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Role of Inflammation in Oral Squamous Cell Carcinoma

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1. Introduction

The most common malignant oral disease is oral squamous cell carcinoma (OSCC), and most of the time this term is used synonymously with oral cancer (1). Oral cancer is a serious and growing problem in many parts of the world. When grouped together with pharyngeal cancers, it is the sixth most common cancer globally (2). There is a wide geographic variation in the incidence of this cancer. This usually depends on the culture, life style factors and level of country development (1). In the South and Southeast Asia, parts of Western (e.g. France) and Eastern Europe, parts of Latin America and the Caribbean and in the Pacific regions, oral cancer rates are higher than the other parts of the world (3). The major risk factors of the disease are cigarette smoking (4), alcohol abuse (5), and viral infections such as HPV (6). These risk factors are primarily based on life style but do not adequately explain the increasing incidence of this cancer among the young population (7) and non-smoking females (8). In addition, genetic susceptibility may play an important role (9, 10, 11). Epidemiological studies have shown that chronic inflammation is associated with various types of cancer (12). It is estimated that 15-20% of all deaths from cancer worldwide are linked to infections and inflammatory responses (13). In the last two decades most chronic diseases, including cancer, have been associated with dysregulated inflammatory response. The identification of transcript factors such as NF- κ B, AP-1 and STAT3 and their gene products such as tumor necrosis factor (TNF), interleukin-1 (IL-1), interleukin-6 (IL-6), chemokines, cyclooxygenase-2 (COX-2), 5 lipooxygenase, matrix metalloproteases (MMP) and vascular endothelial growth factor (VEGF), adhesion molecules and others has provided the molecular basis for the role of inflammation in cancer. These inflammatory pathways are activated by tobacco, stress, dietary agents, obesity, alcohol, infectious agents, irradiation, and environmental stimuli, which, combined, account for as much as 95% of all cancers (14).

2. Inflammation and cancer

2.1 A short overview of inflammation

Inflammation is a crucial, complex host defense against biologic, chemical, physical, and endogenous irritants. The contribution of inflammation to physiological and pathological processes such as wound healing and infection needs to be understood for a better understanding of the role of inflammation in cancer formation. When tissues are injured, a

multifactorial network of chemical signals initiates and maintains a host response designed to heal the afflicted tissue. The response includes activation and directed migration of leukocytes (neutrophils, monocytes and eosinophils) from the venous system to sites of damage. Neutrophils are thought to coordinate recruitment of these inflammatory cells to sites of tissue injury and to the provisional extracellular matrix (ECM). This is a four-step mechanism: first come selectins that include adhesion molecules (L-, P-, and E-selectin) that facilitate rolling along the vascular endothelium; signals are then generated that activate and upregulate leukocyte integrins mediated by cytokines and leukocyte-activating molecules; neutrophils on the surface of the vascular endothelium are immobilized by means of tight adhesion through $\alpha 4\beta 1$ and $\alpha 4\beta 7$ integrins binding to endothelial vascular cell-adhesion molecule-1 (VCAM-1) and MadCAM-1, respectively; this brings about transmigration through the endothelium to sites of injury and is presumably facilitated by extracellular proteases, such as matrix metalloproteinases (MMPs) (15).

Cellular components

Platelet activation and aggregation, in addition to accelerating coagulation, provide a bolus of secreted proteins and α -granule contents to the immediate area, all of which help initiate and accelerate the inflammatory response by the host. Examples of such secreted proteins include arachidonic acid metabolites, heparin, serotonin, thrombin, coagulation factors (factor V), adhesive proteins (fibrinogen and von Willebrand factor), plasma proteins (immunoglobulin- γ and albumin), cell growth factors (platelet-derived growth factor (PDGF), platelet-derived angiogenesis factor, transforming growth factor- α (TGF- α), TGF- β and basic fibroblast growth factor (bFGF)), enzymes (heparinase and factor XIII) and protease inhibitors (plasminogen activator inhibitor-1, $\alpha 2$ -macroglobulin and $\alpha 2$ -antiplasmin). Following platelet-induced hemostasis and release of TGF- $\beta 1$ and PDGF, formation of granulation tissue is facilitated by chemotaxis of neutrophils, monocytes, fibroblasts and myofibroblasts, as well as synthesis of new extracellular matrix (ECM) and neoangiogenesis.

Neutrophils produce cytokines/chemokines required for effector cell recruitment, activation and response (16). These phagocytic cells initiate wound healing by serving as a source of early-response pro-inflammatory cytokines such as tumor necrosis factor- α (TNF- α) (17), and interleukin (IL)- 1α and IL- 1β (18). These cytokines mediate leukocyte adherence to the vascular endothelium, restricting leukocytes to areas of repair, and initiate repair by inducing expression of matrix metalloproteinases (MMPs) and keratinocyte growth factor (KGF/FGF-7) by fibroblasts (19).

Mononuclear phagocytes migrate from the venous system to the site of tissue injury, in response to tissue injury. Chemotactic factors, including PF-4, TGF- β , PDGF, chemokines (monocyte chemoattractant protein-1, -2 and -3 (MCP-1/CCL2, MCP-2/CCL8 and MCP-3/CCL7), macrophage inflammatory protein- 1α and - 1β (MIP- 1α /CCL3 and MIP- 1β /CCL4), and the cytokines IL- 1β and TNF- α , guide them to the site. Deployment of monocytes/macrophages to the site of injury causes the number of neutrophils to decline as they are phagocytosed by macrophages. Once present, however, they differentiate into mature macrophages or immature dendritic cells. After activation, macrophages are the main source of growth factors and cytokines (TGF- $\beta 1$, PDGF, bFGF, TGF- α , insulin-like growth factor (IGF)-I and -II, TNF- α and IL-1) that modulate tissue repair. Cells in their local microenvironment (e.g., endothelial, epithelial, mesenchymal or neuroendocrine cells) are

profoundly affected by macrophage products (20, 21). Following their activation, mast cells are full of stored and newly synthesized inflammatory mediators. This cell type synthesizes and stores histamine, cytokines and proteases complexed to highly sulphated proteoglycans within granules, as well as producing, lipid mediators and cytokines upon stimulation. Once activated by complement or by the binding of antigens to immunoglobulin E (IgE) bound to high-affinity IgE receptors (FcεRI), mast cells degranulate, releasing mediators including heparin, heparinase, histamine, MMPs and serine proteases, and various polypeptide growth factors, including bFGF and vascular endothelial growth factor. These function both in the early initiation phase of inflammation (e.g. vascular reaction and exudation), and in the late phase where leukocyte accumulation and wound healing takes place (15).

Chemotactic cytokines

Chemokines represent the largest family of cytokines (~41 human members), forming a complex network for the chemotactic activation of all leukocytes. Chemokine receptors, members of the seven-transmembrane-spanning G-protein-coupled receptors, vary by cell type and degree of cell activation (22). There is considerable redundancy in chemokine-receptor interaction, as many ligands bind to different receptors.

The composition of chemokines produced at sites of tissue wounding not only recruits downstream effector cells, but also dictates the natural evolution of immune reactivity. For example, MCP-1/CCL2, a potent chemotactic protein for monocytes and lymphocytes, simultaneously induces expression of lymphocyte-derived IL-4 in response to antigen challenge while decreasing expression of IL-12 (23). The net effect of this alteration facilitates a switch from a TH1-type to a TH2-type inflammatory response (15).

Tissue repair

In response to wounding, fibroblasts migrate into the wound bed and initially secrete collagen type III, which is later replaced by collagen type I. Synthesis and deposition of these collagens by fibroblasts is stimulated by factors including TGF-β1, -β2 and -β3, PDGF, IL-1α, -1β and -4, and mast cell tryptase. Once sufficient collagen has been generated, its synthesis stops; thus, during wound repair, production as well as degradation of collagens is under precise spatial and temporal control.

The final phase of the healing process is re-epithelialization and migration of epithelial cells across this amalgam. This is a process that requires both dissolution of the fibrin clot and degradation of the underlying dermal collagen. Epithelial cells at the leading edge of the wound express the uPA receptor, which is important for focal activation of uPA and the collagenolytic enzymes of the MMP family. In the absence of the fibrinolytic enzyme plasmin, derived from plasminogen after activation by uPA and tissue-PA, re-epithelialization is dramatically delayed (24).

The profile of cytokine/chemokines persisting at an inflammatory site is important in the development of chronic disease. The pro-inflammatory cytokine TNF-α (tumor necrosis factor-α) controls inflammatory cell populations and also mediates many of the other aspects of the inflammatory process. In addition, TGF-β1 is important, because it influences the processes of inflammation and repair in both a positive and negative manner. The key

idea is that normal inflammation – i.e., inflammation associated with wound healing – is usually self-limiting; however, dysregulation of any of the converging factors can lead to abnormalities and ultimately, pathogenesis. This seems to be the case during neoplastic progression (15).

3. OSCC and inflammation

Pathologists have known for more than 100 years that almost all tumors are accompanied by inflammatory cells. At present, there is almost unanimous agreement about the causes. The functional association dates back to Virchow, who in 1863 hypothesized that cancer arises in sites of inflammation (12). Today it is accepted that chronic inflammation resulting from low grade, persistent chemical, bacterial, viral agents predisposes the formation of the preneoplastic foci and promotes tumor development (25).

Infectious agents such as *Helicobacter pylori*, with its strong association to gastric cancer, or the relationship of non-infectious chronic inflammation like chronic pancreatitis to pancreatic cancer (12, 15) are examples of infection and inflammation leading to tumor growth. Chronic inflammation caused by infections and chronic irritations are being deeply researched in order to locate the exact mechanism that triggers the cancer.

3.1 Infections of oral cavity and OSCC

OSCC is a multifactorial disease where no single clearly recognizable causative factor has been identified. Inflammation or infection-related carcinogenesis of the oral cavity is currently under investigation. Considering the oral cavity which comprises a variety of different surfaces with a huge diversity of microorganisms, including more than 750 distinct taxa of bacteria, it is not surprising that one or more of these microbes would take part in the carcinogenesis of their habitat (26). Table 1 summarizes the infectious agents and related carcinogenic mechanisms in OSCC development.

The first species of bacteria that has been classified as a definitive cause of cancer in humans is *Helicobacter pylori*, which is associated with gastric adenocarcinoma (27). After this discovery many other possibilities were investigated. Gall bladder carcinoma was associated with *Salmonella typhi*, cervical carcinoma with *Chlamydia trachomatis*, lung cancer with *Chlamydia pneumonia* and intestinal cancer with *Streptococcus bovis* (28). No such direct link was established in OSCC. As mentioned before, the oral cavity is home to a rich microflora which changes composition and quantity from person to person and throughout the lifetime of an individual as a response to a variety of factors (26). In the studies with OSCC, it is essential to identify the organisms in the tumor specimens. Specific bacteria detected in the tumor specimen were *Exiguobacterium oxidotolerans*, *Prevotella melaninogenica*, *Staphylococcus aureus* and *Veillonella parvula* (29). In another study using saliva samples, out of 40 samples three bacteria were found to be elevated in OSCC, namely *Capnocytophaga gingivalis*, *Prevotella melaninogenica* and *Streptococcus mitis* (30).

It has been suggested that specific oral bacteria play a part in carcinogenesis, either through induction of chronic inflammation or by interference, either directly or indirectly, with eukaryotic cell cycle and signaling pathways, or by metabolism of potentially carcinogenic substances like acetaldehyde causing mutagenesis (28).

There are also a number of yeasts sharing the same environment with the bacteria. The most common yeast found in the human oral mucosa and generally regarded as commensals is a species of *Candida* (26). When host defense mechanisms are compromised or when changes occur in the local oral microenvironment *Candida spp.* act as 'opportunistic pathogens' leading to a wide range of oral mucosal infections (31). Besides being opportunistic, it has been shown that leukoplakia with candidal infection (formerly known as candidal leukoplakia) has a higher rate of malignant transformation than non-infected leukoplakia, and the estimated rate is up to 10% (32). Moreover, it has been observed that oral carriage of the most common type of candida, *Candida Albicans*, is higher in patients presenting with leukoplakia or OSCC than in patients without oral pathology (33). *C. albicans* may have a direct or indirect role in oral carcinogenesis. *Candida* might induce OSCC by directly producing carcinogenic compounds (e.g. nitrosamines) (26). The tubular hyphal structure of *C. albicans* is an important factor as it allows access of precursors from saliva and the release of nitrosamine product to keratinocytes, potentially initiating OSCC (34). In a recent study in a mouse model of oral carcinogenesis Dwivedi et al. (35), found that infection with *C. albicans* alone was not capable of inducing dysplasia or OSCC, but it was suggested that *Candida* creates an environment favorable to cell proliferation that may lead to clonal expansion of genetically altered cells. Alcohol consumption is a well-known risk factor in OSCC development. Although ethanol itself is not carcinogenic, its metabolites comprise highly toxic compounds such as acetaldehyde, hydroxyethyl radicals, ethoxy radicals, and hydroxyl radicals (31). The metabolism of alcohol starts in the oral cavity with the conversion of ethanol with enzymes catalyzed by alcohol dehydrogenase (ADH) from the epithelium and also from the oral microorganisms. Acetaldehyde in the mouth can also be derived from tobacco smoke, which contains a number of toxic aldehydes and other substances. Therefore tobacco and alcohol use has a synergistic effect on the risk of developing OSCC (5, 26, 31). From the molecular perspective, mucosal bacterial infections may influence carcinogenesis by inducing chronic inflammation in the adjacent connective tissue leading to upregulation of cytokines and growth factors. Similarly, *C. albicans* has been found to induce IL-8 secretion of endothelial cells by stimulating the cells to produce TNF- α (31, 36). The transcription factor NF- κ B, a key coordinator of innate immunity and inflammation, is also an important tumor promoter (14, 15). Candidal infection may activate particular toll-like receptors (TLRs), which are known to be activated after tissue damage and microbial infection. They can also communicate with the tumor promoter NF- κ B. NF- κ B is involved in carcinogenesis, especially where cancer-related inflammation is evident. The association between *C. albicans*, TLR and NF- κ B, and the production of cytokines and enzymes in the prostoglandin synthesis pathway, such as COX-2, is another potential mechanism that shows how *C. albicans* might influence the development of OSCC (31). Hooper *et al.* (26) suggested that 'Whether or not there is a causal relation between microbes and cancer, there is also a possibility that changes commensal microflora occur in conjunction with cancer development, which could have been used as a diagnostic indicator'. Meurman (37) proposed that it would be fascinating to control oral cancer by controlling oral microbes. The idea is truly fascinating and may not be as far-fetched as thought.

Apart from bacteria and yeasts there is also evidence that viruses take part in oral carcinogenesis. The role of the human papilloma viruses (HPV) and herpes simplex viruses (HSV) has been investigated in a number of studies (38, 39, 40). More than 100 types of HPV are identified, but only 12 types of HPV isolated from the oral cavity were associated with

malignant lesions, including HPV-2,-3,-6, -11,-13,-16,-18,-31,-33,-35,-52 and -57 (41). Studies indicated that HPV-16 and -18 were the most common types detected in individuals with OSCC (42). HPV-16 DNA, in particular, was detected predominantly in oropharyngeal SCCs located in the lingual and palatine tonsillar regions (39). Although the role of HPV in OSCC is smaller than in oropharyngeal cancers, it is important to distinguish HPV (+) OSCC since they are regarded as different entities (43, 44). HPV (+) OSCC are clinically found at young ages and generally in subjects without tobacco or chronic alcohol consumption. The histologically well differentiated and faster growing cancers which respond to chemo-radiotherapy have a clinical outcome—in term of overall survival—better than HPV (-) OSCC patients (44).

Recent studies revealed a synergistic effect between alcohol and HPV, but surprisingly tobacco use did not affect their relation (45). The mechanism of oral carcinogenesis by HPV is related with the E6 and E7 genes. Its genome is made up of early genes (E) with a primary function of episomal replication and late genes (L), which encode viral capsid proteins (41). There are 7 early genes identified and two of these, E6 and E7, have the capacity to immortalize the keratinocytes through inactivation of tumor growth suppression genes p53 and Retinoblastoma (Rb) respectively (39, 41). Generally, there is no clinic lesion or sign of inflammation in HPV (+) OSCC patients, but there is a relation proposed by Tezal et al. (40) that chronic inflammation in periodontal pockets may give an opportunity to initiate HPV infection and its persistency. In this study the base of tongue in squamous cell carcinoma patients were found to be 70% positive for HPV-16 and HPV (+) tumors, and had significantly higher rates of alveolar bone loss, which is indicative of chronic periodontitis.

Infections in the oral cavity are likely to play a role in oral carcinogenesis. Since there are numerous factors that cannot yet be distinguished, further studies with larger sample sizes are warranted.

Risk factor	Potential carcinogenic mechanism	Reference
Oral biofilm (Dental plaque)	Induction of cellular proliferation, inhibition of apoptosis, interference with cellular signalling mechanisms	46
	Mutagenic interaction with saliva	47
	Microbial action on oncogenic inflammatory reactions and proto-oncogenes	48
Periodontal disease	Providing opportunity to initiate HPV infection and serve resevoir for latent virus	40
Viridans streptococci	Interference with cellular signalling mechanism	49
	Converting ethanol to acetaldehyde	50
Candida albicans	Dysplastic changes in oral leukoplakia	26
	Converting ethanol to acetaldehyde	51
Human papilloma virus	Epithelial cell immortalization	52
Herpes simplex virus	Activation of proto-oncogenes inactivation of p53 tumor supressor gene	52

Modified from ref 37.

Table 1. Infectious agents and attributed carcinogenic mechanisms in oral carcinogenesis

3.2 Non-Infectious chronic inflammation and OSCC

Chronic inflammatory diseases such as ulcerative colitis, atrophic gastritis and Barret's esophagus (53) have been causally associated with cancer development. Within the oral cavity, the best example of chronic inflammation are periodontal disease (as mentioned before) and oral lichen planus (OLP), which is regarded as having a malignant potential in a wide range of 0-12,5% (48, 53, 54). OLP was proposed as a unique disease model for studying non-infectious chronic inflammation and its relation to cancer in a recent publication. In the tissue microenvironment of OLP it is expected to find cytokines/chemokines directly associated with oral carcinogenesis, and suggested that OLP-related OSCC is very likely to develop from another pathway than non-OLP OSCC (53). Chronic traumas in the oral cavity were also associated with oral carcinogenesis in some recent studies and case reports (55, 56, 57). Recently, we conducted a study on the etiological factors of tongue carcinoma. Patient and control groups each consisted of 30 male and 17 female subjects with mean ages 53,17 ($\pm 12,565$) and 52,55 ($\pm 11,542$) respectively. Smoking and alcohol abuse proportions were significantly higher in the patient group as expected ($p=0.0001$, $p<0.0001$ respectively). Chronic traumas were observed in 44,7% of the patients and 17% of the control group ($p=0.004$). On regression analysis chronic traumas, such as alcohol abuse or a family history of cancer and smoking ($p=0.0001$) (58) appeared as significant etiologic factors.

We believe that field cancerization is evident in oral and orofarengeal mucosa (in the existence of epigenetic factors) with multiple steps of molecular changes starting from the first sign of dysplasia. In our opinion, the nuance is that, the site of chronic trauma reaches the point of cancer before any other competitive sites of oral mucosa. This finding might be supported by studies that associate inflammation with OSCC.

4. Role of chemokines in cancer

Chemokines are low molecular weight proteins (approximately 8-17kDa) and were originally defined as potent attractants for leukocytes in all inflammatory settings—as well as being regarded as mediators of acute and chronic inflammation (59, 60). More than 45 non-allelic chemokine genes and more than 20 chemokine receptors, which interact combinatorial, have been identified in human genome (59). Chemokines are classified on the basis of the presence of variations on their cysteine group. The first group, the CC subfamily, is composed of 28 members, whereas the CXC subfamily comprises 17 members. The other two smaller subfamilies are the CX3C and XC families, and each is presented with one member. The CXC chemokines are further classified into ELR+ and ELR- subgroups based on presence or absence of their 'glu-leu-arg' motif. ELR+ CXC chemokines are angiogenic, whereas ELR- members (except CXCL12) function as angiostatic to inhibit the formation of blood vessels (60). These are shown in Table 2 with their subgroups, receptors and tumoral impacts.

Chemokines carry a great significance in many biological events, both in physiological such as embryogenesis, lymphoid organ development, in pathology as wound healing angiogenesis, Th1/Th2 development, leukocyte homeostasis and inflammatory diseases (25). Chemokines attract leukocytes to the site of inflammation. Chemokines affect both the pro- and anti-tumor effect in the tumor microenvironment by regulating immune cell infiltration (12).

Systematic name	Chemokine reseptor	P/M/A
<i>CXC chemokine</i>		
ELR+ chemokines		
CXCL1	CXCR2>CXCR1	P
CXCL2	CXCR2	P
CXCL3	CXCR2	P
CXCL4	Unknown	A
CXCL5	CXCR2	P
CXCL6	CXCR1,CXCR2	P
CXCL7	CXCR2	P
CXCL8	CXCR1,CXCR2	P
ELR- chemokines		
CXCL9	CXCR3	A
CXCR10	CXCR3	A
CXCR11	CXCR3	A
CXCR12	CXCR4,CXCR7	M,P
CXCR13	CXCR5	
CXCR14	Unknown	P
CXCR16	CXCR6	
<i>CC chemokine</i>		
CCL1	CCR3	P
CCL2	CCR2	P
CCL3	CCR1,5	P
CCL3L1	CCR1,5	
CCL4	CCR5	P
CCL5	CCR1,3,5	P
CCL6	Unknown	
CCL7	CCR1,2,3	P
CCL8	CCR3,5	P
CCL9/10	CCR1	
CCL11	CCR3	P
CCL12	CCR3	
CCL13	CCR2,3	
CCL14	CCR1,5	
CCL15	CCR1,3	P
CCL16	CCR1,2	P
CCL17	CCR4	
CCL18	Unknown	P
CCL19	CCR7	P
CCL20	CCR6	P
CCL21	CCR7	P,lymph node metastasis
CCL22	CCR4	
CCL23	CCR1	P/M
CCL24	CCR3	
CCL25	CCR9	
CCL26	CCR3	
CCL27	CCR10	
CCL28	CCR3,10	
<i>C chemokine</i>		
XCL1	XCL1	
<i>CX₃CL1 chemokine</i>		
CX ₃ CL1	CX ₃ CL1	P/M

P-tumor progression; M-metastasis; A-Angiostatic (Modified from ref 25)

Table 2. Chemokine superfamily and their receptors

Leukocytes infiltrate the tumor in response to chemokines secreted by the tumor itself. This immune cell recruitment may promote anti-tumor activities such as elimination of tumor cells by macrophages and recruitment of innate and adaptive immune cells (25). As the tumor progresses, the attraction of immune cells by chemokines being secreted from the tumor tissue itself results in an accumulation of leukocytes in order to increase tumor growth and angiogenic mediators for tumor vasculature. Mostly, receptors of these particular chemokines are up-regulated in tumor cells which allow them to take advantage of the persistent chemokines in their microenvironment. Tumors act as immune cells which have the ability to secrete chemokines for progression. The best example is macrophages present in the tumor lesions which secrete chemokines involved in tumor cell proliferation and survival as well as angiogenesis and metastasis (12, 13). In studies based on solid tumors such as breast and prostate cancers, cancer cells were found to express higher levels of chemokine receptors CXCR4, CCR7, CCR9 and CCR10 (61, 62). This might explain the metastatic tropism of each type of cancer, depending on the receptor present on cancer cells and chemokines produced at the site of metastasis. The ligand of CXCR4, CXCL12, is best expressed in the lung, liver and lymph nodes, which are frequently involved in tumor metastasis. Moreover, CCL21, the ligand of CCR7, is produced by lymph nodes, and CCL27, the ligand of CCR10, is secreted by skin (63). The step of tumor progression includes growth of the primary tumor, angiogenesis and metastasis. The chemokines and their receptors described in these steps are as follows: CXCR4/CXCL12 is the most efficient chemokine/chemokine receptor pair in enhancing cell growth (60), CXCR2 ligands, CXCL1, CXCL2 and CXCL8 in promoting angiogenesis (64), CXCR4/CXCL12 (in bone metastasis), CCL19-CCL21/CCR7 (in lymph node metastasis) and CCL27/CCR10 (in skin metastasis) pairs in metastasis (63). Recently, chemokines and their receptors have been identified as molecular targets of cancer therapy. CXCR4 is the most targeted receptor in these studies since it was the first chemokine receptor found to be related with metastasis. CXCR4 antagonists significantly reduced the size of primary tumors in mouse models of melanoma, osteosarcoma, breast and prostate tumors (65). Another promising target is the angiogenic chemokine receptor, CXCR2, and antagonists for this receptor are under consideration for melanoma therapy. Some others, such as CCR5 antagonist, have been approved by the FDA for the treatment of HIV-infected patients. Clinical trials involving a CCR9 antagonist are also in progression for Crohn's disease (60).

4.1 Chemokines and OSCC

Ammar et al. (66) conducted one of the first studies in oral squamous cell carcinoma and chemokine expression and revealed the association of CXCR4 expression in primary site and lymph node metastasis, mode of invasion, tumor recurrence and prognosis of the patients. Parallel with this finding Ishikawa et al. (67) found a highly significant correlation ($p=0.0035$) between CXCR4 expression and lymph node metastasis of OSCC. Another study on chemokine expression and OSCC was reported in 2004, investigating the role of tumor-associated macrophages in oral cavity and oropharyngeal squamous cell carcinoma. CCL2 was found to be up-regulated significantly in tumors compared with normal mucosa (68). Later on Ferreira et al. (69) reported the role of CCL2 in lymph node metastasis of OSCC. Lymph node metastasis was also associated with other chemokine expressions. For example, CCR7 was found to be significantly associated with five clinical factors, including lymph node metastasis. Other factors were large tumors, progressive stages, local recurrences and cancer death (70).

The association of CCR7 expression and lymph node metastasis was confirmed by another study in 2009 that demonstrated CCL21 stimulation increased the ability of CCR7-positive cells, which in turn showed stronger adhesion to lymph nodes (71). Another axis related with lymph nodes was CCL3/CCR1. Silva et al. (72) reported that CCL3/CCR1 expression was significantly higher in OSCC patients than controls and they suggested that CCL3/CCR1 axis may have a role in the spread of tumoral cells to the lymph nodes.

CCL5/CCR5 axis is also studied in OSCC and found related with enhanced migration of oral cancer cells through the increase of matrix metalloproteinase (MMP)-9 production (73).

Beyond the expression profiles there is another important factor related with predisposition and progression of cancer. Single nucleotide polymorphisms (SNPs), in genes for susceptibility factors, may influence gene expression, protein function and disease predisposition in certain individuals (74). Recently, many studies revealed certain functional polymorphisms influencing expression of genes related with inflammation, and have been correlated with an increased risk for developing oral malignancies (75, 76, 77). Vairaktaris et al. (74) studied polymorphisms of a group of interleukins and tumor necrosis factors α and β 162 OSCC patients. Among studied cytokines, IL-6 and TNF- α polymorphisms were found to be related with OSCC occurrence. Gupta et al. (78) confirmed the results of the previously mentioned study in tobacco-related OSCC in Asian Indians. They studied SNPs in TNF- α and TNF receptor genes and TNF- α -308 G/A was found related with susceptibility to OSCC. In a Southern Thailand study on polymorphism of proinflammatory cytokines genes, susceptibility to OSCC appeared to be influenced by variants in inflammatory and immunomodulatory genes (79). Another study, again from the Greek group, was published in 2009, showing that PAI-1, MMP-9, TIMP-2 and ACE polymorphisms, which effect their expression, contributed significantly in OSCC prediction (80). Currently there are not many studies on OSCC and polymorphism of chemokines. In one study for SDF-1 (CXCL12) and CCR5 polymorphisms in head-neck cancers, only SDF-1 genotypes among studied polymorphisms were found to be significantly different from the control group distribution and this was correlated with susceptibility of SCC of the head and neck—but salivary gland tumors were excluded (81). In the other study on CCR5 and its receptor CCL5 polymorphism conducted in Taiwan, 253 OSCC patients were enrolled and SNPs in CCL5-28 and -403 genes revealed increased risk for OSCC, whereas the combined effect of CCL5-28 CG and -403 TT genes were found to increase the risk of OSCC but reduce the clinicopathological development of OSCC patients (82).

There is also a recently published study about chemokine polymorphism and OSCC of our group from Istanbul University (83). We studied the CCL2/CCR2 axis since CCL2 has been identified as a major chemokine inducing the recruitment of macrophages in human tumors, including those of the bladder, cervix, ovary, lung and breast (84, 85, 86, 87, 88). CCL2 expression was detected at the protein level in tumor cells, both in primary tumors and in the metastatic sites (89). Studies indicated that lower levels of CCL2 did form tumors but with substantial delay in onset and growth rate (90). It is shown that the polymorphism A-2518G in the regulatory region of the CCL2 gene influences CCL2 expression in response to inflammatory stimuli (91). The level of expression may vary due to polymorphism in CCL2 and its receptor CCR2 (89). In Istanbul University we therefore studied CCL2 and its receptor CCR2 polymorphisms in OSCC, and to the best of our knowledge it was the first time in the literature. In this study, we hypothesized that genetic polymorphisms in

chemokines and their receptors (CCL2 A-2518G and CCR2-V64I) are involved in leukocyte trafficking and may thus influence the risk of OSCC.

We found a statistically significant difference between the control and OSCC groups for CCL2 A2518G genotypes ($p=0.012$). The frequencies of CCL2 2518 GG genotype and G allele in the OSCC group were higher than those of the control group ($p=0.043$ and $p=0.006$, respectively). Individuals carrying the G allele (GG+AG genotypes) had a 1.89-fold increased risk for OSCC ($p=0.011$; $\chi^2=6.45$; OR=1.89; 95% CI= 1.15-3.09).

The CCR2 V64I genotype frequencies for controls and cases were not significantly different ($p=0.08$). CCR2 V64I wt/wt genotype frequency in the control group was higher than that of patient group ($p=0.027$; $\chi^2=4.88$) and individuals carrying the 64I allele and wt/64I genotype had an increased risk for OSCC individuals ($p=0.027$, $\chi^2=4.88$; $p=0.048$; $\chi^2=3.91$ respectively).

While CCL2 G allele, CCL2 GG genotype, CCR2 64I allele, gender, smoking and alcohol consumption were associated with OSCC in univariate analysis, only CCL2 G allele, CCR2 64I allele, gender and alcohol consumption were associated with this disease in multivariate logistic regression analysis.

Association of tumor progression and the possibility of CCL-2 A2518G and CCR2 V64I polymorphism playing a role in OSCC as a prognostic marker has been studied. No statistically significant differences were found between genotypes.

The genotype distributions of both CCL2 A-2518G and its receptors CCR2-V64I vary in many cancer studies (92, 93, 94). Our findings indicated a relation between CCL2 A- 2518 GG genotype and G allele and OSCC ($p=0.043$ and $p=0.006$ respectively). It seems that individuals carrying the G allele had increased risk for development of OSCC ($p=0.011$). To our best knowledge, six papers have reported an association of CCL2 2518 A/G polymorphism with various cancer types including breast (93), bladder (95, 96), nasopharynx (94), endometrial (97) and non-small cell lung cancer (98). Among these studies CCL2 2518G GG genotype was found to be a risk factor in endometrial cancer (6.7-fold increased risk) (97) and in bladder cancer (3-fold increased risk) (95). In a breast cancer study CCL2 2518 GG genotype and G allele frequency were also found to be significantly different ($p=0.020$ and 0.026 respectively) in patients with metastatic tumors (93). These studies indicated that GG genotype and mutant G allele stand on the tumor side as reported in our study. These results are also consistent with the report suggesting the association of G allele with higher levels of CCL2 expression (89). However, in a nasopharynx cancer study (94), CCL2 2518G AA and AG genotypes, which were suggested to have an association with relatively lower expression of CCL2, were found to be more prone to distant metastasis than those with GG genotype. GG genotype and G allele were also found significantly decreased in non-small cell lung cancer (98) and bladder cancer (96) patients.

The CCR2 V64I wt/wt genotype frequency in the control group was higher than the patient group ($p=0.027$; $\chi^2=4.88$), and individuals carrying the 64I allele and wt/64I genotype had increased risk to develop OSCC.

Although results presented in the current study have suggested that CCR2-V64I polymorphism leading to increased risk for OSCC is similar to bladder (95) and endometrial cancer (97) types in Turkish population, the other results related to hepatocellular carcinoma (99) and non-small cell lung cancers (98) remain controversial.

These conflicting results may be explained in many different ways. First, as these studies were mostly conducted in different countries; ethnic differences may play a part. Several CCL2 A-2518G and CCR2-V64I polymorphism studies were conducted around the world, and the distribution of control group data in these studies reveals genetic variations in distinct geographic areas. These results strengthen the idea that ethnic variations affect gene polymorphisms. Secondly, all mentioned studies were unique in cancer types and none was repeated either in the same or different nation. Thirdly, the sample sizes in the studies are relatively small when compared with the number of patients in their own nation—including our study.

The current study is the first report showing the influences of CCL2 and its receptor CCR2 gene variants on OSCC. Our results suggest that the genetic variants in the CCL2 and CCR2 genes may be associated with susceptibility of OSCC in the Turkish population. We can speculate that CCL2 polymorphism might increase the biological activity of the CCR2 receptor and the development of OSCC risk within this group.

5. Conclusion

Inflammation is a recently defined contributor of oral carcinogenesis. In this multi-step process, inflammation might have a role in initiation as well as progression. Important components of this association are cytokines and chemokines produced by activated innate immune cells, which stimulate tumor growth and progression. Moreover, genetic susceptibility and gene/environment interactions are becoming more important in the attempt to eliminate the burden of cancer. The evidence found so far is sending out signals that OSCC may cease to exist in the future, and the referral will only be for a group of diseases that manifests symptoms of a similar sort. Further studies with larger sample groups in premalignant diseases of oral mucosa as well as OSCC are required to confirm these findings.

6. Summary

Oral cancer accounts more than 2% of all body cancers worldwide and more than 95% of them were found to be squamous cell carcinoma. Despite its relative rareness, high mortality rates (survival is not more than 50% in 5 years), which have not improved over the past 3 decades, have drawn the attention of the investigators. The well-known risk factors of oral squamous cell carcinoma (OSCC) like smoking, alcohol abuse and HPV infection, which are mainly based on life-style factors, seem inadequate to explain the increasing incidence especially among young population. In addition, genetic susceptibility may play an important role but the underlying mechanism of the disease still remains obscure.

Many theories about pathogenesis of the disease have been produced as a result of the clinical observations. One of the best known is about inflammation. Clinicians have experienced that tumor mass is almost always accompanied by an inflammatory zone and pathologists have always observed inflammatory cells in and around the tumors. This is not a new finding and in fact so old, which dates back to famous hypothesis by Virchow in 19th Century and even ancient back to Celsius in the year 50 BC. So what is new? The new issues are the molecular developments which elucidate many unanswered questions about cancer. The relation between inflammation and cancer was one of them.

In clinical researches about the relationship between inflammation and cancer, oral squamous cell carcinoma has an important advantage which is being easily detected by naked eye. Our previous clinical studies about etiology of tongue squamous cell carcinomas revealed that chronic traumas and irritations which lead to chronic inflammation were associated with tongue SCC formation. This encouraged us to move another step into the molecular field to understand the mechanism.

It is suggested that the relationship between cancer and inflammation occurs through two pathways: an extrinsic pathway driven by inflammatory signals such as infections and an intrinsic pathway driven by genetic alterations that cause both inflammation and neoplasia. Main mediators at the intersection of these pathways include transcription factors and primary proinflammatory cytokines.

Chemokines are a family of cytokines which are important mediators of leukocyte trafficking. They involve in defense of microbial infection, angiogenesis and metastasis. Several important polymorphisms of chemokine and chemokine receptors which deregulate chemokine system have been found and it is suggested that they may interfere with inflammatory and other diseases.

This chapter will include a brief review of molecular mechanisms of inflammation that seem responsible for etiology, pathogenesis and prognosis of oral squamous cell carcinoma and the new findings of our study group on chemokine.

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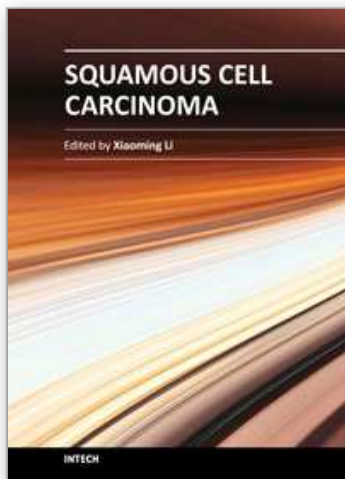
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This book points to some new areas for investigation on squamous cell carcinoma (SCC). Firstly, the features and management of some specific SCC is discussed to give the readers the general principles in dealing with these uncommon and sophisticated conditions. Some new concepts in adjuvant therapy including neoadjuvant therapy and gold nanoparticle-based photo dynamic therapy are introduced. Secondly, a detailed discussion of molecular aspects of tumor invasion and progression in SCC is provided with the emphasis on the roles of some important factors. The role of tumor microenvironment in head and neck SCC is specifically discussed. Thirdly, the roles of cancer stem cells (CSC) in cancer therapy of SCC are described. Molecular mechanisms involving therapeutic resistance and new therapeutic strategies targeting CSC are discussed in detail. Finally, other aspects concerning SCC are included, which involve the assessment, genetic manipulation and its possible clinical implications for the treatment of SCC.

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