The importance of oncogenic transcription factors for oral cancer pathogenesis and treatment

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Oral squamous cell carcinoma is a major cause of morbidity and mortality worldwide. Current experimental evidence shows that most important risk factors for oral cancer include tobacco use and excessive alcohol consumption and less well-defined risks include viral infection and a diet deficient in antioxidants. The positive correlation between various risk/etiologic factors of oral cancer and the activation of various transcription factors (TFs) has been reported in the literature. Although initially, TFs were considered to be very difficult targets for use in clinical treatment, recent technological advances have provided the ability to control these factors of cancer progression. This review focuses on the role of oncogenic transcription factors in oral cancer, their modes of activation through various biological pathways, the promises and pitfalls in viewing them as potent oncotargets, the way they can be controlled based on the current understanding, and the future research to be done in this area. (Oral Surg Oral Med Oral Pathol Oral Radiol 2013;116:179-188)

Oral squamous cell carcinoma (OSCC) is one of the most common cancer worldwide.[1] The etiology of OSCC is multifactorial, and the predominant predisposing risk factors include tobacco use (i.e., tobacco smoking and, to a considerably lesser degree, tobacco chewing) and excess alcohol consumption, although the role of viral infections (e.g., human papillomavirus and herpes simplex viruses) and a diet deficient in antioxidants as risk factors for the development of OSCC remain less well defined.[2] The development of OSCC is a multistage process that progresses sequentially from hyperplasia through dysplasia to carcinomas, although in most cases, the patients present with advanced disease at the time of diagnosis.[3] OSCC is very aggressive in that the disease frequently migrates to and invades distant organs. The poor 5-year survival rate (50%) and patient prognosis have not improved in several decades, indicating the failure of ongoing therapeutic strategies and the importance of finding new drug targets for this neoplasm.[4]

Of late, molecularly targeted approaches have assumed significance as ideal anticancer modalities to overcome the cytotoxicity associated with conventional chemotherapeutic drugs. This type of therapy, although difficult to design, manufacture, and navigate through rigorous clinical trials, has been shown to be important for treating OSCC.[5] Transcription factors are among the most promising molecules that can be targeted for therapeutic purpose.

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Transcription factors (TFs) are proteins that recognize and bind to specific sequences of DNA to activate or repress the recruitment of RNA polymerase either alone or in conjunction with other proteins.[6] Because TFs essentially turn genes on or off, they are regarded as master regulators of cell fate determination and their deregulation leads to various human diseases, including neoplastic transformation.[7] Oncogenic transcription factors (OTFs) are regulated by upstream signaling molecules that are cellular structural components or enzymes via middle-order kinases.[8-11] Much attention has been given to targeting higher-order master molecules and membrane receptors/tyrosine kinases for therapeutic purposes without having a significant advantage. Thus, targeting OTFs may be a reductionist approach to treat malignant neoplasms that would regulate the expression of specific set(s) of genes directly without negatively influencing other cellular processes. There is also substantial evidence to indicate that tumor growth is inhibited when OTFs are targeted.[7,12,13]

Deregulation of various OTFs has been extensively documented in OSCC including animal model.[14-33] This review focuses on the contribution of OTFs to OSCC progression, their general mode of activation, and strategies for targeting OTFs in OSCC. The bottlenecks in achieving OTF-targeted therapy and ways to circumvent them have also been considered.

OTFS THAT PROPEL ORAL CANCER

Various genomic, proteomic, and metabolic studies have revealed that gene expression programs determine the diversity of physiological and pathological

Statement of Clinical Relevance

This study will be verymuch clinically relevant and we hope will boost further research in this area.

Table I. List of some commonly involved OTFs propelling oral cancer and benefits by their targeting

Sl. no.	*OTF*	*Oncogenic potential in OSCC*	*Benefits of its targeting*
1	AP-1	Over expression,[14,15] nuclear expression increased according to the degree of dysplasia,[37] lymph node metastasis,[38] increased transcriptional activity[39,40]	Inhibits invasion[41]
2	NF-κB	Differential expression,[18] activation,[16-18] proliferation,[17] malignant transformation, invasion[16,42,43]	Affects growth[44]
3	c-Myc	Overexpression,[19-22] DNA amplification,[45,46] DNA binding activity,[47] progression of oral cancer[48]	Prevent invasion[49]
4	STAT	Early overexpression and activated form of TF,[23,24] active in OSCC[50-54]	Growth inhibition[23] neoplasm[55]
5	β-catenin	Nuclear overexpression,[25] oral cancer progression,[26] metastasis[56-58]	Inhibits transcription and invasion[59]
6	Snail	Overexpression,[60] activation,[61] invasion,[61] correlated with EMT[27-29]	Reduces cancer stemness property[62]
7	HIF1α	Overexpression,[30,31] progression,[63] expression correlates with poor prognosis,[31,64,65] invasion[66,67]	Affects tumor cell proliferation, angiogenesis, and growth[68]
8	Mutated p53 (GOF)	Inactivated protein,[32] GOF of mutant p53 propel mitosis by expressing cyclin A and cyclin B,[69] GOF leads to shorter disease-free survival,[70] prevention apoptosis after DNA damage,[71] chemoresistance,[72] disease progression[73]	Reduces tumor volume and metastasis[74,75]

EMT, epithelial−mesenchymal transition; *GOF*, gain-of-function.

conditions. TFs bind to DNA at specific sequences and are required by RNA polymerase[34] to identify the region of DNA to be transcribed.[35,36] These TFs are regulated by the cumulative action of a number of carcinogens, growth factors (GF), and immediate upstream kinases, phosphatases, and isomerases. The numbers of OTFs and tissue-specific gene programs that influence cancer are continually increasing, indicating the diverse mechanisms by which gene expression regulated by OTFs contribute to human neoplasms. Given the many ways by which OTFs can contribute to OSCC, there is a surprisingly limited list (Table I) of the gene regulatory proteins that have been identified from oral tumors to mobilize various genes (Figure 1).

In addition to the aforementioned OTFs, the overexpression of other transcription factors, including E2F,[76] HOXB7[77], SOX2[78], RUNX3[79], Ets-1[80], and FOXO3a[81], is associated with OSCC. All these TFs are deregulated, and furthermore, their deregulation is the cause of numerous alterations that affect the delicate cellular homeostatic balance of the oral epithelium.

ACTIVATION OF SIGNALING PATHWAYS IN OSCC THAT FUEL OTFS

Oral cancer is caused by a myriad of genetic and epigenetic factors as well as local exposure to carcinogens. Transcription-mediated progression of this neoplasm has been well-established[82] and is accomplished by many OTFs. A number of immediate upstream kinases, phosphatases, and isomerases, including protein kinase A (PKA), Akt/PKB, PKC, p90 ribosomal S6 kinase/mitogen-activated protein kinase-activating protein, p70 ribosomal S6 kinase, MAPKs, phosphoinositide 3-kinase, Janus kinase (JAS), glycogen synthase kinase 3, protein phosphatase 2A (PP2A), and prolyl isomerase (Pin1), are middle-order modulators that are frequently deregulated in oral carcinogenesis (review[4,11]). Each of these, alone or collectively, can be linked to the deregulation of a number of TFs. Additionally, epidermal growth factor receptor, vascular endothelial growth factor receptor, and platelet-derived growth factor receptor are activators that are implicated in oral carcinogenesis and are stimulated by a number of mitogens, GFs, carcinogens, and common etiologic factors[8-10] or stimulators of oral cancer. To date, these molecules have been extensively studied as potential therapeutic targets of OSCC in various clinical settings. However, most of them impinge on OTFs such as activator protein 1 (AP-1), nuclear factor-kappa B (NF-κB), Myc, signal transducer and activators of transcription (STAT), β-catenin, Snail, hypoxia-inducible factor-1 (HIF-1), and P53 leading to tumor progression.[11] Hence, directly targeting these OTFs individually, in combination or along with other therapy may be a better approach to tackle this neoplasm.

VARIOUS APPROACHES TO TARGET OTFS IN OSCC

OTFs are usually considered difficult targets and undruggable. However, recent studies have demonstrated numerous possible approaches to target these molecules, revealing the potential of this group of oncotargets.[83] Some of the therapeutic intervention strategies used to control these OTFs in oral cancer are discussed here (Figure 2).

Transcription factor decoys

These are oligonucleotide sequences that act as competitive binding sites for a specific TF. This approach entraps activated TFs in the cytoplasm, thus preventing them from binding to their target gene promoter. This technology has been applied efficiently in cell culture