REVIEW ARTICLE

Significance of CC Group of Chemokines in Oral Squamous Cell Carcinoma and Oral Potential Malignant Disorders: A Review

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Abstract

Aim and objective: The underlying association of the CC group of cytokines and its systemic role in fibrosis.

Background: Chemokines the secretory proteins are produced by leukocytes and other tissue cells integrally or after induction, function regionally in a paracrine or autocrine manner.

Review results: Functionally chemokines are split into constitutive (homeostatic, housekeeping, or lymphoid) and inducible (inflammatory) ones presented by cells, based on the conditions of their production or can be both. Chemotactic proteins have a vital role in host defense activities by developing and maintaining innate and acquired immunity. Importantly, chemokines also participate in wound healing, angiogenesis/angiostasis, lymphocyte polarization, apoptosis, fibrosis, and the development and metastasis of tumors.

Conclusion: It reviews the CC chemokine in health and physiology then the role of it in inflammation, immune diseases, oral potentially malignant disorders (OPMDs), and development and metastasis of the tumor.

Clinical significance: The diseases where inflammation and fibrosis play an important role continue to grow and therefore the need for safe and effective anti-fibrotic therapies is great and is also likely to increase.

Keywords: CC chemokines, Chemokines, Oral potentially malignant disorders, Oral squamous cell carcinoma.

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Background

Chemokines the secretory proteins are secreted by leukocytes and other cells integrally or on inducing. They apply their function regionally in a paracrine or autocrine manner. They are basically smaller in structure than cytokines which are usual for leukocyte chemoattractant with a lead role in the stimulation of leukocyte and chemotaxis.[1] Chemokines are basically isolated into categories based on the NH_2-terminal motif of two conserved cysteine residues: C, CC, CXC, and CX^3C. The signaling is by receptors of G protein-coupled (GPCRs), labeled as XCR, CCR, CXCR, and CX3CR as per the nomenclature of chemokine.[2] Functionally chemokines are split into constitutive and inducible or inflammatory types depending on the state of their production or can be both.[1] Homeostatic chemokines are significant for numerous physiological events by regulating subsets of cells during embryogenesis by hematopoiesis, organogenesis, and cell proliferation.[3] And presentation of inducible type is activated through inflammatory stimulus which is expressed by epithelial cells, endothelial cells, fibroblasts, and so on. These proteins have their role in host defense activities by developing and maintaining innate and acquired immunity. Importantly, chemokines aid in wound healing, angiogenesis/angiostasis, lymphocyte polarization, apoptosis, fibrosis tumor development, and metastasis.[4,5]

Many of the chemokines are proved to be major profibrotic mediators, proinflammatory factors, and even angiogenic mediators which aiding in fibrosis in various organs and even major role in tumorigenesis. This review explores the CC chemokine in health and physiology than the role of it in inflammation and immune diseases. The purpose of this paper is to understand the pathophysiology of the CC group of chemokines in oral potentially malignant disorders (OPMDs) and the development and metastasis of the tumor. By understanding the role of these chemokines, the therapeutic intervention targeting them or its activators can be developed.

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Discussion

CC Chemokine

CC chemokines belong to the b-family consist of two adjacent cysteines near the N-terminus are commonly known as CCLs (CC Ligands). Twenty-seven members have been identified of this group and are numbered CCL-1 to CCL-28, as CCL-9 is the same as CCL-10. Mostly, chemokines in this family pertain to four cysteines

(C4-CC chemokines) but some contain six (C6-CC chemokines). They stimulate the migration of monocytes, natural killer cells, and dendritic cells which share some receptors of CC chemokines.[1,6] These secreted proteins traverse by the circulatory system, for activation of an extracellular component of their associated receptors belonging to distinctive cell variants.[7]

CC Chemokine in Health and Physiology

Role of CC Chemokines in Embryonic Development

Chemokines hold a major part during the development of the endometrium of the uterine before the embryo attachment. The chemokine-receptor functioning for maternal–fetal junction provides human embryo to migrate and move into endometrium pertaining to the epithelium.[8] The expression of CX3CR1, CCR1, and CCR3 receptors along with their ligands are seen in the endometrial region of human trophoblasts.[9] The trophoblast even stimulates CXCL1, CXCL2, and CCL8 expression of maternal decidualized stromal cells intervening the signal among them for facilitating fetus impregnation.[10] The interactions for fetomaternal directing trophoblast migration along maternal endometria involvement of CCL14 and CCL4 are noted.[8]

Role of CC Chemokines in Immunity

Almost in all cell types, chemokine-mediated cell migration has been pictured; although its physiological function is mostly involved in chemokine stimulation with the recruitment of immune cells.[10] In both types of immunity, CC chemokines exhibit a crucial role. The CCL19 and CCL21 chemokines prompt CCR7 receptor existing on innate immune cells native T and B cells, mature DC/Langerhans cells (LC), and $CD56^{bright}$ NK cells and trigger the movement to T cell region of secondary immune organs.[11] The ligands of immature dendritic cells explicit CXC receptor 1, CC receptor 1, 2, and 6 for inflammatory chemokines which directs them to the site of inflammation.[11]

The movement of T cells to tissues of secondary lymphoid is moderated by CCL21 which is exhibited profoundly in endothelial cells of lymph node venules.[12] By contradiction, while pathogenic inflammation, like in infection, trauma, or malignancy, channelization of a different array of chemokines can be seen. The channelization of such a set of chemokines mainly is controlled by their formation in the regional site of inflammation.[13] The large range of chemokines is initiated by inducible types as tumor necrosis factor and interferon-γ.[5] Then, the immune components activated are attracted by these chemokines.[14] Mostly, chemokines govern the placement of immune cells via circulation and also in tissue, inclusive of environment-specified stroma and extracellular matrices. In numerous disorders related to autoimmunity and inflammation, like colitis and dermatitis, uncontrolled presentation of numerous chemokines is seen.[6]

CC Chemokines in Wound Healing and Angiogenesis

In the process of appropriate healing of a wound, chemokines have a vital role. The expression of CCL27 speeds up the healing of a wound by the implementation of precursor cells of bone marrow-derived keratinocytes.[15] The initiation of CCR2 present on endothelial cells leads to the expression of CCL2 further mediating neovascularization and also of vascular endothelial growth factor A (VEGF-A) and monocyte chemoattractant protein-1 (MCP-1).[16] The CCL2, CCL11, and CCL16 have a part in regulating angiogenesis.[17] Even the role of these small proteins which either initiate or suppress angiogenesis mediated by chemokines is an important point for healing wounds and inhibiting tumor growth, respectively.

Chemokine Pathophysiology

CC Chemokine in Autoimmune Diseases

The diseases related to autoimmunity are interpreted as a condition with ungoverned inflammation and increased infiltration of immune cells in the connective tissue. Increased expression of various chemokines in disorders as Crohn's or ulcerative colitis is seen, which was directly related to mucosal lymphocyte and leukocyte infiltration.[18,19] Same kind of results is seen in inflammatory dermatological disorders, with the expression of numerous chemokines which are believed to control the chemotaxis of many dermal penetrating effector cells.[20–22] In psoriasis and atopic dermatitis, excursive placement of T cells is performed by a wide variety of chemokines. Correlation of the elevated presentation of certain chemokines with a high invasion of immune cells in lesions and plaques of type 2 diabetes, multiple sclerosis, and atherosclerosis is shown.[23,24]

CC Chemokine in Oral Potentially Malignant Disorders

Oral squamous cell carcinoma (OSCC) sixth-most prevailing malignancy globally, occurs *via* a stepwise model accumulated by genetic abnormalities. They also result from lesions related to OPMDs, which have a high possibility of malignant transformation (MT) than the histologically normal oral mucosa.[25]

Oral lichen planus (OLP) is an OPMD with features of chronic inflammation of the oral mucosal membrane showing immune destruction in basal epithelial cells. The pivotal part is played by chemokines by incorporating T cell selectively by their receptors liberated by affected epithelial cells, and the related inflammatory infiltrate.[26] The receptors CXCR3 and CCR5 express type 1 T cells expression, whereas CCR3, CCR4, and CCR8 express type 2 T cells. Type 1 and 2 cells are differentiated by their secretion of cytokines.[26,27] In OLP, the expression of RANTES/CCL5, CCL20 and CCR1, CCR6 have been noted in lesional keratinocyte cells.[28,29] Even the chemokine CCL18 and 19 were seen elevated in OLP. The lamina propria of OLP presented RNA particular to receptors CXCR3 and CCR5, by this the infiltration of T cells seems to be controlled via these receptors.[30] C-CCL5 and CCL17 and its receptor CCR5 and CCR4, respectively, were found to have a major part in activating and recruitment of T cells in OLP.[31,32]

The CCL2 positivity in basal cells and fibroblasts in oral submucous fibrosis (OSMF) showing a positive correlation with smooth muscle actin (α-SMA) was reported. The study also revealed the increased expression of CCL2 in advanced OSMF stages in comparison to early OSMF. This suggested that fibroblast might have an active part regarding CCL2 secretion associated with OSMF, which has a role in recruiting myofibroblasts at the site of disease. This shows that there could be a key linkage of the CCL2-related recruitment of myofibroblasts pathway in the pathogenesis of OSMF.[4] Table 1 shows the studies related to the CCL group of chemokines in OPMDs.

The etiopathogenesis of OLP related to chemokines studied till now is by the recruitment of T-lymphocytes through chemokine receptors. And in OSMF, the CCL2-related recruitment of the myofibroblasts pathway in fibrosis has been noted in pathogenesis.

CC Chemokine in Cancer

The progression of the tumor is strongly affected by the generation of chemokines by tumor and stromal cells. Leukocytes and tumor

Table 1: Chemokine/chemokine receptor expression in oral potential malignant disorders studies

Lesion	*Chemokine*	*Receptor(s)*	*Sample type*	*Main findings(s)*	*Ref.*
OLP	RANTES/CCL5, CCL18, CCL19, CCL20, CCL17	CCR1, CCR5	Formalin fixed tissues	↑ CCL5 in oral squamous cells	28
			Peripheral blood and tissue	↑ CCL5 ↑mast cell trafficking	29
				↑ CCL5 advocates proliferation and migration of T-cell and inhibition of T-cell apoptosis	31
		CCR6	Tissue	↑ CCL18, CCL19, CCL20 ↑ Langerhans cells and T-cell infiltration	30
		CCR4	Peripheral blood	↑ CCL17 inflammatory infiltration of T cells	32
OSMF	CCL2		Formalin-fixed tissues	↑ CCL2 ↑ oral submucous fibrosis	4

cells are directionalized by chemokines and their receptors for moving and metastasis, access to the circulation, homing, and dissemination to definite tissues. Increased demonstration of chemokines and their receptors causing abnormal signaling and expression has been noted in many malignancies.[33] Table 2 enlists the studies related to the CCL group of chemokines in OSCC.

Numerous studies till now noted the importance of CCL2 in various cancer types[33,34] and notable preclinical antitumor action was clarified by blocking it. Many have revealed the presence of CCL2 in OSCC and HNSCC.[33,35] An increased level of it is seen in OSCC and HNSCC with nodal metastasis and tumor invasion.[33,35] Oral carcinoma-associated fibroblasts (CAFs) which were arbitrated by CCL2 has been observed about the functional affirmation of proliferation, invasion, and tumor growth in OSCC was demonstrated.[36] Higher risk of development of OSCC was explained in a study were gene polymorphism of CCL2 and CCR2 on the patients. This showed allelism of G and GG genotype for CCL2 and allelism of 64I and wt/64I genotype for CCR2 has markedly on the higher side with risk for OSCC. Looking at their results, the polymorphism mechanisms which resulted in aggravation of transcription of chemokine and finally, augmentation of its role was proposed.[35]

The chemokines CCL3 and CCL5 were expressed high with various malignancies. In oral malignancy and even metastatic lymph nodes, CCL3 expression along with its receptor CCR1 is observed.[37,38] Chuang et al. have observed the presence of CCL5 in cell lines of OSCC.[39] Provocation by CCL5 initiated movement and induction of matrix metalloproteinase-9 (MMP-9). A positive association was observed in CCR5 gene types and its genotypes with more chance in OSCC occurrence.[40] To rectify CC chemokine receptor CCR5 which was found dysregulated in a study, treated with interferon-α2b (IFN-α2b), showed downregulation of CCR5.[41] Few investigations revealed the therapeutic advantage of immunotherapy by enhancing T-cell-mediated tumor suppression by IFN-α2b treatment.[42]

The CCL7-mediated cytoskeleton modifications were noted in cells of oral malignancy which had the property of enhancing tumor invasion and migration.[43] The correlation compelled with CCL19/CCL21/CCR7 appearance, showed nodal metastasis and bad prognostication of OSCC in few studies.[44–46] The CCL21/CCR7 initiates cytoskeleton modifications leading to migrating, invading, adhesion, and cell survival of tumor cells by activating PI3K/AKT and MAPK's pathway with the release of MMP-9.[47–50] CCL18 was upregulated in the OSCC patients in an advanced stage with metastasis of cervical lymph node than those with early clinical stage and without cervical lymph node metastasis.[51] The CCL20 expression was first demonstrated in OSCC tissue and six types of OSCC cell lines by Abiko et al.[52] According to their observation, CCL20 upregulation was expressed upon stimulus by bacteria or inflammation in cultured cells of OSCC.[52] In a study conducted, the involvement of CCL20 expression in metastatic nodes with a poor prognosis was seen. Even they noted that suppressing the chemokine CCL20 by interfering with RNA's, decreased migration and invasion.[53]

The study conducted by Wang et al. revealed CCL18 increased the migration of cells causing invasion with the epithelial–mesenchymal transition (EMT). The feature of cancer stem (like) cells is induced by CCL18 in oral cancer cells. Immunohistochemical study on surgical tissue of OSCC showed a positive association with the presence of CCL18 and Bmi-1. The cells treated by CCL18 showed increased association with significantly high results in octamer-binding transcription factor 4 and Bmi-1, and bulks of aldehyde dehydrogenase positive and $CD133^+$ cells when compared with untreated cells. Moreover, Slug expression was upregulated by CCL18 by stimulation of the signaling pathway mTOR in cell line study of OSCC. The reversal of EMT induced by CCL18 and the stem cell-like character at molecular and even in functional levels was seen on blocking of this pathway by INK128, or knockdown of Slug by RNA hindrance.[54]

Lien et al. showed in a study that was *in vitro* and *in vivo* related to oral cancer cells about CCL4 which increased VEGF-C presentation leading to lymphangiogenesis. In favor of it miR-195-3p mimic counteracted CCL4-mediated expression of VEGF-C. In oral malignant cells, the activation of CCL4 intensified JAK2 and STAT3 phosphorylation.[55] CCL18 is a novel marker for the OSCC malignancy and prognosis, including lymph node metastasis, time-to-recurrence, and disease-free survival time.[55] Mao et al. suggested CCL18 is commonly expressed in OSCC tissue and expression status corresponded with tumor differentiation, metastasis, and prognosis.[56] CCL18 was found in the OSCC progression by binding the CCL18–NIR1 axis which might initiate a signaling pathway related to JAK2/STAT3. This axis has seen to manage the proliferative, metastatic, and EMT of oral tumor cells by the JAK2/STAT3 signaling pathway.[57]

The various chemokines and receptors of them are demonstrated by tumors, keratinocytes of OLP, and fibroblasts in OSMF. These expressed chemokines and chemokine receptors can be represented as an ideal target for immunotherapy. The chemokine receptor inhibitors can show promising results when given as combined therapy along with chemotherapeutic drugs or in antibody therapy against immune checkpoints. In the future, the inhibitors of chemokine receptors and chemokines can be used to

Table 2: Chemokine/chemokine receptor expression in oral squamous cell carcinoma studies

Chemokine	*Receptor(s)*	*Sample type in OSCC*	*Main findings(s)*	*Ref.*
CCL2	CCR2	Cell line and xenografts tissue	↑ CCL2 increase ROS and cell proliferation, invasion, and tumor growth	36–38
			↑ CCL2 ↑ lymph node metastasis	
			CCL2 and *CCR2* gene polymorphism ↑ the risk for OSCC	
CCL3	CCR1	Cell lines	CCL3 ↑ nodal metastasis	39
CCL4		Patient serum and tissue	↑CCL4 ↑ VEGF-C ↑ lymphangiogenesis	55
CCL5	CCR1, CCR3, CCR5	Cell line peripheral blood samples	↑ CCL5 ↑ motility ↑ migration of cells with ↑ MMP-9	40–42
			↑ CCL5 ↑ CCR5 increased OSCC	
			CCL5-28 and *CCL5-403* genes increased OSCC	
CCL7	CCR1, CCR2, CCR3, CCR5	Tissue and cell line	CCR1/CCR3 hindrance causing cell invasion	43
CCL19/ CCL21	CCR7	Tissue and cell line tissue	↑ CCR7 and CCL21/CCR7 leading to nodal metastasis. Advancement and increased tumor size with invasion and adhesion to nodes	44–50
		HNSCC	↑ CCR7 causes increased node metastasis, tumor size, clinical staging, local recurrence, and adhesive ability	
		HNSCC cell lines	↑ CCR7 causes increased node metastasis, migration, adhesion, and cytoskeletal reorganization	
			↑ CCR7/CCL19 leading to increase in PI3K, CDC42, and polymerization of actin	
			↑ CCR7 causing increased migration, MMP-9, b1 integrin, and cytoskeletal reorganization	
			↑ CCR7/CCL19 with increases in ERK/JNK; E-cadherin, vimentin, and tumor invasion	
CCL18		Patient serum and tissue cell lines, HSC6, SCC15, CAL33, and tumor tissue OSCC cell lines, patient serum and tissue	↑ Slug expression ↑ (mTOR) signaling pathway	51
			↑ Malignancy and prognosis, including lymph node metastasis, time-to-recurrence, and disease-free survival time	54
			↑ CCL18–NIR1 axis regulates proliferation, metastasis, and EMT of OSCC cells through JAK2/ STAT3 signaling pathway	56,57
CCL20		OSCC cell lines and tissue	↑ CCL20 increased nodal metastasis CCL20 blocking showed cell invasion	43, 53, 52
			↑ CCL20 activation by lipopolysaccharide and TNF-α caused oral immunoresponse to bacterial infection, which in turn involves tumor growth	

regulate the tumor, to subdue chemotherapeutic drug resistance and the optimization of subjects regarding immune response can be done.

Conclusion

Chemokines have predominated in physiology and homeostasis along with tumor pathogenesis and metastasis. It reviews in short about the information that is considered needful regarding recognizing the function of chemokines in human pathophysiology. If we can reduce the burden of chronic inflammation, it will have a huge, positive effect on therapy. Therapeutic intervention targeting cytokines or its activators for cytokine-related disease management can prevent disease initiation and progression. The pattern of cytokines expression and quantitative clinical endpoints such as complete cytokine profiling to exactly know the rate progression of the disease is needed desperately. The burden of disease where inflammation, fibrosis, and tumor progression as major factors continues to grow, so the need for safe and effective anti-fibrotic and immunotherapies is of great value.

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