Original Article

Expression of TNF-α in oral cancer: A prospective diagnostic and prognostic molecular biomarker

Vidya G Doddawad[1], Vidya CS[2]*, Shivananda S[3], B.M. Gurupadayya[4], Divya Rao[5], H.Hari Kishore Bhat[6]

[1]Associate professor, Department of oral pathology and microbiology JSS Dental College and Hospital (A Constituent College of JSS Academy of Higher Education & Research)Mysore-570015, Karnataka, India , Email- drvidyagd@gmail.com

[2]Professor Department of anatomy JSS medical College A constituent college of JSS Academy of Higher Education & Research Mysore-570022 Karnataka, India , Email: vidyacs@jssuni.edu.in

[3]Associate professor, Department of oral and maxillofacial surgery JSS Dental College and Hospital (A Constituent College of JSS Academy of Higher Education & Research) Mysore-570015 Karnataka, India , Email- drshivananda9@gmail.com

[4]Professor Department of Pharmaceutical Chemistry, JSS College of Pharmacy, (A Constituent College of JSS Academy of Higher Education & Research) Mysuru-570 015 , E mail: bmgurupadayya@jssuni.edu.in

[5]JSS Health system management studies A constituent college JSS Academy of Higher Education & Research Mysore-570022 Karnataka, India , Email: divyaraobj@yahoo.com

[6]Reader, Department of Oral and Maxillofacial Surgery, Yenepoya Dental College, Yenepoya Deemed to be University Mangalore-575018, Email: harikishore@yenepoya.edu.in

Abstract

TNF-α is a multifunctional cytokine that regulates cell proliferation and differentiation, as well as immunological and host defense responses to infection. It also induces angiogenesis, modulates tissue remodeling, and controls apoptosis.

TNF-α is a pleiotropic, pro-inflammatory cytokine that has the potential to be both pro-tumorigenic and anti-tumorigenic. TNF-α can be cytotoxic to tumour cells, slowing tumour progression or causing necrosis, and it can also enhance angiogenesis, proliferation, migration, and survival of tumour cells in oral cancer cells. Several research studies clearly imply that TNF-α and its soluble receptors could be effective in detecting, staging, and predicting prognosis in a variety of malignancies, including oral tumours. Well in many studies were conducted to detect the actual response of TNF- α, but lack of knowledge in understanding the true response of TNF-α towards oral precancer and oral cancer.

Keywords: Oral cancer, TNF-alpha, NF-kB, Pathology, Cytokine

1. Introduction

TNF-α or Tumour necrosis factor (Cachexin, Cachectin, TNF) is a cytokine and an adipokine.1 In 1975, Lloyd J. Old of New York coined the term "Tumor Necrosis Factor (TNF)" to describe as a cytotoxic factor produced by macrophages.2 Tumor necrosis factor (TNF) is a 17-kilodalton 157 amino acids protein3 and is a long type II transmembrane protein that occurs in stable homotrimers in solution is structured.3 It produced mainly by activated macrophages, T-lymphocytes, and natural killer (NK) cells. 4,5

The Tumor Necrosis Factor (TNF) superfamily is a type-II transmembrane protein that behaves as a cytokine when extracellular proteolytic cleavage releases it from the cell membrane.

Access this article online	
Quick Response Code:	Website: www.pnrjournal.com
	DOI: 10.47750/pnr.2022.13.04.193

Address for correspondence: Vidya CS, Professor Department of anatomy JSS medical College A constituent college of JSS Academy of Higher Education & Research Mysore-570022 Karnataka, India , Email: vidyacs@jssuni.edu.in

Received date: 11 August 2022 Accepted: 13 September, 2022
Published: 10 October, 2022

How to cite this article: Doddawad G V, Vidya CS , Shivananda S , Gurupadayya M B, Rao D, Kishore Bhat H H, Expression of TNF-α in oral cancer: A prospective diagnostic and prognostic molecular biomarker J Pharm Negative Results 2022;13(4):1384-1390

6 These proteins TNF are primarily expressed by immune cells and affect a variety of cellular processes such as immune response and inflammation, as well as proliferation, differentiation, apoptosis, and embryogenesis.7

TNF-alpha (TNF-α) is a member of the tumor necrosis factor (TNF) superfamily, which encoded by the TNF-α gene and is located on chromosome 6p21.3 in the MHC III polymorphism region, spans approximately 3 kilobases and has four exons.8 This was explained in 1985 and TNF gene was cloned in humans.

TNF-α exists as a transmembrane form (mTNF-α) and as a soluble form (sTNF-α). 9

mTNF-α is mainly expressed on monocytes/macrophages while mTNF-α binds to both TNFR1 and TNFR2.

sTNF-α is produced by enzymatic cleavage of mTNF-α, and only binds to TNFR1.

TNF signaling occurs through two receptors: TNFR1 and TNFR2.10,11

Most cell types express TNFR1 constitutively, and TNFR1 signaling is pro-inflammatory and apoptosis. Inhibition of TNFR1 signaling is beneficial in the treatment of autoimmune diseases. TNF-α binds irreversibly to TNFR1.

TNFR2 is primarily found in endothelial, epithelial, and immune cell types. The anti-inflammatory and cell-proliferative properties of TNFR2 signaling are well known. Wound healing is supported by TNFR2 signaling. TNF-α binds reversibly to TNFR2.

Behaviour Of Tnf-A :

TNF αis found in two forms: membrane-bound and soluble. During production, TNF-α migrates to the cell membrane, where the TNF-converting enzyme transforms the 26 kDa molecule to a 17 kDa protein that is released into the extracellular milieu.12,13 TNF is released from the plasma membrane by this enzyme, which also cleaves TNF receptors from the surface, resulting in suppression of TNF-α action. 13 TNF-α that is bound to the membrane and TNF-α that has been released are both active, but their effects differ depending on where they are located.14

TNF-α is produced by a variety of cell types, including adipose tissue, lymphoid cells, cardiac myocytes, neurons, fibroblasts, endothelial cells, and mast cells, and was previously thought to be primarily produced by macrophages.15,16 Large amounts of TNF-α are released in response to lipopolysaccharide, other bacterial products, and interleukin-1 (IL-1). Mast cells are responsible for the primary source of active TNF-α in the skin, which can be released due to inflammatory stimulation.17 TNF-α is mainly involved in the regulation of immune cells and can cause fever, apoptotic cell death, cachexia, and inflammation, as well as block carcinogenesis and viral replication.18,19

Action Of Tnf-A On Other Organs:

In the liver, TNF-α increases C-reactive protein and several other mediators by stimulating the acute phase response. It also causes insulin resistance by increasing insulin receptor substrate-1 (IRS-1) serine phosphorylation, which interferes with insulin signaling.20

On the immune system, TNF-α acts as a chemoattractant for neutrophils, promotes the adhesion molecules on endothelial cells, and therefore it causes the neutrophil migration.21

On macrophages, TNF-α promotes phagocytosis and the production of IL-1 oxidants and the pro-inflammatory lipid prostaglandin E2 (PGE2).22

Insulin resistance develops in various tissues. TNF-α phosphorylates serine residues on insulin receptors, preventing signal transmission.

Regulates the perception of bitter taste and influences metabolism and food intake. Obesity causes an increase in TNF-α and IL-6 levels.

Heat, swelling, redness, discomfort, and loss of function are all cardinal indicators of inflammation. TNF-α released by macrophages which is essential for granuloma initiation and formation. It plays a crucial role in the defense of intracellular organisms against invasion and activate the immune complex (ICs) through transportation of leukocytes.23

The most common cytokines associated with COVID-19 severity and mortality are TNF-α and IL-6.24

Bone remodeling directly regulates osteoclast precursor levels in the bone marrow by upregulating c-fms expression and activates osteoclasts by enhancing the signalling processes of the NF-B receptor activator (RANK).

On the nerves: The role of TNF-α in neurodegeneration Transgenic mice overexpressing CNS-specific TNF showed invading CD4+ and CD8+ T lymphocytes, astrocytosis, microgliosis, and demyelination.7

On a human tooth, large amounts of TNF-α have been found in the dental pulp tissue of people whose teeth were infected. The level of TNF-α is slowly increesease from mild inflammation to necrosis but it will be less in healthy pulp. Similar findings were discovered in rat teeth after pulp inflammation.

As a result, the literature data revealed that during the degranulation process released oral MC granules containing TNF-α, could be the source of TNF-α. Mast cell histamine, a potent arterial dilator, and modulator of vascular permeability have been found to play a role in the development of dental pulp inflammation. 25

The Tale Of Tnf-A In Oral Cancer

A variety of oral ailments, including autoimmune diseases including lichen planus, oral cancer, psoriasis, inflammation, and oral cancer, can be seen as a result of TNF-α

dysregulation. The role of TNF-α action in oral cavity cancer is highlighted in this article.

Among all the malignancies, the approximately 30% is the head and neck malignancies, and 80% of these tumors are oral squamous cell carcinoma (OSCC). Oral and pharyngeal cancer is one of the most common types of cancer and the sixth most common cancer worldwide. It is particularly common in Southeast Asia. 26

Oral cancer is the most frequent type of head and neck cancer, with 354,864 new cases and 177,384 cancer-related deaths globally in 2018.27 Lip and oral cavity cancers are very common in South Asia and are also the leading cause of mortality in men in India and Sri Lanka.28 Males have higher rates of OSCC morbidity and mortality (6.6 and 3.1 per 100,000, respectively) than females (2.9 and 1.4 per 100,000, respectively).

OSCC is caused by several factors, including the combined effect of genetic and environmental carcinogen exposure. 29 It also includes tobacco, betel nut, and alcohol, all of which have genotoxic effects and cause oral cell dysplasia. 30 The International Agency for Research on Cancer (IARC) has classified betel quid chewing or smoking as a Group I carcinogen, and it may play an etiological role in the development of oral and pharyngeal SCC (OPSCC).31

OSCC without metastasis has a 59 percent survival rate, while SCC with metastasis has a 70 percent survival rate. This survival and morbidity rate should concern all oncologists and researchers, and prompt them to better understand and focus on the pathogenesis of SCC.

The tumor microenvironment (TME) is made up of various kinds of mesenchymal cells, extracellular matrix, and inflammatory cells and also dysplastic epithelium with underlying connective tissue stroma. 32,33 TME facilitates communication between tumor cells and inflammatory cytokines such as TNF-α. These cytokines attract and recruit more inflammatory cells into the tumor microenvironment, thereby enhancing tumor proliferation, development, growth, invasion, and metastasis. 34

Recent research has identified a new link between the inflammation and dysplastic epithelial cell invasion through TNF-α mechanism. TNF-α which accelerate the migration of neutrophil , matrix degradation and invadopodia which explains the TNF-dependent mechanism in the oral cancer. This was demonstrated by a high level of TNF-α in the saliva of SCC patients, which acts as an inflammatory mediator promoting the up-regulation of genes involved in recruitment, matrix degradation, invadopodia, and invasion. 34

The Tnf-A Storm In Oral Cancer

TNF's role in HNSCC is uncertain and under investigation, however it appears to be linked to its various quantities at different phases of carcinogenesis. 35 TNF- α (tumour necrosis factor-alpha) is a powerful inflammatory and immunological mediator that works in both the paracrine and endocrine systems.36 It's also thought to control the proliferation and differentiation of a number of distinct cell types. Activated macrophages, T lymphocytes, and natural killer (NK) cells are the main producers of TNF-α.The main regulators of its bioactivity are soluble TNF-binding receptors. 31

A high level of tumour necrosis factor-alpha (TNF-α) in saliva can be used as an early indicator of OSCC.37,38,39 TNF-α is a pro-inflammatory cytokine that is produced largely during the chronic inflammatory response, especially in reaction to foreign particles.40 As a result, TNF-α overexpression has been linked to smokeless tobacco tissue deposits. The gene expression of different interleukins and TNF-α is altered by long-term use of smokeless tobacco, rendering high-risk patients more vulnerable.41,42 Tobacco chewing or components of betel quid (BQ) cause oral keratinocytes to release tumour necrosis factor-alpha (TNF-α), causing a cytokine cascade that leads to oral mucosa inflammation and cancer. 31

Previous studies have linked high TNF- αlevels to oral SCC, but it's unclear if high TNF-α levels are mostly a reflection of the oral cancer microenvironment or if TNF-α plays a more active role in the disease process.31

TNF-α stimulates NF-kB, a cell cycle regulator that allows cells to resist apoptosis and proliferate.43,44,45 TNF-α may also act as an endogenous mutagen by stimulating the creation of reactive oxygen species, which causes direct DNA damage.46,47 When comparing TNF-α treated cells to non-TNF-treated cells, there was a significant increase in genetic instability. 48

Because a transmembrane molecule activates a soluble protease, TNF-α can have both tumor-necrotic and tumor-promoting actions. 49,50 TNF-α may thus play a significant part in carcinogenesis by controlling proliferation, invasion, and metastasis. TNF-α expression was observed to be higher in HPV-infected SCC, implying that TNF-α plays a role in HPV response and subsequent carcinogenesis. 35 The soluble TNF-α can cause hemorrhagic necrosis by selective destruction of tumor blood vessels and generation of a specific anti-tumor T-cell response. It is critical for the activation, proliferation, and hypertrophy of mononuclear and phagocytic cells. 51,52 Endogenous membrane TNF-α can stimulate VEGF, interleukins, IL-6, IL-8, and their receptors, as well as tissue remodeling by inducing matrix metalloproteinases such as MMP-9.53,54,55

Hence, endogenous TNF-α, which shows and plays a key role in intiation, proliferation and progression of oral cancer,56 TNF-α and TNF-β have previously been connected to prothrombotic events via increased production of plasminogen activator inhibitor-1, which has also been linked to an increased risk of oral cancer. 57

Understanding Tnf-A AND Nf-Kb Signaling System

Elevated TNF-α and constitutive NF-kB activity has been found in precancerous and cancerous lesions of the oral cavity. Although the NF-kB pathway is necessary for human health, abnormal activation of the protein can lead to autoimmunity, inflammation, and malignancies illnesses such as oral cancer. Recent research has shown that IKK expression is involved in the major pathway of pro-inflammatory genes along with TNF-mediated NF-kB activation and expression (see Figure 1). 29, 58

TNF-α is produced by macrophages, T lymphocytes, and natural killer cells in response to a variety of stimuli, including alcohol, tobacco and its products, and microbes. TNF-α receptors can be found on both epithelial and stromal cells. Tumor necrosis factor receptor type-1 (TNFR-1) associated DEATH domain protein encoded by the human TRADD gene, and TNF receptor-associated factor-2 (TNFR-2), a protein encoded by the human TRAF2 gene.

Caspases 8 and mitochondrial pathways are linked in TNFR1 which induces TRADD and leads to apoptosis. TRAF2 and NF-B inducing kinase (NIK), a signaling protein that activates and initiates the Nuclear Factor Kappa-Light-Chain Enhancer of Activated B Cells (NF-B) pathway. These NF-kB signaling pathways activate IKK, which degrades IkB and releases NF-kB dimers. Later, upon further activation, NF-kB is transported to the nucleus and interacts with the gene to stimulate transcription of the target gene. The NF-kB signaling pathway in the nucleus contains receptors, and proximal signaling via the conventional and noncanonical NF-kB pathways has been well studied. In IKK/NF-kB signaling, both canonical (classical) and non-canonical (alternative) signaling pathways determine whether a cell lives or dies. TNFR2 also activates transcription factors such as activator protein-1 (AP1) or IB kinases (MEKKs), which promote cell proliferation and invasion.

TNF-α activates the NF-kB pathway, which promotes tumour cell proliferation while blocking apoptosis, as well as enhancing tumour angiogenesis, invasion, and distant metastasis, all of which are important in the development of oral cancer. 59

Well-Studied Tnf-A In Oral Cancer

TNF-α has been shown in preclinical and clinical trials to have pathogenic and therapeutic anti-tumor effects in oral cancer, but there is emerging evidence that it may also promote cancer development and dissemination.31 TNF-α was studied and quantified using enzyme-linked immunosorbent assay (ELISA) and polymerase chain reaction (PCR), as well as immunohistochemistry, in situ hybridization (ISH), and reverse transcription-polymerase chain reaction (RT-PCR) (RT-PCR).59

Waqar Muhammad et.al. investigate In unstimulated whole saliva, snuff dippers showed higher levels of TNF-α and cellular micronuclei than healthy controls, and the researchers concluded that TNF-α and micronuclei are prospective salivary biomarkers for an oral biological effect in snuff dippers. 30

Cheng-Mei Yang et al. used TaqMan real-time assays were used to determine the genotypes of cancer patients and healthy individuals who routinely chewed BQ. In OPSCC patients, they discovered no link between TNF-α genotypes and clinicopathologic results or patient survival. 31

M. Ameena et.al, found that TNF-α levels were found to be greater in oral cancer patients in Europe than in healthy people. 60

Rajkumar Krishnan et al. investigated the relationship between serum and salivary TNF-α and histological grading in oral cancer, as well as their role in distinguishing between premalignant and malignant oral disease, and discovered that OSCC patients had higher TNF- levels in both serum and saliva than healthy controls and PMD patients. Even the histological grading of OSCC and TNF-α revealed a link between the two. 26

Deepti et al. noted that there is an increase in salivary TNF-α levels from controls through leukoplakia to OSCC, supporting the concept that TNF-α is a pro-tumorigenic factor. They suggest that saliva be used to estimate biomarkers and evaluate TNF-α as a prognostic marker and a sign of neoplastic changes from OPMD to cancer.29

Patil et al. found that OSCC had a very high salivary TNF-α concentration compared to leukoplakia and controls. The quantitative sandwich ELISA technique was used to determine TNF-α concentrations.61

Jureti et al. suggested that salivary TNF-α levels were measured using an ELISA assay in patients with premalignant lesions, patients with OSCC, and healthy controls. When compared to OPML and control, OSCC patients showed the highest TNF-α.62

Rhodus et al. discovered a significant difference in TNF-α levels in three groups of patients with Oral PreMalignant Lesion, Oral Squamous cell Carcinoma, and controls using an ELISA test. TNF-α levels in OSCC saliva were elevated as compared to OPML and controls.63

SahebJamee et al. in a study with nine OSCC patients and nine controls found a statistically insignificant relation of TNF-α level and determined by the quantitative sandwich ELISA technique. 64

Strategies To Manage Tnf-A

TNF-α serves as an inflammatory mediator in the tumor microenvironment, triggering the epithelial mesenchymal transition of the tumor cell and promoting tumor metastasis. Cancer cell invasion and metastasis are thought to be aided by TNF-activated signalling pathways and transcription factors. Normal cells are less sensitive to transcription factors than cancer cells. Cancer cell proliferation is reduced, and

apoptosis of cancer cell is promoted, resulting in specific suppression of transcription factors and signaling pathways. TNF-α increases oral cancer cell invasion and metastasis, which depend on activation of the NF-kB pathway. 58

TNF-α, which is produced in oral malignancies, may promote carcinogenesis by enhancing local blood flow and causing tissue remodeling.65 In a therapeutic context, TNF-α synthesis by OSCC cells could result in resistance to the cytotoxic effects of host-derived TNF-α or exogenous recombinant TNF-α. TNF-α has been tested in cancer patients in several clinical trials, but no substantial survival advantages have been found. 12

Drugs that block the effect of TNF-α or NF-kB pathway are used to treat oral cancer are 5-fluorouracil, cisplatin, docetaxel. 66

5-fluorouracil

In the case of 5-fluorouracil, researchers showed that NF-kB has also been linked to cancer (5-FU). The administration of 5-FU to a human cancer cell line, NUGC3 cells (5-fluorouracil sensitive), resulted in the stimulation of NF-kB. The fact that inhibiting NF-kB reduces chemoresistance and boosted apoptosis can provide the potential of addressing a major problem in chemotherapy, namely chemoresistance development.

Cisplatin

The chemotherapeutic efficacy of cisplatin can be enhanced by inhibiting NF-kB in vitro and in vivo. An in vitro model of NF-kB-mediated carcinogenesis was described in 2014. The researchers used a cell-based phenotypic readout to extract 12 genetic components from lentiviral libraries encoding 20 or 50 amino acid-long polypeptides that activates NF-kB activity by causing apoptosis.

Docetaxel

Cyclosporin inhibits the NF-kB pathway through anti-NF-kB medication has the potential to be used in cancer patients. Docetaxel (Taxotere)-induced apoptosis was boosted in human cancer cells by activating NF-kB, which inhibited the anti-apoptotic NF-kB impact. It has been suggested that inhibiting NF-kB could help in cancer treatment.

TNF-α seems to be a promising biomarker for the most accurate diagnosis of OSCC, and early detection of such changes could help patients be selected for early interventional therapy.The level of this marker, on the other hand, must be examined in other oral inflammatory diseases as well. 26 Hence, supression of the NF-kB signaling system could be helpful in the cancer therapy. 58

Conclusion

Tumor necrosis factor-α is a pleiotropic cytokine that affects a wide range of cells and has different effects on different cells. TNF-α released macrophages/monocytes, lymphocytes, and neutrophils, among other hemopoietic effects. TNF-α is a cytokine released in the inflammatory cascade that has been linked to OSCC pathogenic pathways. The determination of whether a cell will proliferate or apoptosis or differentiate in response to these TNF depends on specific characteristics of the cell type. Despite extensive research on the disease, neither the etiology nor the pathology of OSCC is understood. A better knowledge of the disease has led to the development of additional biological or molecular diagnostic markers that may supplement or even replace some of the less objective convectional criteria.

Ethical approval

Not applicable

Funding details

There is no funding source available

Conflict of interest

All autors claims that there is no conflict of interest

Informed Consent

Not applicable

Authorship contributions

VCS, VGD wrote the paper with revision and the corresponding author. GBM put the study design, idea of manuscript. SS, HKB, DR proof reading and approved the final version of the manuscript.

References

Balkwill FR. Evidence for tumour necrosis factor/cachectin production in cancer. The Lancet. 1987;330(8570):1229–32.

Ruddle NH. Tumor necrosis factor (TNF-alpha) and lymphotoxin (TNF-beta). Current Opinion in Immunology 1992;4(3):327–32.

Bahia MS, Silakari O. Tumor necrosis factor alpha converting enzyme: an encouraging target for various inflammatory disorders. Chem Biol Drug Des 2010;75(5):415-43.

Yoneda K, Osaki T, Yamamoto T, Ueta E. Effects of tumour necrosis factor-alpha (TNF-alpha), IL-1 beta and monocytes on lymphokine-activated killer (LAK) induction from natural killer (NK) cells and T lymphocytes. Clin Exp Immunol 1993 ;93(2):229-36.

Daub H, Traxler L, Ismajli F, Groitl B, Itzen A, Rant U. The trimer to monomer transition of Tumor Necrosis Factor-Alpha is a dynamic process that is significantly altered by therapeutic antibodies. Sci Rep 2020;10(1):9265.

Lantz M. Infusion of tumor necrosis factor (TNF) causes an increase in circulating TNF-binding protein in humans. Cytokine 1990;2(6):402–6.

H Wajant, K Pfizenmaier and P Scheurich. Tumor necrosis factor signaling.

Cell Death and Differentiation 2003;10: 45–65.
Ruddle NH. Tumor necrosis factor (TNF-alpha) and lymphotoxin (TNF-beta). Current Opinion in Immunology 1992;4(3):327–32.
Yang S, Wang J, Brand DD, Zheng SG. Role of TNF-TNF Receptor 2 Signal in Regulatory T Cells and Its Therapeutic Implications. Front Immunol 2018; 9:784.
Wajant H, Siegmund D. TNFR1 and TNFR2 in the Control of the Life and Death Balance of Macrophages. Front Cell Dev Biol 2019; 7:91.
MacEwan DJ. TNF ligands and receptors--a matter of life and death. Br J Pharmacol 2002;135(4):855-75.
Mohan MJ, Seaton T, Mitchell J, Howe A, Blackburn K, Burkhart W, Moyer M, Patel I, Waitt GM, Becherer JD, Moss ML, Milla ME. The tumor necrosis factor-alpha converting enzyme (TACE): a unique metalloproteinase with highly defined substrate selectivity. Biochemistry 2002;41(30):9462-9.
Afonina IS, Müller C, Martin SJ, Beyaert R. Proteolytic Processing of Interleukin-1 Family Cytokines: Variations on a Common Theme. Immunity 2015;42(6):991-1004.
Urschel K, Cicha I. TNF-α in the cardiovascular system: from physiology to therapy. International Journal of Interferon, Cytokine and Mediator Research 2015;7:9-25
Kewalramani G, Puthanveetil P, Wang F, Kim MS, Deppe S, Abrahani A, Luciani DS, Johnson JD, Rodrigues B. AMP-activated protein kinase confers protection against TNF-{alpha}-induced cardiac cell death. Cardiovasc Res 2009;84(1):42-53.
Pandi P, Jain A, Raju S, Khan W. Therapeutic approaches for the delivery of TNF-α siRNA. Ther Deliv 2017;8(5):343-355.
van der Bruggen T, Nijenhuis S, van Raaij E, Verhoef J, van Asbeck BS. Lipopolysaccharide-induced tumor necrosis factor alpha production by human monocytes involves the raf-1/MEK1-MEK2/ERK1-ERK2 pathway. Infect Immun 1999;67(8):3824-9.
Victor FC, Gottlieb AB. TNF-alpha and apoptosis: implications for the pathogenesis and treatment of psoriasis. J Drugs Dermatol 2002;1(3):264-75.
Wang X, Lin Y. Tumor necrosis factor and cancer, buddies or foes? Acta Pharmacol Sin 2008;29(11):1275-88.
de Luca C, Olefsky JM. Inflammation and insulin resistance. FEBS Lett.2008;582(1):97-105.
Sun WY, Pitson SM, Bonder CS. Tumor necrosis factor-induced neutrophil adhesion occurs via sphingosine kinase-1-dependent activation of endothelial {alpha}5{beta}1 integrin. Am J Pathol 2010;177(1):436-46.
Wehmeyer C. Sclerostin inhibition promotes TNF-dependent inflammatory joint destruction. Science Translational Medicine 2016;8(330): 1-4.
Han N. Increased tumor-infiltrating plasmacytoid dendritic cells promote cancer cell proliferation and invasion via TNF-α/NF-κB/CXCR-4 pathway in oral squamous cell carcinoma. Journal of Cancer 2021;12(10):3045–56.
Masso-Silva JA, et.al. Increased peripheral blood neutrophil activation phenotypes and NETosis in critically ill COVID-19 patients: a case series and review of the literature. Clinical Infectious Diseases 2022;74(3):479-489.
Gaje PN, Amalia Ceausu R, Jitariu A, Stratul SI, Rusu LC, Popovici RA, et.al. Mast Cells: Key Players in the Shadow in Oral Inflammation and in Squamous Cell Carcinoma of the Oral Cavity. Biomed Res Int 2016; 2016:9235080.
Krishnan R, Thayalan DK, Padmanaban R, Ramadas R, Annasamy RK, Anandan N. Association of serum and salivary tumor necrosis factor-α with histological grading in oral cancer and its role in differentiating premalignant and malignant oral disease. Asian Pac J Cancer Prev 2014;15(17):7141-8.
Bradshaw G. Cancer-related deaths in children and adolescents. Journal of Palliative Medicine 2016;8(1):86–95.
Tiyuri A. The incidence and mortality of lip and oral cavity cancer and its relationship to the 2012 Human Development Index of Asia. Biomedical Research and Therapy 2017;4(2):1147–65.
G D, Nandan SRK, Kulkarni PG. Salivary Tumour Necrosis Factor-α as a Biomarker in Oral Leukoplakia and Oral Squamous Cell Carcinoma. Asian Pac J Cancer Prev 2019;20(7):2087-2093.
Muhammad W, Khan MM, Zafar S, Alqutub MN, AlMubarak AM, Mokeem S, Khan ZA, et.al. Assessment of Unstimulated Whole Salivary Tumor Necrosis Factor Alpha (TNF-α) and Cellular Micronuclei Levels in Snuff (Naswar) Users and Non-Users for Early Diagnosis of Oral Squamous Cell Carcinoma. Int J Environ Res Public Health 2021;18(14):7230.
Yang CM, Hou YY, Chiu YT, Chen HC, Chu ST, Chi CC, et.al. Interaction between tumour necrosis factor-α gene polymorphisms and substance use on risk of betel quid-related oral and pharyngeal squamous cell carcinoma in Taiwan. Arch Oral Biol 2011;56(10):1162-9.
Moraes JA. Adipose Tissue-Derived Extracellular Vesicles and the Tumor Microenvironment: Revisiting the Hallmarks of Cancer. Cancer 2021;13(13):13.
Abrahamsson A. Equal Pro-inflammatory Profiles of CCLs, CXCLs, and Matrix Metalloproteinases in the Extracellular Microenvironment In Vivo in Human Dense Breast Tissue and Breast Cancer. Frontiers in Immunology 2018;8:1994–1994.
Goertzen C, Mahdi H, Laliberte C, Meirson T, Eymael D, Gil-Henn H, Magalhaes M. Oral inflammation promotes oral squamous cell carcinoma invasion. Oncotarget 2018;9(49):29047-29063.
Jin L, Sturgis EM, Zhang Y, Huang Z, Song X, Li C, Wei Q, Li G. Association of tumor necrosis factor-alpha promoter variants with risk of HPV-associated oral squamous cell carcinoma Mol Cancer 2013;12:80.
Gupta S. Genetic polymorphism of tumor necrosis factor alpha (TNF-α) and tumor necrosis factor beta (TNF-β) genes and risk of oral pre-cancer and cancer in North Indian population. Oral and Maxillofacial Surgery 2021;1–11.
Partanen R. Tumour necrosis factor-alpha (TNF-alpha) in patients who have asbestosis and develop cancer. Occupational and Environmental Medicine 2016;52(5):316–9.
Scheff NN. Tumor necrosis factor alpha secreted from oral squamous cell carcinoma contributes to cancer pain and associated inflammation. Pain 2017;158(12):2396–409.
Hsing EW. TNF-α-induced miR-450a mediates TMEM182 expression to promote oral squamous cell carcinoma motility. PLOS ONE 2019;14(3): e0213463.
Eliassen LT. TNF 41-62 and TNF 78-96 have distinct effects on LPS-induced tissue factor activity and the production of cytokines in human blood cells. Thrombosis and Haemostasis 2016;83(4):598–604.
Multani S. Gene polymorphisms and oral cancer risk in tobacco habitués. Tumor Biology 2016;37(5):6169–76.
Karimi MY. Genetic polymorphisms in FAS (CD95) and FAS ligand (CD178) promoters and risk of tobacco-related oral carcinoma: gene-gene interactions in high-risk Indians. Cancer Investigation 2016;31(1):1–6.
Volland S. TNF accelerates the S-phase of the cell cycle in tumor cells. International Journal of Cancer 2016;56(5):698–705.
Kim MKH. Caspase 8 expression may determine the survival of women with ovarian cancer. Cell Death and Disease 2016;7(1).
Van Antwerp D. Inhibition of TNF-induced apoptosis by NF-κB. Trends in Cell Biology 2016;8(3):107–11.
Chang Y-T. Reactive oxygen species mediate soft corals-derived sinuleptolide-induced antiproliferation and DNA damage in oral cancer cells. OncoTargets and Therapy 2017; 10:3289–97.
Bahar G. Salivary analysis in oral cancer patients: DNA and protein oxidation, reactive nitrogen species, and antioxidant profile. Cancer 2016;109(1):54–9.
Brailo V, Vucicevic-Boras V, Lukac J, Biocina-Lukenda D, Zilic-Alajbeg I, Milenovic A, Balija M. Salivary and serum interleukin 1 beta, interleukin 6 and tumor necrosis factor alpha in patients with leukoplakia and oral cancer. Med Oral Patol Oral Cir Bucal 2012;17(1): e10-5.
Chen TC. Soluble TNF-alpha receptors are constitutively shed and downregulate adhesion molecule expression in malignant gliomas. Journal of Neuropathology and Experimental Neurology. 2016;56(5):541–50.
Solomon SS. Identification of specific sites in the TNF-α molecule promoting insulin resistance in H-411E cells. Journal of Laboratory and Clinical Medicine. 2016;130(2):139–46.
Fulda S. Targeting Inhibitor of Apoptosis Proteins for Cancer Therapy: A Double-Edge Sword? Journal of Clinical Oncology. 2016;32(28):3190–1.

Garg R. Activation of Nuclear Factor κB (NF-κB) in Prostate Cancer Is Mediated by Protein Kinase C ϵ (PKCϵ). Journal of Biological Chemistry. 2016;287(44):37570–82.

Honorati MC. IL-17, IL-1β and TNF-α stimulate VEGF production by dedifferentiated chondrocytes. Osteoarthritis and Cartilage. 2016;12(9):683–91.

Joyce DA. Tumor necrosis factor alpha and interleukin-1 alpha stimulate late shedding of p75 TNF receptors but not p55 TNF receptors from human monocytes. Journal of Interferon and Cytokine Research. 2016;15(11):947–54.

Trân-Thang C. Modulation of the plasminogen activation system by inflammatory cytokines in human colon carcinoma cells. British Journal of Cancer. 2016;74(6):846–52.

Yapijakis C, Serefoglou Z, Vylliotis A, Nkenke E, Derka S, Vassiliou S, Avgoustidis D, Neukam FW, Patsouris E, Vairaktaris E. Association of polymorphisms in Tumor Necrosis Factor Alpha and Beta genes with increased risk for oral cancer. Anticancer Res. 2009;29(6):2379-86.

Hinsbergh WM, Berg EA, Fiers W and Dooijewaard G: Tumor necrosis factor induces the production of urokinase-type plasminogen activator by human endothelial cells. Blood 1990 May 15;75(10):1991-8.

Tang D, Tao D, Fang Y, Deng C, Xu Q, Zhou J. TNF-Alpha Promotes Invasion and Metastasis via NF-Kappa B Pathway in Oral Squamous Cell Carcinoma. Med Sci Monit Basic Res. 2017 ;23:141-149.

Sahibzada HA, Khurshid Z, Khan RS, Naseem M, Siddique KM, Mali M, Zafar MS. Salivary IL-8, IL-6 and TNF-α as Potential Diagnostic Biomarkers for Oral Cancer. Diagnostics (Basel). 2017;7(2):21

Ameena M, Rathy R. Evaluation of tumor necrosis factor: Alpha in the saliva of oral cancer, leukoplakia, and healthy controls – A comparative study. J Int Oral Health 2019;11:92-9.

Patil S, Kaswan S, Rahman F, Dhoni B, Wadhawan R. Salivary and serum tumor necrosis factor alpha, interleukin 1 alpha, interleukin 1 beta, interleukin 6 and interleukin 8 in patients with oral carcinoma and leukoplakia. J Nepal Dent Assoc 2013;13:33-8.

Juretie M, Cerović R, Belušić-Gobić M, Brekalo Pršo I, Kqiku L, Špalj S, et al. Salivary levels of TNF-α and IL-6 in patients with oral premalignant and malignant lesions. Folia Biol 2013;59:99-102.

Rhodus NL, Ho V, Miller CS, Myers S, Ondrey F. NF-kappaB dependent cytokine levels in saliva of patients with oral preneoplastic lesions and oral squamous cell carcinoma. Cancer Detect Prev 2005;29:42-45.

SahebJamee M, Eslami M, AtarbashiMoghadam F, Sarafnejad A. Salivary concentration of TNFalpha, IL1 alpha, IL6, and IL8 in oral squamous cell carcinoma. Med Oral Patol Oral Cir Bucal 2008;13:E292-5.

Arnott CH, Scott KA, Moore RJ, Robinson SC, Thompson RG, Balkwill FR. Expression of both TNF-alpha receptor subtypes is essential for optimal skin tumour development. Oncogene. 2004;23(10):1902-10.

Björn L.D.M. Brücher, Florian Lang, and Ijaz S. Jamall. NF-kB signaling and crosstalk during carcinogenesis. 4open 2019; 2: 13.

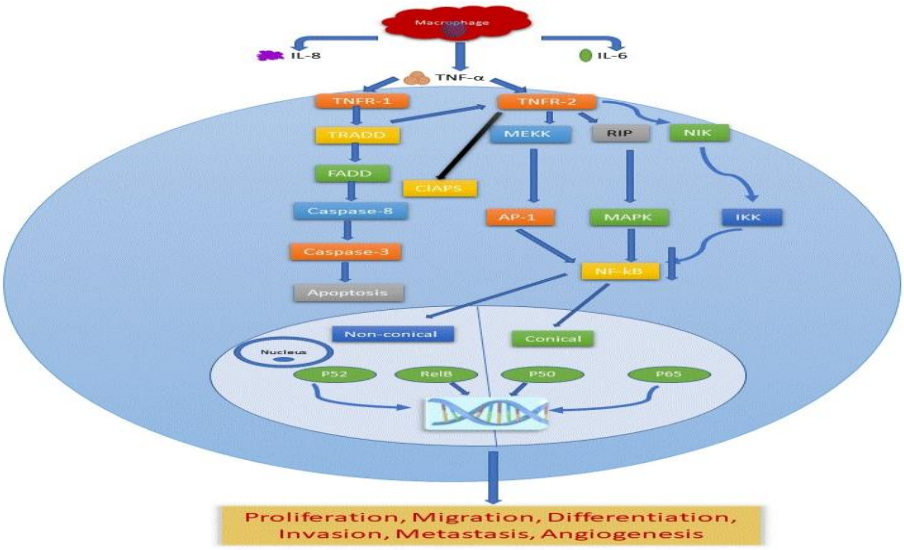

Figure 1. A schematic diagram illustrates the activation of TNF-α by activated Macrophages/ T-lymphocytes/ Natural killer cells and the NF-kB signaling pathways in tumor microenvironments.