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ORIGINAL ARTICLE

# c-Jun alterations in oral squamous cell carcinoma

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## *Summary*

*Oral carcinogenetic process is based on a variety of genomic imbalances (gross chromosome or specific gene alterations) leading normal oral mucosa to its dysplastic epithelial form and finally to the totally malignant tissue transformation. Suppressor genes' downregulation combined with oncogenes' overactivation are crucial genetic events in pre-malignant and malignant neoplastic epithelia. Additionally, deregulation of specific transcription factors negatively affects the normal expression of genes. Among these, c-Jun (chromosome location: 1p32-p31) is critical forming with c-Fos the activator protein-1 (AP-1) complex early acting as a response transcription factor. In the current special molecular article we explored the role of altered c-Jun gene in oral squamous cell carcinoma (OSCC).*

***Key words:*** *c-Jun, oncogene, signaling pathway, oral, carcinoma*

## Introduction

Head and Neck Squamous Cell Carcinomas (HNSCC) represent a superfamily of pathological entities with specific etiopathogenetic characteristics [1]. Concerning oral cavity, SCC is the prominent pathological type of malignancy. In fact, oral SCCs (OSCC) demonstrate an aggressive phenotype due to their increased capability to locally metastasize combined with distant lymph node metastases due to specific abnormalities in signaling transduction pathways, such as Notch [2]. Extensive molecular analyses have shown that gross chromosome instability (CI- polysomy/aneuploidy) and specific gene alterations (amplification, deletion, point mutations) or epigenetic (aberrant promoter methylation, microRNAs deregulation) are implicated in the development and progression of solid malignancies, including OSCC [3,4]. OSCC demonstrates increased rates in populations characterized by chronic irritating factors including tobacco and alcohol consumption and also viral mediated deregulation [5,6]. Concerning viral oncogenic activity, persistent Human Papilloma Virus (HPV) infection is responsible for malignant transformation of the corresponding oral mucosa [7]. Among the genes that are involved in OSCC development and progression, overactivated proto-oncogenes involved in signaling transduction pathways play a significant role in modifying nuclear micro-environment [8,9]. Especially, deregulation

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of specific transcription factors negatively affects the normal expression of other genes. In the current special molecular article, we explored the impact of c-Jun gene alterations in OSCC development and biological behavior.

## Introducing the c-Jun gene and protein

c-Fos/c-Jun complex influences intracellular signal transduction to the nucleus and modifies the expression of other genes, such as ras [10]. C-Jun and c-Fos proteins are implicated in critical cell functions including differentiation, proliferation, survival and also tissue homeostasis affected by hypoxia and angiogenesis. C-Jun is a proto-oncogene representing the human homolog of the viral oncoprotein v-jun (gene locus: 1p32-p31). The gene encodes a 65 kDa protein (p39), forming heterodimer with c-Fos -another strong transcription factor- resulting in the formation of AP-1 (Activator Protein-1) complex (Figure 1). The Jun protein complex comprises c-Jun, JunB and JunD, respectively [11,12]. In fact, c-Jun was the first pure oncogenic transcription factor discovered [13]. It is the homolog of the viral oncoprotein v-jun. V-jun was initially discovered in avian sarcoma virus 17. In normal cells, c-Jun is implicated in important functions including proliferation, apoptosis, survival, and tissue morphogenesis. Furthermore, the protein interacts with signal transduction pathways [14]. Interestingly, the gene region on chromosome 1 that hosts the gene is frequently the target of translocations and deletions (breakpoints) in solid malignancies including OSCC detected by implementing karyotype-based analysis [15].

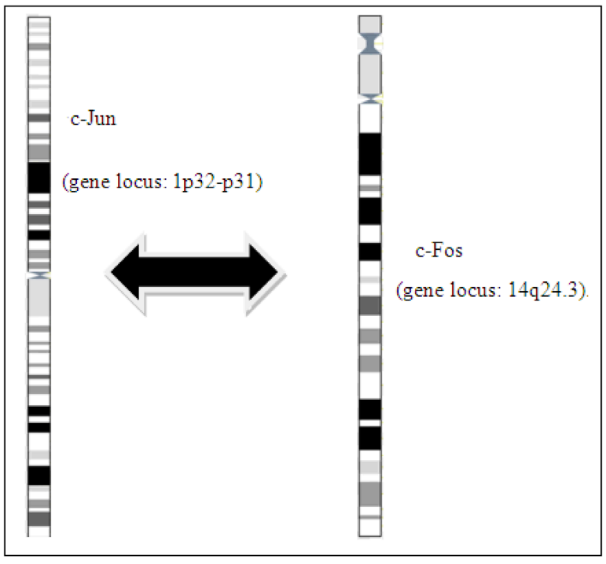


**Figure 1.** Ideogram of c-Jun/c-Fos complex. Note the corresponding genes on Chromosomes 1 and 14, respectively.

## c-Jun in OSCC

Recently published molecular studies detected overactivation of c-Jun/c-Fos complex in invasive parts -compared to adjacent non-malignant epithelia- of HNSCC in different anatomic regions including OSCC. Referring also to HPV-mediated carcinogenesis in oral mucosa, some studies have already detected overactivation of strong transcriptional factors. A combination of nuclear and perinuclear cytoplasmic diffuse immunostaining was observed, especially in cases demonstrating lymph node metastasis implicating also CD44-dependent signal transduction pathway [16]. In fact, c-Jun phosphorylation/nuclear translocation and CD44 overexpression are combined with co-localization of HPV 16 E7 oncoprotein in a specific SCC cell line analysis. The study group also reported that targeting HA/CD44-mediated c-Jun signaling by applying HPV16 E6- specific small interfering RNAs affects positively cisplatin chemosensitivity in HPV16E6-positive OPSCC cells. Based on data extracted by protein expression analysis, c-Jun in normal, dysplastic and neoplastic/malignant oral mucosa was found to be progressively over activated [17]. This is an indirect evidence of c-Jun deregulation in early stages of oral carcinogenesis. Additionally, specific gene signatures in OSSC -including c-Jun- seem to be associated to an aggressive phenotype in subgroups of patients. Another genetic analysis showed that the CCND1/c-Jun/SPP1 complex deregulation leads to an aggressive OSCC phenotype characterized by extended lymph node metastasis [18]. Furthermore, HPV16 E6/E7 oncogenic activation drives NF-κB to abnormal expression in subgroups of OSCC combined with p50 overexpression [19]. Besides HR-HPV persistent infection, another genotoxic factor involved in OSCC development that induces AP-1 (c-Jun/c-Fos complex) is tobacco systematic consumption promoting in parallel neoplasm's angiogenesis [20].

In conclusion, overactivation of c-Jun oncogene is a frequent and also crucial genetic event in OSCC development and progression. Combined with other oncogenes upregulation and suppressor genes downregulation, c-Jun deregulation affects the biological behavior of the malignancy in patients with specific genetic signatures. Novel agents that reduce the corresponding oncoprotein levels inhibiting their activity should be a very promising approach for applying targeted therapeutic strategies in selected group of OSCC patients.

## Conflict of interests

The authors declare no conflict of interests.

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