

Immunogenetic contribution of the *fractalkine/CX3CR1* axis in oral squamous cell carcinoma

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Mario Alberto Alarcón-Sánchez^{1,2}, Lilibeth-Stephania Escoto-Vasquez³,
Julieta Sarai Becerra-Ruiz⁴, Rolando Rivera-Solano⁵ and Artak Heboyán⁶

Abstract

Oral squamous cell carcinoma (OSCC) is a malignant neoplasm with high mortality and recurrence. Its etiology is multifactorial and involves environmental factors such as smoking, alcohol, and human papilloma virus infection, as well as genetic factors such as single nucleotide polymorphisms. The *fractalkine/CX3CR1* axis is key in the regulation of cell apoptosis, proliferation, migration, and invasion, which are fundamental processes in cancer development. The *CX3CL1* gene, which encodes fractalkine, presents variants such as rs223815 (G > C) and rs682082 (G > A), associated with resistance to chemotherapy in ovarian cancer. In OSCC, its increased expression correlates with shorter survival. On the other hand, the *CX3CR1* gene, which encodes its receptor, has variants such as T280M and V249I, which are associated with reduced cell adhesion and deficiencies in chemotaxis. These variants have been implicated in various diseases and in reduced immune response against cancer. Although the *fractalkine/CX3CR1* axis may have protective or tumorigenic effects depending on the type of cancer, in OSCC its activation seems to favor tumor invasion and metastasis. Future studies could determine its impact on the development and treatment of this disease.

Keywords

chemokines markers, gene expression and/or profile methods, head and neck cancer disease sites

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Conceptual framework

Oral squamous cell carcinoma (OSCC) is a malignant neoplasm that has become a major social, economic, and public health problem to date. OSCC has a high mortality and morbidity rate because of metastasis and recurrence. It has been shown that at 5 years the survival rate is 50% and as the stage of the disease progresses it decreases to 30%.¹ OSCC can take various clinical forms ranging from bleeding ulcers with irregular margins that do not heal, to volume enlargements that can cause facial disfigurement and functional impairment. The etiology of OSCC is multifactorial, as several environmental factors have been proposed, such as smoking, alcohol, human papilloma virus infection, as well as genetic factors such as single nucleotide polymorphisms (SNPs).²

The role of the immune system in cancer progression has been a topic of great interest for the scientific community. The low molecular weight of chemokines is a characteristic that distinguishes them from other mediators as these

¹Molecular Biology Department, University Center of Health Sciences, University of Guadalajara (CUCS-UdeG), Jalisco, Mexico

²Institute of Research in Dentistry, Department of Integral Dental Clinics, University Center of Health Sciences, University of Guadalajara (CUCS-UdeG), Jalisco, Mexico

³Department of Oral Medicine and Pathology, Postgraduate Division, Dental School, National Autonomous University of Mexico, Mexico

⁴Department of Clinics, Los Altos University Center, University of Guadalajara, Tepetitlán de Morelos, Jalisco, Mexico

⁵South Pacific Dental Institute, Guerrero, Mexico

⁶Department of Prosthodontics, Faculty of Stomatology, Yerevan State Medical University after Mkhitar Heratsi, Yerevan, Armenia

Corresponding authors:

Mario Alberto Alarcón-Sánchez, Molecular Biology Department, University Center of Health Sciences, University of Guadalajara (CUCS-UdeG), Guadalajara 44340, Jalisco, Mexico.
Email: marioaasanchez@hotmail.com

Artak Heboyán, Department of Prosthodontics, Faculty of Stomatology, Yerevan State Medical University after Mkhitar Heratsi, Str. Koryun 2, Yerevan 0025, Armenia.
Email: heboyán.artak@gmail.com



proteins generally regulate directed migration, cell–cell interactions, cell positioning, and adhesion. Chemokines mediate some critical aspects during tumorigenesis, including activation, recruitment, phenotype, and function of immune cells, stromal cells, and tumor cells.³

Fractalkine, chemokine ligand 1 (CX3C motif) (CX3CL1) or neurotactin, was discovered by Bazan et al.⁴ This chemokine belongs to the CX3C subfamily, because it has a three amino acid (aa) residue separation in its N-terminal motif. It is also classified as a δ -category chemokine because it has a dual function as a cell adhesion molecule and chemoattractant.⁵

The *CX3CL1* gene locus is 16q13. Regarding its structure, it has its promoter, 3 exons, 3 introns and its 5'UTR and 3'UTR regions. The full-length messenger RNA (mRNA) initiates translation in exon 1 and terminates in exon 3. There are four isoforms of CX3CL1. The canonical form encodes a protein consisting of 397 aa, containing a 24 aa signal peptide. The mature transmembrane protein (free of the signal peptide) consists of 373 aa and is characterized by presenting four major domains. Its molecular weight is 17.5 kDa, but it is 95 kDa after glycosylation.⁵ In turn, it is also found in its soluble form (CX3CL1s), which originates from proteolysis of the transmembrane domain by matrix metalloproteases (MMPs) such as ADAM-17 (TACE), ADAM-10, Cathepsin-S and MMP-2 and MMP-3. Both forms of the protein recognize and bind to the chemokine ligand receptor 1 (CX3C motif) (CX3CR1).⁵ The membrane-bound protein acts primarily as a cell adhesion molecule, whereas the soluble form is a potent chemoattractant.⁵

The fractalkine receptor was first identified by Combadiere et al.⁶ and forms part of the superfamily of membrane receptors coupled to G proteins. This receptor can interact with other chemokines (CCL26); however, its affinity is 10- to 20-fold lower.⁵

The *CX3CR1* gene locus is 3p22.2. Regarding its structure, it has three promoters, six exons (of which only two contain coding regions), three introns and its 5'UTR and 3'UTR regions. The full-length mRNA initiates translation in exon 1 and terminates in exon 3. Four isoforms produced by alternative splicing are described. The canonical form encodes a protein consisting of 333 aa, with a molecular weight of 40 kDa.⁵

The term genetic variant is used to describe a change in the nucleotide sequence of DNA. The presence of at least two forms of a gene in a population (with a frequency greater than 1%) is what defines SNPs, which can result from the substitution of 1 nucleotide in the sequence for another; inserting or deleting 1 or more nucleotides or inserting repetitive sequences. In this way, changes can occur in the regulatory sequence of the gene (promoter), which can affect the rate of transcription; changes can occur in the non-coding sequence (intron), which can produce a biological effect on alternative splicing; or changes in the protein-coding part of the gene (exon), which can change the structure and function of the encoded protein.⁷

In cancer, four variants of the *fractalkine/CX3CR1* axis have been studied, that are rs223815, rs682082,⁵ V249I, and T280M.⁸

First, for fractalkine, the rs223815 variant corresponds to an exonic variant in which there is a base pair change from a G>C. However, the rs682082 variant corresponds to an intronic variant, in which there is a base pair change from a G>A.⁷ Regarding the genetic variants rs223815 (G>C) and rs682082 (G>A) of the *CX3CL1* gene, these SNPs have been shown to affect the clinical efficacy of carboplatin in the treatment of ovarian cancer as resistance to this drug, suggesting that when choosing to use carboplatin for ovarian cancer chemotherapy, it is necessary to detect both genotypes to provide a clinical reference.⁷ It is still unclear whether these two genetic variants may be associated with an increased risk of developing OSCC. At the gene level, increased expression of CX3CL1 has been demonstrated in OSCC compared to adjacent non-tumorigenic samples.⁹ However, at the protein level, serum levels have not yet been reported. On the other hand, it has been shown that salivary levels of CX3CL1 were increased in patients with irradiated head and neck cancer compared to the control group. In that study, the authors found that the p53 apoptotic pathway—which is a direct target of CX3CL1—had been altered, suggesting increased tumor suppression and apoptosis in treated patients.¹⁰ Locally, in tissue biopsies of OSCC, immunohistochemical staining for CX3CL1 levels was higher as the tumor stage increased, thus higher levels of CX3CL1 expression correlated with poor overall survival.⁹

Second, for *CX3CR1*, the T280M variant is an exonic variant, in which there is an aa change; in this case methionine replaces the threonine residue. However, the V249I variant is also exonic and in it, valine is replaced by the isoleucine residue. In relation to the genetic variants T280M and V249I of the *CX3CR1* gene, both have been shown to be in strong linkage disequilibrium. The problem observed is related to a reduced number of binding sites for their ligand, deficiencies in cell adhesion mechanisms, and a decrease in signaling and chemotaxis.⁸

On the other hand, different conditions—such as age-related macular degeneration, increased susceptibility to human immunodeficiency virus infection, coronary artery disease, atherosclerosis and Crohn's disease—have been associated with the M280 and I249 genetic variants.⁸ With respect to cancer, it has been shown that subjects carrying allele I could play a minor or partial role in colorectal cancer.⁸ On the other hand, one study also showed that subjects carrying M and I alleles could develop cancer after renal transplantation, probably due to lower CX3CL1-dependent antitumorigenic effects, so these genetic markers could help clinicians to determine the risk profile of recipients and to optimize pre-transplant and post-transplant treatment strategies.¹¹ However, in OSCC, it is still unclear whether these variants could play a protective role or an increased risk of disease development.

The *fractalkine/CX3CR1* axis regulates mechanisms such as apoptosis, proliferation, migration, and invasion, which are important functions for cancer survival.⁵ However, there are conflicting data on its role in tumor progression and prognosis depending on the specific type of cancer; for example, it has been reported that this axis predicts a better prognosis and fewer recurrences in hepatocellular carcinoma. In contrast, activation of the axis promotes tumorigenesis and progression of ovarian, pancreatic, and renal cancer.¹² In relation to OSCC, a recent study demonstrated that activation of this axis up-regulates ICAM-1 expression, leading to tumor invasiveness and metastasis.⁹ Additionally, the study published by Martínez-Flores et al.¹³ demonstrated that fractalkine correlated with tumor budding in OSCC.

In conclusion, accumulating evidence surrounding the *fractalkine/CX3CR1* axis suggests that this signaling system may play a key role in OSCC progression by influencing critical cellular processes such as migration, adhesion, and immune evasion. Although there is still some uncertainty regarding the precise role of its genetic variants in the pathogenesis of this type of cancer, the current findings open new possibilities for the development of more personalized diagnostic and therapeutic tools. In the future, the detection of specific SNPs could facilitate risk stratification in predisposed patients, while pharmacological modulation of the *fractalkine/CX3CR1* axis could offer targeted alternatives to limit tumor dissemination or improve the efficacy of existing treatments. To achieve this goal, further studies to clarify the functional effects of these variants and evaluate their clinical utility in large, well-characterized cohorts will be essential.

Abbreviations

aa	amino acid
ADAM-10	A Disintegrin and Metalloprotease-10
ADAM-17	A Disintegrin and Metalloprotease-17
CX3CL1	fractalkine
CX3CR1	chemokine ligand 1 (CX3C motif)
MMP-2	matrix metalloprotease 2
MMP-3	matrix metalloprotease 3
MMPs	matrix metalloproteases
mRNA	messenger RNA
OSCC	oral squamous cell carcinoma
SNPs	single nucleotide polymorphism

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Author's note

Rolando Rivera-Solano is currently affiliated with UNICLA Contemporary University of the Americas Pantel CDMX, Mexico City, Mexico.

ORCID iD

Artak Heboyán  <https://orcid.org/0000-0001-8329-3205>

Author contributions

Conceptualization, M.A.A.-S., L.S.E.-V., J.S.B.-R., R.R.-S. and A.H.; formal analysis, M.A.A.-S., L.S.E.-V., J.S.B.-R. and A.H.; investigation, M.A.A.-S., L.S.E.-V., J.S.B.-R. and A.H.; resources, M.A.A.-S., L.S.E.-V., J.S.B.-R. and A.H.; data curation, M.A.A.-S., L.S.E.-V., J.S.B.-R. and A.H.; writing—original draft preparation, M.A.A.-S., L.S.E.-V., J.S.B.-R., R.R.-S. and A.H.; writing—review and editing, M.A.A.-S., L.S.E.-V., J.S.B.-R., R.R.-S. and A.H.; visualization, M.A.A.-S., L.S.E.-V., J.S.B.-R., R.R.-S. and A.H.; supervision, M.A.A.-S., L.S.E.-V., J.S.B.-R. and A.H.; project administration, M.A.A.-S., L.S.E.-V. and A.H.; All authors have read and agreed to the published version of the manuscript.

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Data availability statement

The data supporting this study's findings are available from one of the corresponding authors upon reasonable request.

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