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SPECIAL MOLECULAR REVIEW

c-Jun/c-Fos complex in laryngeal squamous cell carcinoma

Evangelos Tsiambas[1], Nicholas Mastronikolis[2], Panagiotis P. Fotiades[3], Efthymios Kyrodimos[4], Aristeidis Chrysovergis[4], Vasileios Papanikolaou[4], Stylianos Mastronikolis[5], Dimitrios Peschos[6], Dimitrios Roukas[7], Vasileios Ragos[8]

[1]Department of Pathology-Cytology, 401 GAH, Athens, Greece; [2]Department of Otorhinolaryngology, Head and Neck Surgery, Medical School, University of Patras, Greece; [3]Department of Surgery, 424 General Army Hospital, Thessaloniki, Greece; [3]Department of Physiology, University of Ioannina, Greece; [4]1st ENT Department, Hippocration Hospital, University of Athens, Athens, Greece; [5]Department of Medicine, School of Health Sciences, University of Crete, Heraklion, Greece; [6]Department of Physiology, University of Ioannina, Greece; [7]Department of Psychiatry, 417 VA Hospital (NIMTS), Athens, Greece; [8]Department of Maxillofacial Surgery, Medical School, University of Ioannina, Greece.

Summary

During laryngeal carcinogenesis, a variety of genomic imbalances are involved in hyperplastic and dysplastic laryngeal epithelia as early or progressive genetic events, respectively. Oncogenes' overactivation is a crucial genetic event in malignant and pre-malignant neoplastic epithelia. Especially, deregulation of crucial pathways including transcription factors - such as c-Fos and c-Jun - leads to an aberrant expression of other crucial genes responsible for cell homeostasis. Upregulation of c-Fos and c-Jun proto-oncogenes -due to increased copy numbers (amplification) or intra-genic point mutations- seems to be correlated with aggressive biological behaviour in laryngeal squamous cell carcinomas (LSCCs). In the current special molecular article we explored the role of c-Fos/c-Jun complex deregulation in LSCC.

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

Introduction

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) are implicated in the development and progression of solid malignancies, including laryngeal squamous cell carcinoma (LSCC) [1]. It is well known that LSCC is the prominent histopathological entity among head and neck squamous cell carcinomas (HNSCCs). It demonstrates increased rates due to etiopathogenetic factors including tobacco, chronic alcohol consumption and also viral-mediated deregulation [2]. Concerning viral oncogenic activity, persistent human papilloma virus (HPV) infection is responsible for malignant transformation of the corresponding laryngeal epithelia [3]. Among the genes that are involved in LSCC development, overactivated proto-oncogenes in signaling transduction pathways play a significant role due to modified nuclear microenvironment [4,5]. In the current special molecular article we explored the role of c-Fos/c-Jun complex deregulation in LSCC development and biological behavior.

Introducing the c-Fos and c-Jun gene and protein

Fos protooncogene or AP-1 Transcription Factor Subunit (c-Fos) represents a well analyzed gene involved in solid malignancies' development

Corresponding author: Evangelos Tsiambas, Cytopathologist, MD, MSc, PhD. 17 Patriarchou Grigoriou E΄ Street, Ag. Paraskevi, 153 41 Athens, Greece.
Fax: +30 210 6526259, Email: tsiambasecyto@yahoo.gr
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and progression. The corresponding protein forms heterodimer with c-jun, a strong transcription factor [6]. The Fos super family includes c-Fos, FosB, FosL1, and FosL2 genes. c-Fos is a protooncogene that is the human homolog of the retroviral oncogene v-fos (gene locus:14q24.3). It was initially analyzed and cloned in rat fibroblasts as the transforming gene of Finkel–Biskis–Jinkins murine osteogenic sarcoma virus [7]. The gene encodes a 62 kDa protein (380 amino acids), forming heterodimer with c-jun, a strong transcription factor), resulting in the formation of AP-1 (Activator Protein-1) complex. c-Fos/c-Jun complex influences intracellular signal transduction to the nucleus. c-Fos protein is implicated in critical cell functions including differentiation, proliferation, survival and also tissue homeostasis affected by hypoxia and angiogenesis [8].

Beside c-Fos, c-Jun is also a very critical gene modifying the expression rates of other genes inside signal transduction pathways. C-Jun protein is encoded by the corresponding gene hosted on chromosome 1 (gene locus:1p32-p31) [9]. In fact, c-Jun was the first pure oncogenic transcription factor discovered [10]. It is the homolog of the viral oncoprotein v-Jun. The protein interacts with c-Fos forming the AP-1 early response transcription factor. 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. Interestingly, the gene region on chromosome 1 is frequently the target of translocations and deletions in solid malignancies implicating also other oncogenes, such members of ras family [11].

c-Fos/c-Jun complex in LSCC

Gene numerical imbalances and especially increased copy number due to amplification is a frequent deregulation mechanism in protooncogenes' overactivation, leading also to protein overexpression. Recently published molecular studies detected overactivation of c-Fos in invasive parts -compared to adjacent non-malignant epithelia- of head and neck squamous cell carcinomas (HNSCC) in different anatomic regions such as oral. 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 [12]. Similarly, CD44 interaction with matrix hyaluronan (HA) has been found be involved in c-Jun phosphorylation and its nuclear translocation in HPV16 persistent infection in the oropharyngeal and laryngeal area. A study group analyzing the influence of HA/CD44 complex in c-Jun-dependent signaling pathways in oropharyngeal carcinoma -using a mouse xenograft model - concluded that is critical in the cases of HPV16 E6 gene overexpression upregulation affecting the levels of chemoresistance (ie cisplatin) in HPV16+ infected cells [13]. Additionally, c-Jun aberrant expression is involved in mechanisms that provide chemoresistance in specific agents such as docetaxel-cisplatin-5-FU (TPF) triplet regimen in LSCC cases. A combined gene microarray-based expression analysis focused on Wnt and p53 signaling pathways and also Mapk10, Jun, Vegfb, Pik3r5, Pld1, Tek, Itga6 genes reported that there are subgroups of patients who could earn benefits by applying TPF chemotherapy [14]. In particular, another agent -bleomycin-A2- seems to affect apoptotic pathways implicating also c-Jun molecule by its deglycosylation. In particular, this metabolic process is responsible for c-Jun NH2-terminal kinase-dependent apoptosis on JNK activation and independent of caspases activation in LSCC cells [15]. Concerning other agents that are potentially involved in LSCC development and progression, retinoic acid receptor beta (RARbeta) provides transrepression of activator protein-1 (AP-1) transcription factor activity. A study group analyzed the protein expression levels of c-Jun/c-Fos/AP-1 and RARbeta. They detected a progressive upregulation of them by their predominantly nuclear expression from normal-appearing laryngeal epithelium, hyperplastic laryngeal epithelium, laryngeal epithelium and well to poorly-differentiated LSCC, respectively [16]. Interestingly, c-Fos/c-Jun complex seems to interact with specific enzymes such as glutathione S-transferase (GST)-pi. A protein analysis-based study reported that a group of patients with LSCC demonstrated high relapse levels in GST-pi, c-Jun, or c-H-Ras upregulation. The researchers suggested that combined GST-pi/c-Jun/c-Fos/c-H-Ras expression is modified by applying radiation protocols in LSCC and for this reason should be a risk factor for relapse of malignancy [17]. Furthermore, analysis of multidrug resistance genes (MDR) in LSCC patients have shown that c-Fos is implicated also in vincristine-dependent chemotherapy response in HEp-2 cell lines [18]. Another important study showed that well-known carcinogens, such as tobacco, induce overexpression of c-Fos/c-Jun activator protein 1 (AP-1) associated pathways and their oncogenic activity has been detected in both pre-malignant and LSCC tissues [19]. Finally, the role of telomerase reverse transcriptase (TERT) in LSCC in conjunction with the deregulation of c-Jun/c-Fos is under investigation. A study group showed that TERT upregulation was combined with c-Jun/c-Fos mRNA

and protein overexpression promoting increased proliferation in human laryngeal carcinoma cells through activation of the AP-1 [20].

In conclusion, overactivation of c-Fos/c-Jun complex is a frequent and crucial genetic event in LSCC development and progression and combined with upregulation of other oncogenes and suppressor genes downregulation affect 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 groups of LSCC patients.

Conflict of interests

The authors declare no conflict of interests.

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