REVIEW ARTICLE

Inflammation and Oral Cancer: An Update Review on Targeted Therapies

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ABSTRACT

In the recent past, numerous inflammation-mediated molecular pathways have been explored and studied as important events in carcinogenesis with respect to oral squamous cell carcinoma (OSCC). These pathways are engaged in numerous stages during tumorigenesis; which includes processes, like initiation, promotion, malignant conversion, invasion and metastasis. The inflammation-mediated/related carcinogenesis pathways reported in OSCC involves COX-2, epidermal growth factor receptor (EGFR), p38α MAP kinase, NF-κB, STAT, RhoC, PPARγ, etc. Many researchers are trying to target these pathways to explore more effective therapeutic interventions in OSCC. The aim of the present paper is to briefly discuss these pathways, with special emphasis on the therapeutic utilities. The therapeutic targets for the aforementioned pathways were searched in databases pubmed and scopus with no restriction to date of publication. Articles published in English medical literature on OSCC were selected for discussion. The recent combinations, modifications in dosage and frequency, or the use of new anti-inflammatory compounds, may exemplify the next generation care for OSCC.

Keywords: AP-1, Cancer-associated inflammation, Connective tissue growth factor, COX-2, Epidermal growth factor receptor, MAP kinase, NF-κB, Oral cancer, p38α, PPARγ, RhoC, STAT-3.

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INTRODUCTION

Worldwide, oral squamous cell carcinoma (OSCC) is the sixth most common type of cancer, while in certain developing countries its frequency is very high with dramatic implications for public health.[1-3] Nonetheless, a number of socioeconomic and related factors impede prevention and/or early discovery, as a result patients with OSCC frequently report with advanced stages of the disease. Despite recent advances in surgery, radiation and chemotherapy, prognosis for OSCC remains dismal with minimal improvement has been seen in the past few decades.[4,5] Furthermore, the probability of a second primary upper aerodigestive tract malignancy stands high among the survivors.[6-8]

The aforementioned discouraging facts and figures mandate the need for advancements of novel cancer treatment and therapy for patients with OSCC. It is generally agreed that knowledge of molecular mechanisms underlying the pathogenesis and progression of OSCC is crucial for the development of more rational and successful techniques and practices for its prompt diagnosis, accurate prognostication and effective treatment. Although our knowledge of the molecular basis of OSCC remains limited, a number of cellular and molecular events that underline the occurrence and progression of OSCC are gradually unfolding, including—oncogenic alterations and dysregulation of cell death mechanisms.[9-11] Among the discovered and explored molecular pathways, inflammation-mediated carcinogenesis holds one of the

most assuring tool for the therapeutic targets in OSCC. Inflammation is depicted in various stages of tumor development namely initiation, promotion, malignant conversion, invasion and metastasis. Therefore, cancer-related inflammation has been aptly suggested to represent the seventh trademark of cancer.[12]

The inflammation-mediated/related carcinogenesis pathways reported in OSCC are COX-2, epidermal growth factor receptor (EGFR), p38α MAP kinase, NF-κB, STAT, RhoC, PPARγ, etc. The aim of this paper is to briefly discuss these pathways with special emphasis on the therapeutic opportunities. The English medical literature was searched using databases, such as PubMed and scopus. The search terms used are the aforementioned molecular pathways. In the present paper, article pertaining to OSCC chemoprevention and/or treatment (patients/cell lines) were selected for the review and discussion. The abbreviations used are shown in Table 1.

Pathogenesis of Inflammation-mediated Carcinogenesis

Several lines of evidences, including general or cell-specific gene inactivation and population-based studies, are consistent and coherent with the view that inflammation plays a significant role in the progression of malignancy (Table 2).[13] Cytokines, chemokines, prostaglandins and reactive oxygen and nitrogen radicals accumulate in the microenvironment of tissues affected by chronic inflammatory reaction. If persistent, these inflammatory

Table 1: The list of abbreviations used in the article

Abbreviation	
Akt	Protein Kinase B
AP-1	Activator protein 1
Bcl-2	B-cell lymphoma 2
c-Jun	A protein encoded by the JUN gene
COX-2	Cyclooxygenase 2
EGFR	Epidermal growth factor receptor
ERK	Extracellular-signal-regulated kinases
FAK	Focal adhesion kinase
HMG-CoA	3-hydroxy-3-methylglutaryl-coenzyme A
IL-1β	Interleukin 1 beta
MCL-1	Myeloid leukemia cell differentiation protein
mTOR	Mammalian target of rapamycin
NF-κB	Nuclear factor kappa-light-chain-enhancer of activated B cells
p38 MAP	p38 mitogen-activated protein
PI3k	Phosphoinositide (PI) 3-kinase
RhoC	Ras homolog gene family, member C
SAP-kinase	Stress-activated protein kinase
STAT	Signal transducer and activator of transcription pathway
TNF-α	Tumor necrosis factor alpha
PPARs	Peroxisome proliferator-activated receptors

Table 2. The links between cancer and inflammation[13]

Sl. no.	The links between cancer and inflammation
1	Chronic inflammation increases risk of cancer, and many cancers arise at sites of chronic inflammation
2	The immune cells that mediate chronic inflammation are found in cancers and promote tumor growth in cell transfer experiments
3	The chemical mediators that regulate inflammation are produced by cancers
4	Deletion or inhibition of inflammatory mediators inhibits development of experimental cancers
5	Genetic variations in inflammatory genes alter susceptibility to and severity of cancer
6	Long-term use of nonsteroidal anti-inflammatory agents reduces risk of some cancers

factors have the potential to induce cell proliferation and stimulate prolonged cell survival through activation of oncogenes and subsequent inactivation of tumor-suppressor genes. This may result in genetic instability with an increased risk of cancer (the affected tissue becomes potentially malignant).[14] Hence, in our classification of oral potentially—malignant-disorders, we have included a separate category for such lesions called 'group II: morphologically altered tissue in which chronic persistent inflammation is responsible for malignant transformation (chronic inflammation-mediated carcinogenesis)'.[15-17] Once an inflammatory microenvironment has been established, reciprocal interactions between the evolving tumor cells and their stromal cells sustain cancer cell proliferation and promote the progression of tumor. Common transcription factors that normally regulate genes producing inflammatory mediators and genes controlling cell survival and proliferation are the link between cancer and inflammation. Hence, inflammation-mediated pathways in carcinogenesis demonstrate to be crucial therapeutic targets especially in cancer chemoprevention.

Inflammation-mediated Targets in Therapy of OSCC

Cyclooxygenase 2 Inhibitors: Cyclooxygenase (COX), also known as prostaglandin synthase, is the rate-limiting enzyme that accounts for the conversion of arachidonic acid into numerous prostaglandins, a family of lipid mediators which have extensive and varied biological functions.[18] Two distinct isoforms of COX have been found: COX-1 and COX-2. The COX-2 gene, located at chromosome 1q25.2 to 25.3, comprises of 10 exons and nine introns. Along with Hogness box, CAAT/enhancer binding protein and cAMP response elements in the 5'-terminal nucleotide sequence, the gene is approximately 8.3 kb in size.[19] Certain binding sites are also present in the gene sequence, such as the activator

protein-2 (AP-2) binding site and the nuclear factor-kappa B (NF-κB) binding site.[20] COX-2 is composed of 604 amino acid residues and its expression is absent in normal tissues and organs under physiological conditions, except the constituted expression in kidney and brain. It can be activated in response to certain stimuli, such as cytokines and growth factors.

Cyclooxygenase-2 is involved in several pathological processes, such as inflammation and carcinogenesis.[21] Several inflammation networks have been confirmed to play vital roles in the microenvironment of carcinogenesis, and COX-2/PGE2 network is the most significant pathway.[22,23] The COX-2-mediated intracellular oncogenic pathways ensure in sustained cell survival, amplified cell proliferation and migration and neoangiogenesis. A positive feedback loop is created, whereby COX-2 ultimately upregulates its own expression resulting in increased production of prostaglandin E-2, perpetuating a malignant cycle.[14] Thus, COX-2 pathways are potential targets for therapeutic intervention in OSCC treatment. *In vitro* studies have displayed that nonsteroidal anti-inflammatory drugs (NSAIDs) may potentially encourage apoptosis in several cancers including colon, hepatocellular, prostate and OSCC by hindering the COX-2 pathway. Cyclooxygenase-2 inhibition has been demonstrated to result in cell growth inhibition in OSCC cell lines.[24] The dysplastic mucosa of OSCC patients presented expression of COX-2 at distinctive stages of carcinogenesis but not in normal mucosa.[25] This suggests a likely role of COX-2 inhibition in OSCC chemoprevention. Studies using the COX-2 inhibitor as a single agent in oral premalignant lesions displayed evidence of regression in dysplasia.[26] A number of chemopreventive and therapeutic trials in OSCC using COX-2 inhibitors are underway.[27] Studies also indicate that NSAIDs may have a similar effect in retarding OSCC cell lines growth.[28]

Celecoxib, a NSAID that selectively inhibits COX-2, has displayed an important anti-carcinogenic effect for the treatment of OSCC. Oral squamous cell carcinoma is characterized by over activation of the Akt (also known as protein kinase B) signaling pathway which regulates cellular processes, such as metabolism, cell size, proliferation, invasion and apoptosis; thus, ultimately regulating cell growth and endurance.[29] Thus, drugs that target Akt directly or indirectly via its signaling pathway, are likely candidates for OSCC treatment. Apoptosis induced by COX-2 inhibitors is associated not only with the attenuation of Akt and its subsequent effectors, such as Bcl-2-associated death promoter and procaspase-9, but also with diminished levels of the antiapoptotic protein MCL-1 and the phosphorylated SAP-kinase; which signifies that these proteins could be possible

COX-2-inhibitors' targets for cancer. A new celecoxib analog (3-phosphoinositide-dependent protein kinase-1 inhibitor) potentially inhibited tumor growth, while inhibiting Akt signaling and disabling breast cancer cells that overexpress EGFR.[30,31] This new celecoxib analog has spawned research opportunities for trials in treatment and chemoprevention of OSCC.

Epidermal growth factor receptor signaling contributes in the management of cell proliferation and differentiation during development and, in tumor cells, contributes to proliferation, invasion and metastasis. It is directly/indirectly associated with inflammation-mediated carcinogenesis. The literature suggests the link between COX-2 and EGFR (COX-2 mediated transactivation of EGFR). Thus, therapeutically targeting these two pathways can synergistically or additively block OSCC progression and growth.[24,32-34] The combination of erlotinib and celecoxib has been exhibited to synergistically constrain OSCC cancer cell growth in preclinical studies.[24-32] Recently, Saba et al reported positive results of a phase I clinical trial and pharmacokinetic studies of this combination in oral premalignant lesions.[34]

Connective tissue growth factor: Recently, Chuang et al reported that connective tissue growth factor (CTGF) intervenes down-regulation of COX-2 and reduction in migration of OSCC cells.[35] Connective tissue growth factor belongs to the CCN family. This family consists of six members including CTGF, and all possess an N-terminal signal peptide, distinguishing them as secreted proteins.[36] Connective tissue growth factors probably carry out their biological activity through binding and activating of the cell surface integrins.[36] The CTGF constraints COX-2 expression by binding to the αvβ5 integrin receptor and reduction of FAK, PI3K and Akt, which inhibits binding of c-Jun to AP-1 site; resulting in diminution of tumor migration.[35] A better understanding of the functions and interactions of CTGF can open newer avenues to wider and effective use of these proteins in the treatment and chemoprevention of OSCC.

p38 Mitogen-activated protein kinase: The p38 mitogen-activated protein (p38 MAP) kinase pathway is involved in inflammation, cell differentiation, growth, apoptosis and proinflammatory cytokines'—TNF-α and IL-1β production. The overproduced cytokines play an important role in supporting the proinflammatory microenvironment of the tumor. There are four isoforms of p38MAPK: α, β, γ and δ. All mitogen-activated protein kinases (MAPK) pathways operate through sequential phosphorylation events, phosphorylating transcription factors and regulate gene expression. These MAP kinases are activated by dual phosphorylation of threonine and tyrosine residues in 'TXY' (where X is Gly in case of p38α)

and further activate transcription factors, by phosphorylation using adenosine triphosphate as a substrate. They can also phosphorylate cytosolic targets for regulation of intracellular events. Mitogen-activated protein kinases are phosphorylated and stimulated by MAPK kinases (MKKs), which in turn are phosphorylated and activated by MKK kinases (proto-oncogene serine/threonine-protein kinase and MKKK).[37] The final objective of this cascade is the regulation of cellular proliferation, differentiation, development, regulation of cell cycle, induction of G2/M checkpoint due to double stranded breaks in DNA during somatic recombination in B cells, and transmission of oncogenic signals via gene transcription.[38] Significantly high levels of p38α MAPK have been associated with OSCC.[39] Hence, p38α MAP kinase inhibitor can be a potential therapeutic agent against OSCC. Gill K et al have designed a tetrapeptide, VWCS as p38α inhibitor on the basis of structural information of the ATP binding sites using molecular modeling.[40] It potentially repressed cell growth and induced apoptosis in OSCC prompting the future scope for *in vivo* studies.[40] The hemolytic studies revealed that the peptide was virtually nontoxic to human erythrocytes. This characteristic of the peptide exhibited that it can be delivered via the intravenous route, although further evaluation is essential.

NF-κB and STAT: Inflammatory mediators have the capacity to activate the nuclear signal transducers and activators of transcription-3, the AP-1 and the nuclear factor-κB (NF-kB). The nuclear factor-κB transcription factors and the signaling pathways are central coordinators in innate and adaptive immune responses. Signal transducer and activator of transcription (STAT) proteins are a family of cytoplasmic transcription factors consisting of seven members—STAT1 to STAT6, STAT5a and STAT5b.[41] STAT3 and 5 are constantly stimulated in many human cancer cell lines. They are not only involved in cancer development and progression but also contribute to their survival.[42] STAT3 regulates the expression of a variety of genes in response to cellular stimuli, and thus play a crucial role in cell growth and apoptosis. The activation and interaction between STAT3 and NF-κB plays a dynamic role in controlling the communication between cancer cells and inflammatory cells. The NF-κB and STAT3 are two major factors administrating the ability of preneoplastic and malignant cells to resist apoptosis-based tumor-surveillance and regulating tumor angiogenesis and invasiveness. Comprehending the molecular mechanisms of NF-κB and STAT3 cooperation in cancer will offer opportunities for the design of new chemopreventive and chemotherapeutic approaches.[43]

Vander Broek et al reviewed several such agents that inhibit the NF-κB pathway in OSCC.[44] Retinoids (tocopherols and tocotrienols) have been studied most extensively but have displayed limited potential in human trials. Epidermal growth factor receptor inhibitors and PI3K-mTOR inhibitors (rapamycin) might benefit a subset of patients. Other agents, like green tea extracts and curcumin are appealing and popular because they are generally regarded safe. In a stark contrast, there is evidence that vitamin E supplementation may actually increase the mortality rate in cancer patients. Natural compounds, like berry extracts, genistein (natural isoflavonoid found in soybeans) and resveratrol (natural phenol found in grape skins) act through NF-κB pathways. The other NF-κB-inhibitory compounds currently being tested for their chemopreventive potential are: pomegranate juice, luteolin, lycopene, and other fruit and vegetable extracts. Future research is required to develop agents with minimal toxicity and higher specificity for the NF-κB pathway, and targeting these therapies to individual patients' genetic signatures should help to escalate the utility of these agents for OSCC chemoprevention.[40]

Guggulsterone (GS), [4,17(20)-pregnadiene-3, 16-dione], derived from the plant Commiphora mukul, inhibits inducible nitric oxide synthetase and NF-κB induced by various carcinogens and tumor promoters, and thus restrains inflammation.[45,46] It is reported that treatment with GS induces apoptosis and repress proliferation of a wide variety of human tumor cell types.[45-50] Guggulsterone inhibits invasion, angiogenesis and metastasis of tumor cells and shows reversal of chemoresistance.[48-50] It has also been depicted to obstruct both constitutive and inducible STAT3 pathways in head and neck cancer cell lines.[51,52] Recently, Leeman-Neill et al showed that anti-proliferative effects of GS are partially reliant on STAT3 inactivation.[51] They presented that striking down the expression of STAT3 using small interfering RNA in OSCC cells reduced GS-induced cell death as compared to the no transfection controls.

Recently, Macha et al reported inhibition of the activation of NF-κB and STAT3 proteins in OSCC cells by guggulsterone.[53] Importantly, treatment of OSCC cells with guggulsterone abrogated both smokeless tobacco and nicotine-induced nuclear activation of NF-κB and pSTAT3 proteins, and their downstream targets COX-2 and vascular endothelial growth factor. Furthermore, guggulsterone treatment decreased the levels of smokeless tobacco and nicotine-induced interleukin-6 secretions in culture media of OSCC cells. Guggulsterone treatment not only inhibited proliferation, but also induced apoptosis by abrogating the effects of smokeless tobacco and nicotine on PI3K/Akt pathway in OSCC cells.[54]

RhoC: Among the Ras homology protein family, RhoC has been associated with a wide range of cellular activities, including downstream expression of inflammatory genes and chemokines, cell proliferation, intracellular signaling, and cytoskeletal organization.[55] Fascinatingly, overexpression of RhoC has been documented in inflammatory breast cancer and exclusively in invasive breast carcinoma.[56,57]

A handful of studies have investigated the role of RhoC in OSCC till date. Studies on gene expression profiling of stage III and IV regionally-metastatic OSCC expressed that there are elevated levels of RhoC when compared to stage I and II localized malignancy.[58] Furthermore, an elevated RhoC expression in tumors of patients with OSCC was noted when compared to normal squamous cell epithelium.[59] It is also accounted that increased RhoC expression is fervently associated with lymph node metastasis and could also be used to predict metastasis even in small primary tumors (T1, T2).[60] Recently, Kleer et al investigated the role of RhoC in head and neck metastasis by hindering its function using RNA interference (RNAi).[60] *In vitro* findings revealed that inhibiting RhoC function ardently reduced cell motility and invasion. Furthermore, there was an astonishing fall in tumor metastasis and microvessel density in severe combined immunodeficiency (SCID) mice injected with RhoC knockdown cell lines. These findings suggest that impeding RhoC function in OSCC can diminish a tumor's aggressive behavior, thus opening new doors for future drug therapies targeting this pathway.[61]

Atorvastatin belongs to the statin family of drugs that inhibits cholesterol biosynthesis by blocking the activity of HMG-CoA reductase and averting the conversion of HMG-CoA to mevalonate. Consequently, this pathway also prevents the activity of geranylgeranyl pyrophosphate which is responsible for prenylation or lipidation of Rho proteins, including RhoC, and is an essential step that is needed for their functional biological activity.[62] Therefore, statins are considered good candidates for not only inhibiting cholesterol biosynthesis, but also preventing the prenylation of Rho proteins, including RhoC.

The findings presented by Islam et al demonstrate that atorvastatin plays an important role in modulating RhoC function *in vitro* by decreasing cell motility, invasiveness, stress fiber integrity, proliferation and anchorage dependent colony formation, and also by depleting the phosphorylation of ERK1/2 and STAT3.[61] Furthermore, *in vivo* studies show a marked reduction in neovascularization and distant lung metastasis in SCID mice. Therefore, elucidating the molecular mechanisms by which statins regulate RhoC activation will be an important step toward a more effective treatment of OSCC.

Peroxisome proliferator-activated receptors: Peroxisome proliferator-activated receptors (PPARs) are a family of ligand-activated transcription factor that belong to the nuclear receptor superfamily. This family has a structure and function that is comparable to other steroid type receptors, with an N-terminal ligand-independent activation domain, a central DNA binding domain, and a large carboxy-terminal ligand binding domain that comprises of an activation domain responsible for ligand-dependent activation.[63]

With regard to anti-inflammatory effects in macrophages, PPARγ represses gene transcriptional responses that are mediated by other classes of signal-dependent transcription factors via a process called transrepression.[64] Activation of PPARγ has been found to be linked with anti-proliferative, proapoptotic, prodifferentiation, anti-inflammatory and anti-metastatic properties in various cancer cell lines and rodent carcinogenesis model systems.[65] Bren-Mattison et al studied the mechanism responsible for suppression of carcinogenesis by activation of PPARγ, and found that increased PPARγ resulted in a proportional decrease in COX-2 expression and protection from urethane-induced tumor formation.[66]

Yoshida et al using the carcinogen 4-nitroquinoline-1oxide (4-NQO) to induce tongue tumors, demonstrated that increasing dose of troglitazone cuts the incidence of tumor as compared to controls and severe dysplasia.[67] A retrospective analysis of a database from 10 veteran affairs medical centers was performed by Govind rajan et al to examine the effect of thiazolidinediones (TZDs) on cancer risk in diabetic patients.[68] The risk of OSCC decreased by 14 to 55% with the use of TZDs, either alone or with other antidiabetic agents. More recently, a population based cohort study from France examined the association between pioglitazone and cancer risk in 1,491,060 diabetic patients. The risk of head and neck cancer was declined by 15%.[69]

Cancer-associated Inflammation and Pharmacokinetics of Anticancer Drugs

It is important to keep in mind that cancer-associated inflammation can also influence the pharmacokinetics of anticancer drugs. Much of the interpatient variability in the clearance of chemotherapy is due to altered levels of drug metabolizing enzymes, namely cytochrome P450 (CYP) 3A4.[70] Patients with progressed cancer have significantly reduced hepatic CYP3A4 activity, associated with increased plasma concentrations of inflammatory mediators.[71] The relationship between inflammation and CYP activity has been comprehensively studied in various animal models of acute inflammation and cancer.[72] The inflammatory response directs to diminished CYP levels,

decreased microsomal metabolism, and CYP-mediated drug clearance.[73-75] Future therapies aimed at reducing the tumor-related inflammatory response, e.g. inhibitors of IL6, TNF-α, NF-β, and COX-2 could improve cytotoxic chemotherapy in patients with advanced cancer.

Future Directions

Although the role of inflammation in tumorigenesis is now widely accredited and it is evident that inflammatory responses play a critical role at different stages of tumor development, yet the molecular mechanisms about how inflammation is involved in tumorigenesis are far from being completely understood. The distinctions between tumor-promoting inflammation and tumor-suppressive immunity are still ambiguous. With this view in mind, Balkwill et al proposed the following aspects that will help us to develop an effective cancer therapy and some-day even prevention: (1) recognition of tumor-promoting inflammation and tumor-suppressive immunity in tumor development, including stages of tumor initiation, pro-motion, malignant conversion, invasion and metastasis; (2) identify which cell type performs tumor promoting inflammation and which cell type performs tumor supp-ressive immunity in tumor development; (3) isolation of signal transduction pathways which mediate the cell-type specific tumor-promoting inflammation or tumor suppressive immunity; (4) put together the dynamic functional interaction map entailed in innate immune cells, adaptive immune cells, stromal and cancer cells.[13]

Since, monotherapy is generally insufficient for cancer treatment, combined use of drug targets discussed in the present article and conventional cancer therapy is an interesting area of research for the future.

Some cytokines and inflammatory mediators influ-ence the pharmacodynamics of anticancer drugs, at least *in vitro*. Further research in these areas may lead to more rational treatments for patients in whom a significant inflammatory response is detectable.

SUMMARY

Chemoprevention of OSCC, a disease associated with a high mortality rate and frequent occurrence of a second primary tumor, is a clinical goal of paramount impor-tance. The role of inflammation has been validated in processes, like initiation, progression, and prognosis of OSCC. Moreover, cancer-associated inflammation can also influence the pharmacokinetics of anticancer drugs. Inflammation-mediated oral carcinogenesis and associated signaling pathways have opened all new avenues and opportunities for targeted therapies in OSCC. These therapies act directly or indirectly on the signaling pathways and hold promising prospects for oral cancer chemoprevention and treatment. The recent combinations of agents, dosage and/or frequency modi-fications, or the use of completely new anti-inflammatory compounds, may represent the next generation of care for cancers. Further research into the area is necessitated. Many downstream molecules are linked with inflamma-tion-mediated carcinogenesis pathways in OSCC, e.g. PI3k/Akt/mTOR axis. Independently, these pathways have numerous therapeutic opportunities. However, it is beyond the scope of the present article to discuss them.

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