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Review

Significance of chemokine and chemokine receptors in head and neck squamous cell carcinoma: A critical review

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SUMMARY

Chemokines are small chemotactic proteins that coordinate circulation of immune/inflammatory cells throughout body compartments. Because of this property chemokines and their cell surface receptors are implicated in several physiological and pathological conditions, including cancer. These molecules are expressed by neoplastic or stromal cells and have effects at tumor primary site (e.g. stimulating angiogenesis and tumor cells motility) and lymph nodes (creating a gradient to direct migration of neoplastic cells). In this article we review the current knowledge about the function(s) of chemokines and receptors in squamous cell carcinoma from the oral cavity and head and neck region. Accumulating evidence suggests some chemokine(s) and receptor(s) as potential targets in adjuvant therapies for these malignancies.

Introduction

Squamous cell carcinoma (SCC) is the most common malignancy of head and neck region arising from mucosal linings of the upper aerodigestive tract, comprising (1) nasal cavity and paranasal sinuses, (2) nasopharynx, (3) hypopharynx, larynx, and trachea, and (4) oral cavity and oropharynx [1,2]. Head and neck squamous cell carcinomas (HNSCC) are characterized by high morbidity and mortality rates and strong tendency to regional and distant metastasis [1–4]. These tumor characteristics depend on individual properties of neoplastic cells and tumor microenvironment, which is comprised by diverse inflammatory/immune cells population; stromal cells; cancer stem cells; nutrients, growth factors, and a network of cytokines and chemokines [5–7]. It is widely accepted that cancer progression and prognosis is affected by immune/inflammatory cell infiltration into the tumor [6,8], a process tighly regulated by chemokines [9,10].

Chemokines are chemotactic cytokines able to control cell trafficking and positioning throughout the body compartments [11]. Chemokines have a defined chemical structure and comprise four subfamilies – CC, CXC, C and CX3C – distinguished according to the position of the first two cysteines adjacent to the amino terminus region. In chemokine nomenclature [12], the letter "L" followed by a number denotes a specific chemokine (e.g. CCL2 or CXCL8) [9,12]. The receptors are labelled by the letter R followed by the number (e.g. CCR2 or CXCR1). These molecules have key roles in tissue homeostasis, adaptive and acute immune responses [11]. In cancer, chemokines are implicated in progression by affecting tumor microenvironment and organ-specific spread of different tumor cells (e.g. breast, ovarian and colorectal) [13–15]. The biological and clinical relevance of these molecules is achieved by successful results from studies blocking chemokines system in some cancers [16–18].

Abbreviations: SCC, squamous cell carcinoma; HNSCC, head and neck squamous cell carcinoma; OSCC, oral squamous cell carcinoma; CAF's, carcinoma associated fibroblasts; MMP-9, matrix metalloproteinase-9; PI3K, phosphoinositide 3-kinase; AKT/PKB, protein kinase b; MAPK'S, mitogen activated protein kinases; EGFR, epidermal growth factor receptor; EMT, epithelial–mesenquimal transition; SNP'S, single nucleotide polymorphisms; OLK, oral leukoplakia; ERK1/2, extracellular signal-regulated kinase; NF-KB, nuclear factor kappa-light-chain-enhancer of activated b cells; FDA, food and drug administration.

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Concerning SCC of oral cavity and head and neck region, a considerable number of studies were published, particularly in the last ten years, and had contributed to delineate the relevance of chemokines in this malignancy [19–70]. Nevertheless, despite accumulated knowledge, clinical trials targeting chemokines as part of chemotherapy regimen are incipient and included a small numbers of patients [16,18]. Herein, we review the most important studies on SCC of oral cavity and head and neck region and chemokines. In Table 1, we summarize the main findings of in vivo and in vitro studies highlighting the function and clinical relevance of these molecules in oral cancer. We also provide a critical perspective of exploiting the chemokine system as future chemotherapeutic opportunities for SCC.

CC chemokines

CCL2

A significant number of studies highlighted the CCL2 importance in different cancer types [71,72] and striking preclinical antitumor activity was verified blocking CCL2 [16–18] (Table 2). In addition, studies have shown expression of CCL2 in SCC from oral cavity (OSCC) and HNSCC [19–22,73,74]. One study did observed an increase of CCL2 expression in OSCC and in metastatic lymph nodes [73]. Similarly, CCL2 expression in HNSCC was associated with tumor invasion [20]. A functional evidence of CCL2 in OSCC was demonstrated by observation that proliferation, invasion and tumor growth induced by oral carcinoma-associated fibroblasts (CAF's) are mediated by CCL2 [19]. Therefore, inhibition of CCL2 resulted in significant reduction of tumor burden in vivo [19].

Genetic polymorphisms of CCL2 and CCR2 genes and increased risk of developing OSCC were described [74]. In this study patients with G allele and GG genotype of CCL2 and 64I allele and wt/64I genotype of CCR2 had significative increased risk for OSCC. The underlying proposed mechanism is that polymorphism results in increase of chemokine transcription and consequently augment of its biological activity [74].

CCL3 and CCL5

The expression of CCL3 and CCL5 was observed in different types of malignancies as hematological disorders, colitis-associated carcinogenesis, breast and prostate carcinomas [75–79]. Although there are no clinical trial targeting these molecules, one ongoing study is testing an approved agent for inhibition of CCL3 and CCL5 receptor, CCR5 (Maraviroc), to treat metastatic colorectal cancer (Table 2). In the context of oral cancer, just one report showed an augmented expression of CCL3 and its receptor CCR1 in OSCC and in metastatic lymph nodes [80].

Regarding CCL5, Chuang et al. [24] did observe its expression in OSCC cells lines. Stimulation of these cells with CCL5 induced directed migration and production of matrix metalloproteinase-9 (MMP-9). Consistently, blockade of MMP-9 using small interfering RNA inhibited the CCL5-induced cell motility providing evidence of CCL5/CCR5 axis involvement in invasive and metastatic phenotype of oral cancer cells [24]. However, it remains unclear the specific receptor (s) involved in the CCL5 effects in HNSCC.

CCL5 and CCR5 gene polymorphisms were correlated with increased risk for OSCC development in two case-control studies [81,82]. It was observed a positive association of CCR5 gene variants, delta32 and 59029 A/G, and of genotypes CCL5-28 CG, CCL5-28 CG or GG, CCL5-28 CG/-403 CT and CCL5-28 CG/-403 TT with increased risk for OSCC development [81,82].

CCL7

CCL7 exhibited marked up regulation in colorectal and gastric tumors and were correlated with metastasis [15,83]. Recently, CCL7 has been identified as a key regulator of OSCC cell invasion and migration in vitro and in vivo [25]. Jung et al. [25] demonstrated that CCL7 stimulated cytoskeleton changes in oral cancer cells enhancing invasion and migration. Accordingly, the invasiveness was inhibited by treatment with neutralizing antibodies against CCL7 or it receptors CCR1 and CCR3 [25]. These findings might put CCL7 as a candidate for therapeutic intervention in oral cancer, but clearly, questions regarding another functions of CCL7 and its receptors needs to be answered.

CCL19 and CCL21

Some studies showed significant correlation between CCL19/CCL21/CCR7 expression, lymph node metastasis and poor prognosis of OSCC [27,84] and HNSCC [29]. In these studies, increased expression of CCR7 in primary tumors and lymph nodes was correlated with tumor size, clinical stage, recurrence, lymph node metastasis and poor survival rates [27,29,84]. Additionally, using heterotopic transplantation of HNSCC cells in mouse, it was observed an increase of CCR7-expressing cells in the lymph nodes of mice [29]. In contrast, Oliveira et al. [85] did not find any association between CCL19/CCL21/CCR7 expression with microscopic and clinical parameters of OSCC.

Data from in vitro experiments demonstrated that CCR7-positive SCC cells had increased capacity to adhere to lymph nodes, which was inhibited when these cells were treated with anti-CCR7 antibody [27]. Additionally, CCL21 is a potent stimuli for SCC migration [27]. Accordingly, CCL21 receptor – CCR7 – induces cytoskeleton modifications which in turn stimulate tumor cell migration, invasion, adhesion and survival of HNSCC cells via activation of PI3K/AKT and MAPK's and MMP-9 release [30,32–34].

CCL20

Abiko et al. [86] were first to demonstrate CCL20 expression in OSCC samples and in six different oral SCC lines. They observed CCL20 upregulation after bacterial or inflammatory stimuli of OSCC cell cultures. A recent study found an association of CCL20 expression with nodal metastasis and worse prognosis of OSCC [35]. In line with these findings, the suppression of CCL20 in SCC cell line using interfering RNA's reduced migration and invasion [35].

CXC chemokines

CXCL1 and CXCL2

CXCL1/CXCR2 axis was found to mediate angiogenesis, and promote tumor progression in different types of cancer, (e.g. gastric, colorectal and pancreatic) [87–90]. Shintani et al. [37] observed an increased CXCL1 expression in different SCC cell lines and tumor specimens and correlated it with microvessel density, leukocyte infiltration and lymph node metastasis. Moreover, one additional study demonstrated that CXCL1 production is essential to activate Epidermal Growth Factor Receptor (EGFR) signaling and to increase proliferation of human dysplastic oral keratinocytes [38].

The expression of CXCL2 was also demonstrated in human samples and SCC cell lines. This molecule seems to be involved in cancer-induced bone destruction and invasion once CXCL2-expressing OSCC cells injected into calvaria of athymic mice induced bone resorption via activation of pro-osteoclastogenic pathways [39]. Therefore, a significant reduction of osteoclast formation was observed after blocking CXCL2 [39].

CXCL8

In human cancers, it is well established that CXCL8/CXCR1 and CXCL8/CXCR2 axis can induce angiogenesis, tumor growth, motility of neoplastic cells and Epithelial–mesenquimal transition (EMT) [89–92]. In the context of oral cancer, it was previously shown that expression of CXCL8, CXCL6 (a CXCL8 homologue) and CXCR2 in tumor samples correlates with lymph node