization (WHO) for 2020 show that OSCC is the first in incidence and mortality among head and neck cancers [43]. 377,713 cases (264,211 men and 113,502 women) of carcinoma of the lips and oral cavity were registered worldwide for the 2020. The recorded deaths were 177,757 - 125,022 males and 52,735 females [44,1].
For Bulgaria the data ranks OSCC in the 19th place in terms of frequency among malignant diseases, as in 2020 455 cases were registered, which is 1.2% of malignant tumors [43].
Oral leukoplakia, oral erythroplakia, submucosal fibrosis and oral lichen planus are the most common oral potentially malignant lesions [45,6].
A meta-analysis by Mello et al. 2018 reported 4.47% global overall incidence for OPMD with male predominance (59.99%) [28]. About 50% of oral carcinoma cases have been reported to develop from precursor lesions [17].
Biopsy is the leading diagnostic method for OSCC and OPMD [2,40].
Examination of salivary cytokine levels is among the current trends with marked ambition for early diagnosis and screening of oral premalignant lesions and OSCC [20].
Many salivary proteins have been investigated as molecular markers for oral carcinoma and OPMD [31,36].
A starting point studying salivary composition changes in oral oncological cases is the understanding of the complex interactions between multiple signaling molecules in the tumor microenvironment (TME) [11]. It is believed that saliva cytokine composition is mainly due to locally produced molecules from oral lesions [32,34] and the direct contact saliva-pathological lesion leads to changes in the fluid composition near the tumor [20,26].

Tumor microenvironment

The fundamental idea for the TME existence dates from the 1860s and belongs to R. Virchow, who first noticed the presence of leukocytes around tumor cells [9]. The TME is a complex environment that differs in composition and regulation from the normal tissues [11].
Cell populations in the tumor stroma are considered "tumor-associated cells" (TACs) and include fibroblasts, endothelial cells, macrophages, monocytes, neutrophils, NK-cells, T- and B-lymphocytes and others cell types [9,4].
The TME is highly modified by tumor cells, TACs, tumor stroma, adjacent healthy tissue through cytokines, enzymes and extracellular matrix components secreted by cellular elements. The local microenvironment is important in the processes of tumorigenesis, tumor progression and metastasis [23,10].
At this highly altered environment some cell populations undergo epithelial-mesenchymal transformation (EMT) with phenotypic changes. This leads to significant adaptive morphological and functional changes [9,4].

Biological role of cytokines and significance in OSSC and OPMD

IL6

IL6 is an acute phase inflammatory cytokine and a pyrogen, produced by vast majority of immune cells. It increases the formation of endothelial growth factor (VEGF), stimulates angiogenesis and proliferation of keratinocytes [16,15].

The membrane-bound IL6 receptor has two subunits, α- and β-chains. The β-chain (designated as gp130) is an activator of the signaling pathways – JAK, STAT1 and STAT3, Ras-MAPK. Through the Ras-MARK pathway, IL6 is involved in the regulation of cell division and differentiation. STATs increase formation of anti-apoptotic proteins of the Bcl-family – Bcl2, Bclxl, Bcl6 [16,15]
In head and neck cancers IL6 has an indirect pathway of action via osteopontin (OPN), leading to accelerated growth, increased invasiveness and migration of tumor cells [35]. IL6 has been found with elevated salivary levels in OPMD [19,21]. It is associated with more invasive tumor growth [31]. Some authors consider that higher expression of IL6 in patients with OSCC is a poor prognostic sign [37].

IL8

IL8 is considered as a pro-inflammatory and oncogenic cytokine [31].
The signal transduction is via CXCR1 and CXCR2 receptors expressed mainly by immune cells. The receptors are not strictly specific for IL8 and binds also some growth factors. Activated receptors trigger PI3/Akt, MAPK and STAT3 pathways associated with cell proliferation and epithelial-mesenchymal transformation [42].
IL8 stimulates angiogenesis, migration of keratinocytes and changes their adhesion properties to the extracellular environment [20,18].
In the TME IL8 is important for activation of TAN-cells (tumour-associated neutrophils) and their N1- and N2-phenotype switching. N2 cells possess pro-tumor and immunosuppressive effect. N1 cells possess anti-tumor properties [7,29].
Higher IL8 salivary levels have been reported in cases of OPMD and OSCC [21]. Some authors declare correlation with the tumor size [3] and increased potential for cell migration and secretion of matrix metalloproteinase 7 [41].

IL1-RA

IL1-RA is an anti-inflammatory cytokine, a competitive inhibitor of the membrane-bound receptor for IL1 [8,27].
The role of IL1-RA in tumors has not been elucidated yet. Some authors believe that IL1 creates a pro-tumor environment and possess pro-angiogenic effects [25,12]. Others showed that IL1-RA affects the PI3K/NFkB signaling pathway and inhibits tumor proliferation and angiogenesis [5].
Higher levels of IL1-RA have been reported in saliva samples from patients with OSCC compared to healthy controls and OPMD [31]. It has been reported that IL1-RA can be used as a biomarker for oral malignancies [39].

TNFα

TNFα (tumor necrosis factor alpha) is a major cytokine involved in protective immunological responses [38].
There are two receptors for TNFα - TNFR1 and TNFR2. The TNFR1 receptor could be a promoter of cell survival, activating the NF-kB and JNK/MAPK pathways. Activation of TNFR2 increases cell proliferation and survival, participates in epithelial-mesenchymal transformation [33,14].
Some authors consider TNFα to be an antitumor agent due to its property to trigger cell apoptosis and necrosis in tumor cells via TNFR1 [24,30]. Others believe that TNFα increases the invasiveness of tumor cells [31,13].
There are evidences that TNFα expression in the serum, saliva and tissue samples in patients with OSCC is elevated compared to OPMD and healthy controls. Correlation of TNFα levels with the differentiation grade in OSCC and dysplastic changes in premalignant lesions has been observed [19,22].

Conclusion

There are accumulating evidences that saliva is a reliable diagnostic medium for oral diseases, including oral oncological lesions. There are evidences that OPMD and malignant lesions influence cytokine presence in saliva. The biological properties of the signaling molecules are known, but there are still cytokines whose significance in OPMD and OSCC is not fully understood. Some cytokines show significant changes and potential significance as prognostic factors. More researches are needed to confirm the importance of salivary cytokines as prognostic or predictive factors and to elucidate the influence of other diseases in the oral cavity.

CONFLICTS OF INTEREST

The authors declare no conflict of interests.

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