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Role of Interleukin 8 in Oral Squamous Cell Carcinoma: A Systematic Review.

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ABSTRACT

The objective of this study was to systematically review the scientific literature on the relationship between the levels of Interleukin 8 (IL-8) and Oral Squamous Cell Carcinoma (OSCC). There have been numerous studies in recent years that have shown a potential for the levels of salivary or serum IL-8 to be used as a simple diagnostic medium to detect the presence of squamous cell carcinoma. In this study we electronically searched the PubMed index for relevant articles and tried to summarize them to make a concise text that would help researchers for future investigations in the field.

Keywords: Interleukin 8, CXCL8, Oral Squamous Cell Carcinoma, Head and Neck Squamous Cell Carcinoma

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INTRODUCTION

Interleukin 8 (IL-8) or CXCL8 as now it is known (1) is a potent chemoattractant molecule discovered in 1987 (2-4).It is a proinflammatory, proangiogenic cytokine. The human chemokines are divided into 4 groups namely CXC, CC, CX3C and C, here C is NH2-terminal cystine and X is the intervening amino acid (1). Interleukin 8 belongs to the CXC chemokine family. There are 2 cell surface G-protein coupled receptors for IL-8 namely CXCR1 and CXCR2 (5,6). Apart from its chemotactic function, IL-8 is now said to have a role in proliferation and metastasis of cancer cells (7). Elevated levels of IL-8 are found in cancer patients' serum as well as in non-vascular extracellular fluids such as saliva, cyst fluid, CSF, urine etc.(7).

Oral cancer is the eighth most common cancer in the world and one of the third most common cancers in South-Central Asia (8). Using smoking and smokeless tobacco, betel nut and betel quid as well as alcohol consumption are contributing factors (9-13). In this study we tried to take a review of the scientific literature regarding the relationship between the levels of Interleukin 8 and oral squamous cell carcinoma (OSCC).

METHOD

We searched the PubMed index with the combinations of terms “IL 8” or “Interleukin 8” and “oral squamous cell carcinoma” or “OSCC” or “head and neck squamous cell carcinoma” or “HNSCC”. There were total 425 search results obtained. After excluding duplicates and refining the results, 32 relevant articles were selected. Out of those, 25 full text PDFs were accessible and were used for this review. Table-1 shows the search queries used in the advanced search of PubMed and the number of results thus obtained-

Table-1

Search Query	Number of Results
IL8 AND Oral squamous cell carcinoma	77 -17 results out of 77 were relevant. 16 selected 1 was in Chinese thus omitted.
Interleukin 8 AND Oral squamous cell carcinoma	57 -14 results out of 57 were relevant (including one in Chinese) all included in the above results.
Interleukin 8 AND OSCC	22 -10 results out of 22 were relevant (including one in Chinese) all included in the above results.
IL 8 AND OSCC	30 -14 results out of 30 were relevant. 1 selected, rest included in the above results.
IL 8 AND HNSCC	52 -9 results out of 52 were relevant. 5 selected, rest included in the above results.
Interleukin 8 AND HNSCC	36 -5 results out of 36 were relevant, all included in the above results.
Interleukin 8 AND head and neck squamous cell carcinoma	60 -11 results out of 60 were relevant 4 selected, rest included in the above results.
IL 8 AND head and neck squamous cell carcinoma	91 -20 results out of 91 were relevant. 6 selected, rest included in the above results.

No statistical analysis was conducted.

Review of the Literature

Oral squamous cell carcinoma still has high mortality and morbidity rates (14) despite of the improvements in the surgical and medical treatments. Normally OSCCs are diagnosed by the biopsy of the lesion. It is a time consuming and labor intensive procedure which needs specialized personnel in the field of pathology. It also requires patient cooperation and hence is not appropriate for community based screening procedures. All the following studies aim at finding a salivary (or serum) biomarker which will diagnose OSCC at its early stages or even predict the cancer in high risk groups so as to start preventive treatment leading to a better prognosis.

Initial evidence of relationship between elevated levels of IL-8 in the saliva of OSCC patients was given by St John et al in 2004 (15). They investigated the levels of IL-6 and IL-8 in the saliva and serum of OSCC patients. They selected T1 and T2 stage oral or oropharyngeal squamous cell carcinoma cases. Reverse Transcription-Polymerase Chain Reaction analysis (RT-PCR) was used for measuring IL-6 and IL-8 expression at messenger RNA (mRNA). Enzyme Linked Immunosorbent Assay (ELISA) was used for measuring IL-6 and IL-8 protein levels in saliva and serum of cases and controls. The results indicated that IL-6 levels in the serum and IL-8 levels in the saliva of cases were significantly higher than the respective levels of controls. They went a step further towards establishing saliva as a diagnostic medium by conducting sensitivity and specificity tests on the results. The combination of IL-6 in serum (threshold value greater than 0pg/ml) and IL-8 in saliva (threshold value greater than 600 pg/ml) gave sensitivity of 99% and specificity of 90%.

As the above study was done in the United States the results were specific for the American population. To determine whether the conclusion was consistent in other ethnic groups a similar study was conducted in the Serbian population by Brinkmann et al (16). They included T1, T2 as well as T3, T4 cases of OSCC and studied the salivary levels of 6 mRNA markers namely IL-1β, IL-8, SAT1, S100P, DUSP1, OAZ1 and 3 salivary protein markers- IL-1, IL-8, M2BP in them. They concluded that the levels of all 3 protein markers and 4 of the transcriptomic markers were raised in the OSCC patients and were statistically significant. This demonstrated that the previously found salivary biomarkers in the American population were valid in a different cohort and probably independent of ethnicity. They also concluded that rather than a single biomarker, the combination of certain biomarkers has a higher sensitivity and specificity towards detecting OSCC. A study by Elashoff et al (17) established the validity of 7 mRNA markers (IL-8, SAT, IL-1β, OAZ1, H3F3A, DUSP, S100P) and 3 protein markers (IL-8, IL-1β and M2BP) in the saliva of OSCC patients across 5 different cohorts. 395 subjects were investigated based on a case control design in 2 separate laboratories. The study showed the consistency of these biomarkers in 5 cohorts as well as their validity and reproducibility when tested in an outside reference laboratory.

This conclusion led to the derivation that in order to clinically use saliva for detection of cancer, it was necessary to be as effective in multiplex assays as in single-plex assays. To determine this efficacy, Arellano-Garcia et al (18) compared the Luminex Multianalyte Profiling (xMAP) technology for measurement of salivary proteins (multiplex) with single-plex ELISA. They concluded that both were equally effective in determining the levels of cytokines (IL-1β and IL-8) in the saliva of OSCC patients and controls.

Gokhale et al (19) studied the levels of IL-8, Vascular Endothelial Growth Factor (VEGF) and Epidermal Growth Factor Receptor (EGFR) in the serum of patients of head and neck squamous cell carcinoma. The subjects were divided into 6 groups- normal controls, stage I/II newly detected disease, stage III/IV newly detected disease, regional or local recurrence, metastasis and irradiated controls. There were no statistically significant differences between the serum IL-8 levels of normal controls and those of newly diagnose disease cases (either early or late stages). We can see that these results are consistent with those of St John et al (15). There was significant difference in the serum levels of IL-8 in recurrence and metastasis cases as compared to normal controls. Levels of VEGF and EGFR showed no statistically significant differences between normal controls against all other categories of cases. Another study having a partial concurrency to the above was conducted by Katakura et al [20] in 2007. This study demonstrated elevated levels of IL-6 and IL-8 in the saliva of OSCC cases as compared to healthy controls, although the values of IL-8 detected were not statistically significant, as found by the earlier researchers (15-17), instead those of IL-6 were found to be statistically significant. This study was conducted in Tokyo, Japan giving another example of how the biomarkers are valid across different continents irrespective of the ethnicity. Katakura et al also detected raised levels of IL-1β and osteopontin in the saliva of OSCC patients but these too were not statistically significant (20).

Korostoff et al (21) studied tongue squamous cell carcinoma (TSCC) particularly as it has poorer prognosis than similar stage lesions at other sites (22). Tongue is also the most common site for oral and oropharyngeal squamous cell carcinomas, constituting around 41% (23). Grossly, TSCC can be divided into exophytic and endophytic types. Exophytic tumors are usually papillary growths on a broad base or a narrow stalk whereas endophytic tumors are deep infiltrating and ulcerative (24,25). Korostoff and associates hypothesized that the levels of cancer related cytokines should be higher for a more invasive tumor, proposing that they will be higher in endophytic TSCC tumors than in exophytic. Cytokines studied were IL-1α, -6, -8, VEGF and TNF-α. They had 2 groups in cases- exophytic and endophytic TSCC and 4 groups within controls- healthy, smoking, drinking, smoking-and-drinking controls. They used ELISA to determine the salivary cytokine levels. Levels of Il-1α, IL-8, VEGF and TNF-α were raised in endophytic TSCC as compare to all other groups. Values of IL-6 were raised for exophytic and endophytic TSCC than in controls. All high risk controls had significantly higher levels of IL-8 than the healthy controls. The above results led to the conclusion that proinflammatory cytokine levels have a direct correlation with increased disease severity and patient mortality. Particularly IL-8 was shown to be important as its elevated levels in high risk groups would help in early detection and prevention of the disease and it also has a potential to detect recurrence [22], leading to a better prognosis.

Christofakis et al (26) studied the role of CXCL8 (or IL-8) in the growth of head and neck squamous cell carcinoma and motility of cancerous cells. Their aim was to determine if IL-8 can be targeted during treatment so as to limit the tumor growth and metastasis. They studied two cell lines, one from a primary tumor site of tongue squamous cell carcinoma and another from its synchronous nodal metastasis. They determined the presence and levels of IL-8 through Western Blot and quantitative real-time PCR (qRT-PCR). They also conducted proliferation, migration and invasion assays to investigate the effect of IL-8 on these aspects of tumor growth. They concluded that IL-8 expression was elevated in both the cell lines, leading to increased proliferation and cell motility. Further to limit the same they targeted IL-8 with shRNA plasmid, downregulating IL-8 expression upto 60%. The cells in which IL-8 was repressed by shRNA showed decreased rate of growth and migration. They reported that IL-8 regulates tumor cell growth and migration and can be studied in future as a target for therapeutic interventions. They have previously reported that CXCL5 has an important role in tumorigenesis and its inhibition affects tumor proliferation and motility (27).

Linkov et al (28) proposed that multiplexed profiling, using an expanded panel of biomarker would be more accurate in diagnosing cancer as compared to measuring a single cytokine. They considered total 60 serum biomarkers initially, from which they narrowed down 25 with the highest diagnostic powers. Those 25 included IL-8 along with other cytokines, chemokines and other tumor markers like matrix metalloproteinases, IFN-α, IFN-γ, IL-7, IL-17, vascular cell adhesion molecule, granulocyte colony-stimulating factor etc among others. LabMAP technology was used to analyze multiple biomarkers simultaneously. They concluded that in combination, these 25 biomarkers gave high sensitivity and specificity to identify HNSCC, classifying 92% of patients correctly.

Chen, Z., et al (29) also studied head and neck squamous cell carcinoma. Their aim was to determine the levels of proinflammatory and proangiogenic cytokines in HNSCC cell culture supernatants of University of Michigan Squamous Cell Carcinoma (UM-SCC) cell lines and to find if these cytokines are also expressed in tumor environment or tissue specimen and systemically in HNSCC patients. ELISA was used for the former and immunohistochemistry for the later. The UM-SCC cell lines were developed from patients who had squamous cell carcinoma of base of the tongue, tonsil, hypopharynx and floor of the mouth. The patients from which the primary SCC cell lines, tissue specimen and serum were obtained had HNSCC associated with nasopharynx, lateral tongue, retromolar trigone, supraglottis, base of the tongue, tonsil, maxillary sinus and pyriform sinus. 14 cytokines were taken into consideration including but not limited to IL-1α, IL-1β, IL-6, IL-8, Tumor Necrosis Factor (TNF)-α, Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF), Vascular Endothelial Growth Factor (VEGF), and basic Fibroblast Growth Factor (FGF). The UM-SCC cell culture supernatants and the tumor micro environment showed the presence of IL-1α, IL-6, IL-8, GM-CSF and VEGF. The same cytokines were also raised in the serum of the HNSCC patients thus concluding that the levels of proinflammatory and proangiogenic cytokines are raised in cell culture supernatants as well as in situ and systemically in patients.

Pries, R., et al (30) analyzed the permanent cell lines of head and neck squamous cell carcinoma to define the levels of cytokines IL-4, IL-6, IL-8 and IL-10 in the absence of immune cells. They used 4 different permanent HNSCC cell lines- NHY, ANT-1, PCI-1 and PCI-13. The above mentioned cytokines were measured

using Bio-Plex Cytokine Assay. The study revealed that IL-6 and IL-8 were secreted in the greatest amounts by all cell lines. IL-4 was detected in very low levels by all cell lines and no significant levels of IL-10 could be detected in any of the supernatants. The solid squamous cell carcinoma tumors are commonly infiltrated by immune cells hence it is important to differentiate between cytokines secreted directly by the tumor cells and those secreted by tumor triggered immune cells (31-33).

The relationship between clinicopathological features of head and neck squamous cell carcinoma, the serum levels of certain cytokines as well as telomerase expression by peripheral blood mononuclear cells (PBMCs) of the patients was studied by Hong, D. Y., et al (34). They also tried to relate these to the survival of the cases. IL-6, IL-8, Vascular Endothelial Growth Factor (VEGF); Hepatocyte Growth Factor (HGF) and Matrix Metalloproteinase (MMP)-9 were the cytokines studied. They found a positive correlation between higher telomerase expression and clinical presence of lymph node metastasis with an advanced stage III or stage IV lesion. There was no apparent relationship between the levels of IL-6, IL-8, HGF and the clinical stage of the disease. However, T3 and T4 lesions with lymph node metastasis showed significantly higher levels of VEGF. As it can be deduced, raised level of VEGF was also related to higher telomerase expression.

Allen Clint et al (35) conducted a prospective study. They studied patients of oropharyngeal squamous cell carcinoma before treatment (baseline) and then after every 3 months during the first year of undergoing chemoradiation therapy. Serum samples were taken from 30 patients with locally advanced stage III or IV lesions and the biomarkers considered were IL-6, IL-8, Vascular Endothelial Growth Factor (VEGF), Hepatocyte Growth Factor (HGF) and Growth-Related Oncogene-1 (GRO-1). These biomarkers functionally affect the pathogenicity of HNSCC29 and therefore were chosen to be investigated. They evaluated the relationship between the stages of HNSCC, the longitudinal changes in the levels of these cytokines and correlated it with the smoking status of the patients. They concluded that increased levels of 3 or more of the NF-κB modulated factors was indeed associated with the disease progression and decreased survival. Research also suggests that inhibition of these cytokines can inhibit tumorigenesis of xenografts in immunodeficient mice (36,37).

Rhodus et al (38) in 2005 included cases of oral premalignant lesions in their research, comparing the salivary levels of NF-κB- dependent cytokines in the premalignant cases with those of OSCC cases and controls. The cytokines studied were Tumor Necrosis Factor-alpha (TNF-α), Interleukin-1 (IL-1), Interleukin-6 (IL-6), and interleukin-8 (IL-8). Their results showed that the levels of these cytokines were significantly elevated in the oral premalignant lesion cases as compared to controls. Similarly, there were significant differences in the cytokine levels in the saliva of OSCC cases as compared to the premalignant lesion cases. A similar study was carried out by Punyani et al (39) recently; studying the salivary IL-8 levels in OSCC cases, oral premalignant lesion patients and healthy controls. Their results were similar to the above showing statistically significant increase in the IL-8 levels of OSCC patients as compared to cases of oral premalignant lesions and healthy controls.

SahebJamee et al (40) conducted a study similar to that conducted by Rhodus et al (38) in 2005, comparing the salivary concentrations of TNF-α, IL-1α, IL-6, and IL-8 in OSCC patients with controls, difference being that they did not have a group of oral premalignant lesion cases. Their results though were different from others. When subjected to ELISA the samples showed elevated levels of IL-6 which were statistically significant as compared to controls. As opposed to this the levels of TNF-α, IL-1α and IL-8 were raised in the controls as compared to the cases but the difference was not statistically significant. It should be noted that the controls in this study were matched not only by age and sex but also by their gingival conditions using the Modified Gingival Index unlike other studies.

CONCLUSION

Saliva is said to be the mirror of the body. It is an accessible medium representing the changes taking place during disease. It can help overcome one of the hurdles in clinical diagnosis which is the need of easy sampling with minimum discomfort to the patient (41). Future research is required to determine the threshold values of these biomarkers above which OSCC can be diagnosed with certainty. Another avenue for future research is to determine whether a single biomarker is accurate enough to diagnose cancer or a combination of various biomarkers is required (16). Also, studies at different stages of the disease, before and after treatment or in recurrent cases are needed to understand the behavior of biomarkers (34). Large multi-

institutional studies are needed so as to use saliva or serum clinically to diagnose oral squamous cell carcinoma (42).

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REFERENCES

[1] Zlotnik A, Yoshie O. Chemokines: a new classification system and their role in immunity. Immunity 2000;12(2):121-127.
[2] Yoshimura T, Matsushima K, Tanaka S, Robinson EA, Appella E, Oppenheim JJ, et al. Purification of a human monocyte-derived neutrophil chemotactic factor that has peptide sequence similarity to other host defense cytokines. Proc Natl Acad Sci U S A 1987 Dec;84(24):9233-9237.
[3] Walz A, Peveri P, Aschauer H, Baggiolini M. Purification and amino acid sequencing of NAF, a novel neutrophil-activating factor produced by monocytes. Biochem Biophys Res Commun 1987;149(2):755-761.
[4] Schroder JM, Mrowietz U, Morita E, Christophers E. Purification and partial biochemical characterization of a human monocyte-derived, neutrophil-activating peptide that lacks interleukin 1 activity. J Immunol 1987 Nov 15;139(10):3474-3483.
[5] Holmes WE, Lee J, Kuang WJ, Rice GC, Wood WI. Structure and functional expression of a human interleukin-8 receptor. Science 1991 Sep 13;253(5025):1278-1280.
[6] Murphy PM, Tiffany HL. Cloning of complementary DNA encoding a functional human interleukin-8 receptor. Science 1991 Sep 13;253(5025):1280-1283.
[7] Kotyza J. Interleukin-8 (CXCL8) in tumor associated non-vascular extracellular fluids: its diagnostic and prognostic values. A review. Int J Biol Markers 2012 Oct 8;27(3):169-178.
[8] World Health Organization. World Health Report 2003: A vision for global health. Shaping the future. : World Health Organization; 2003.
[9] Blot WJ, McLaughlin JK, Winn DM, Austin DF, Greenberg RS, Preston-Martin S, et al. Smoking and drinking in relation to oral and pharyngeal cancer. Cancer Res 1988 Jun 1;48(11):3282-3287.
[10] Hashibe M, Brennan P, Chuang SC, Boccia S, Castellsague X, Chen C, et al. Interaction between tobacco and alcohol use and the risk of head and neck cancer: pooled analysis in the International Head and Neck Cancer Epidemiology Consortium. Cancer Epidemiol Biomarkers Prev 2009 Feb;18(2):541-550.
[11] International Agency for Research on Cancer. Betel-quid and areca-nut chewing and some areca-nut-derived nitrosamines. : International Agency for Research on Cancer; 2004.
[12] Jayalekshmi P, Gangadharan P, Akiba S, Nair R, Tsuji M, Rajan B. Tobacco chewing and female oral cavity cancer risk in Karunagappally cohort, India. Br J Cancer 2009;100(5):848-852.
[13] Wen CP, Tsai MK, Chung WSI, Hsu HL, Chang YC, Chan HT, et al. Cancer risks from betel quid chewing beyond oral cancer: a multiple-site carcinogen when acting with smoking. Cancer causes & control 2010;21(9):1427-1435.
[14] Massano J, Regateiro FS, Januário G, Ferreira A. Oral squamous cell carcinoma: review of prognostic and predictive factors. Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology 2006;102(1):67-76.
[15] John MAS, Li Y, Zhou X, Denny P, Ho C, Montemagno C, et al. Interleukin 6 and interleukin 8 as potential biomarkers for oral cavity and oropharyngeal squamous cell carcinoma. Archives of Otolaryngology–Head & Neck Surgery 2004;130(8):929-935.
[16] Brinkmann O, Kastratovic DA, Dimitrijevic MV, Konstantinovic VS, Jelovac DB, Antic J, et al. Oral squamous cell carcinoma detection by salivary biomarkers in a Serbian population. Oral Oncol 2011;47(1):51-55.
[17] Elashoff D, Zhou H, Reiss J, Wang J, Xiao H, Henson B, et al. Prevalidation of salivary biomarkers for oral cancer detection. Cancer Epidemiol Biomarkers Prev 2012 Apr;21(4):664-672.
[18] Arellano-Garcia M, Hu S, Wang J, Henson B, Zhou H, Chia D, et al. Multiplexed immunobead-based assay for detection of oral cancer protein biomarkers in saliva. Oral Dis 2008;14(8):705-712.
[19] Gokhale AS, Haddad RI, Cavacini LA, Wirth L, Weeks L, Hallar M, et al. Serum concentrations of interleukin-8, vascular endothelial growth factor, and epidermal growth factor receptor in patients with squamous cell cancer of the head and neck. Oral Oncol 2005;41(1):70-76.

[20] Katakura A, Kamiyama I, Takano N, Shibahara T, Muramatsu T, Ishihara K, et al. Comparison of salivary cytokine levels in oral cancer patients and healthy subjects. Bull Tokyo Dent Coll 2007;48(4):199-203.
[21] Korostoff A, Reder L, Masood R, Sinha UK. The role of salivary cytokine biomarkers in tongue cancer invasion and mortality. Oral Oncol 2011;47(4):282-287.
[22] Rusthoven K, Ballonoff A, Raben D, Chen C. Poor prognosis in patients with stage I and II oral tongue squamous cell carcinoma. Cancer 2008;112(2):345-351.
[23] Patel RS, Clark JR, Dirven R, Wyten R, Gao K, O'Brien CJ. Prognostic factors in the surgical treatment of patients with oral carcinoma. ANZ J Surg 2009;79(1-2):19-22.
[24] Kirita T, Okabe S, Izumo T, Sugimura M. Risk factors for the postoperative local recurrence of tongue carcinoma. Journal of oral and maxillofacial surgery 1994;52(2):149-154.
[25] Sato J, Yamazaki Y, Satoh A, Notani K, Kitagawa Y. Pain is associated with an endophytic cancer growth pattern in patients with oral squamous cell carcinoma before treatment. Odontology 2010;98(1):60-64.
[26] Christofakis EP, Miyazaki H, Rubink DS, Yeudall WA. Roles of CXCL8 in squamous cell carcinoma proliferation and migration. Oral Oncol 2008;44(10):920-926.
[27] Miyazaki H, Patel V, Wang H, Edmunds RK, Gutkind JS, Yeudall WA. Down-regulation of CXCL5 inhibits squamous carcinogenesis. Cancer Res 2006 Apr 15;66(8):4279-4284.
[28] Linkov F, Lisovich A, Yurkovetsky Z, Marrangoni A, Velikokhatnaya L, Nolen B, et al. Early detection of head and neck cancer: development of a novel screening tool using multiplexed immunobead-based biomarker profiling. Cancer Epidemiol Biomarkers Prev 2007 Jan;16(1):102-107.
[29] Chen Z, Malhotra PS, Thomas GR, Ondrey FG, Duffey DC, Smith CW, et al. Expression of proinflammatory and proangiogenic cytokines in patients with head and neck cancer. Clin Cancer Res 1999 Jun;5(6):1369-1379.
[30] Pries R, Thiel A, Brocks C, Wollenberg B. Secretion of tumor-promoting and immune suppressive cytokines by cell lines of head and neck squamous cell carcinoma. In Vivo 2006 Jan-Feb;20(1):45-48.
[31] Hartmann E, Wollenberg B, Rothenfusser S, Wagner M, Wellisch D, Mack B, et al. Identification and functional analysis of tumor-infiltrating plasmacytoid dendritic cells in head and neck cancer. Cancer Res 2003 Oct 1;63(19):6478-6487.
[32] Veltri RW, T SUSAN MR, Maxim PE. and Immune Regulation in Patients With Squamous Cell Carcinoma of the Head and Neck. Cancer 1986;57:2295-2308.
[33] Heimdal JH, Aarstad HJ, Olofsson J. Peripheral Blood T-Lymphocyte and Monocyte Function and Survival in Patients With Head and Neck Carcinoma. Laryngoscope 2000;110(3):402-407.
[34] Hong D, Lee B, Lee J, Choi J, Wang S, Ro J. Expression of VEGF, HGF, IL-6, IL-8, MMP-9, telomerase in peripheral blood of patients with head and neck squamous cell carcinoma. Clinical and experimental otorhinolaryngology 2009;2(4):186-192.
[35] Allen C, Duffy S, Teknos T, Islam M, Chen Z, Albert PS, et al. Nuclear factor-kappaB-related serum factors as longitudinal biomarkers of response and survival in advanced oropharyngeal carcinoma. Clin Cancer Res 2007 Jun 1;13(11):3182-3190.
[36] Duffey DC, Chen Z, Dong G, Ondrey FG, Wolf JS, Brown K, et al. Expression of a dominant-negative mutant inhibitor-kappaBalpha of nuclear factor-kappaB in human head and neck squamous cell carcinoma inhibits survival, proinflammatory cytokine expression, and tumor growth in vivo. Cancer Res 1999 Jul 15;59(14):3468-3474.
[37] Bancroft CC, Chen Z, Dong G, Sunwoo JB, Yeh N, Park C, et al. Coexpression of proangiogenic factors IL-8 and VEGF by human head and neck squamous cell carcinoma involves coactivation by MEK-MAPK and IKK-NF-kappaB signal pathways. Clin Cancer Res 2001 Feb;7(2):435-442.
[38] Rhodus NL, Ho V, Miller CS, Myers S, Ondrey F. NF-κB dependent cytokine levels in saliva of patients with oral preneoplastic lesions and oral squamous cell carcinoma. Cancer Detect Prev 2005;29(1):42-45.
[39] Punyani SR, Sathawane RS. Salivary level of interleukin-8 in oral precancer and oral squamous cell carcinoma. Clin Oral Investig 2013;17(2):517-524.
[40] SahebJamee M, Eslami M, AtarbashiMoghadam F, Sarafnejad A. Salivary concentration of TNF alpha, IL1 alpha, IL6, and IL8 in oral squamous cell carcinoma. Medicina Oral Patologia Oral y Cirugia Bucal 2008;13(5):292.
[41] Lee J, Garon E, Wong D. Salivary diagnostics. Orthodontics & craniofacial research 2009;12(3):206-211.
[42] Lee KD, Lee HS, Jeon CH. Body fluid biomarkers for early detection of head and neck squamous cell carcinomas. Anticancer Res 2011 Apr;31(4):1161-1167.