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Impact of C-FOS/C-JUN Transcriptional Factors Co-Expression in Non–small Cell Lung Carcinoma

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Abstract. *Background/Aim: Significant transcription factors – including c-Fos (gene locus: 14q24.3) and c-Jun (gene locus: 1p32-p31) – regulate cell homeostasis preventing abnormal signal transduction to nucleus. Their over-activation seems to be associated with an aggressive phenotype in non-small cell lung carcinomas (NSCLCs). In the current study, our aim was to co-analyze c-FOS/c-JUN protein expression in a series of NSCLCs correlating them to the corresponding clinico-pathological features. Materials and Methods: A set of fifty (n=50) paraffin embedded NSCLC tissue sections were selected comprising of adenocarcinomas (n=25) and squamous cell carcinomas (n=25), respectively. Immunocytochemistry (IHC) for the c-FOS/c-JUN markers was implemented. Digital image analysis (DIA) was also performed for evaluating objectively the corresponding immunostaining intensity levels of the examined proteins. Results: All the examined tissue samples expressed the markers in different protein levels. High staining intensity levels were detected in 34/50 (68%) and 24/50 (48%), respectively. C-FOS over expression was statistically significant correlated to stage (p=0.033), whereas C-JUN over expression was associated with NSCLC histotype (p=0.05) and with maximum tumor diameter (p=0.046). Conclusion: C-FOS/C-JUN co- over activation is observed frequently in NSCLC, playing potentially a central role in the aggressiveness of the malignancy's phenotype (advanced stage, increased metastatic potential). Development and implementation of novel agents that target these transcription factors is a promising approach for applying targeted therapeutic strategies in NSCC patients based on specific genetic signatures and protein profiles.*

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Among the molecules that act inside the cell microenvironment, transcription factors regulate a variety of signaling transduction pathways influencing critical cell functions (1). They are referred to specific proteins implicated in the DNA to messenger (m) RNA transcription process by using a DNA-binding domain. They interact with the promoter/enhancer region of other genes controlling their expression levels (2). Since now, approximately

1500 different transcription factors have been defined and cloned. They are categorized in two main, recognizable types: the general and upstream (3). Under the pressure of numerical (amplification) and structural (mutation) genetic imbalances, transcription factors demonstrate oncogenic activity affecting negatively the normal expression of other genes (4).

Fos Proto-Oncogene or AP-1 Transcription Factor Subunit (c-FOS) is a critical molecule, a member of the Fos superfamily. The last includes four main proteins: c-Fos, FosB, FosL1, and FosL2, respectively (5). C-FOS is the human homolog of the retroviral oncogene v-FS (gene locus: 14q24.3) encoding for a 62 kDa protein. Rat fibroblasts were the eligible substrate for the initial detection and cloning of the Finkel–Biskis–Jinkins murine osteogenic sarcoma virus transforming gene (6). Interestingly, the c-FOS protein forms a heterodimeric complex with the c-JUN, another significant molecule acting also as a strong transcription factor. C-Jun protein is encoded by the corresponding gene on chromosome 1 (gene locus: 1p32-p31) (7). This gene was the first detected and cloned transcription factor with potential oncogenic activity (8). In fact, it is the homolog of the viral oncoprotein v-Jun (avian sarcoma virus 17). The protein interacts with c-FOS forming the AP-1 early response transcription factor (9). In normal cells, the c-FOS/c-JUN complex is involved in cell functions and mechanisms such as tissue morphogenesis, differentiation, survival, proliferation, apoptosis, and regulation of signal transduction pathways (10).

In the current study, we co-analyzed c-FOS/c-JUN protein expression levels in non – small cell lung carcinoma (NSCLC) tissue substrates in order to explore their potential impact on the clinic-pathological features of the examined malignancies.

Materials and Methods

Study group. Focused on our research purpose to co-analyze c-FOS/c-JUN protein markers, a pool of fifty (n=50) archival, formalin-fixed, and paraffin-embedded tissue specimens of histologically confirmed primary NSCLC were selected and used. It should be mentioned that all the corresponding histopathological material was derived from surgical operations at the beginning of the diagnosis of the disease as a primary malignancy and not from a local recurrence. The Department of Pathology and the corresponding Ethics Committee of National and Kapodistrian University of Athens consented to the use of these tissues for research purposes (Reference ID research protocol:1920028233/21-05-20), according to World Medical Association Declaration of Helsinki guidelines (2008, revised 2014). The tissue samples were fixed in 10% neutral-buffered formalin. Hematoxylin and eosin (H&E)-stained slides of the corresponding samples were reviewed for confirmation of the histopathological diagnoses. All lesions were classified according to the histological typing and staging criteria of the World Health Organization (WHO) Pathology Series (11). In order to establish a balance regarding the analyzed NSCLC sub-types, we selected equally adenocarcinomas (n=25) and squamous cell carcinomas (n=25). Clinicopathological data of the examined cases are demonstrated in Table I.

Table I. *Clinicopathological parameters and total combined c-FOS/c-JUN IHC results (0-255 staining intensity values).*

Sex, male/female; n (%)	36 (72.0)/14 (28.0)
Type, SCC/ADC; n (%)	25 (50.0)/25 (50.0)
Localization, Left/Right lung; n (%)	26 (52.0)/24 (48.0)
Grade, Low/Moderate/High; n (%)	25 (50.0)/20 (40.0)/5 (10.0)
p-Stage, n (%)	
Tis	1 (2.0)
IA	15 (30.0)
IB	13 (26.0)
IIA	4 (8.0)
IIB	9 (18.0)
IIIA	7 (14.0)
IIIB	1 (2.0)
Age, mean±SD (min-max)	71.74±6.77 (59-87)
Maximum diameter, mean±SD (min-max)	3.86±1.72 (1.2-7.5)
c-FOS IHC, mean±SD (min-max)	125.29±16.16 (93.9-176.1)
c-JUN IHC, mean±SD (min-max)	143.52±13.77 (112.1-187.5)

IHC: Immunohistochemistry; SCC: squamous cell carcinoma; ADC: adenocarcinoma.

Antibodies and immunohistochemistry assay (IHC). Combined c-FOS/c-JUN protein analysis was based on IHC assays modified for each marker. We selected and applied the ready-to-use anti- mouse monoclonal antibodies anti-c-FOS (clone CF2, Novocastra, Leica Biosystems, Newcastle, UK) (dilution 1: 40) and anti- c-JUN mouse monoclonal (clone DK4, Novocastra, Leica Biosystems) (dilution 1:60). The IHC protocols for the antigens were implemented on 3-4 μm thick serial tissue sections as it was described in our previous published research (12). For negative control slides, the primary antibody was omitted. IHC protocol was performed by the use of an automated staining system (I 6000 Biogenex, Fremont, CA, USA). Nuclear predominantly and also cytoplasmic staining pattern was considered an acceptable staining pattern for evaluating specificity of the examined proteins, according to antibody manufacturer's instructions (Figure 1a, b). Normal (non-cancerous) skin tissue sections demonstrating c-FOS/c-JUN expression was used as positive markers.

Digital image analysis assay (DIA). c-FOS/c-JUN protein expression levels were evaluated quantitatively by calculating the corresponding staining intensity levels (densitometry evaluation) in the stained malignant tissues. We performed DIA using a semi-automated system (Microscope: CX-31, Olympus, Melville, NY, USA; Digital camera: Sony, Tokyo, Japan; Software: NIS-Elements Software AR v3.0, Nikon Corp, Tokyo, Japan) (Figure 1c). Measurements were performed by implementing a specific macro algorithm as it was reported in our previous published research (13).

Statistical analysis. Descriptive statistics were carried out using the statistical package SPSS version 21.00 (IBM Corporation, Armonk, NY, USA). Data were expressed as mean±SD for quantitative variables and as percentages for qualitative variables. The Kolmogorov—Smirnov test was utilized for normality analysis of the quantitative variables. Unifactorial analyses were made using the Student t-test, One-way ANOVA model (Bonferroni test for pairwise comparisons) and Pearson's correlation coefficients to analyze the relation between the outcome variables (c-FOS and c-JUN) and the quantitative, qualitative demographic and clinical

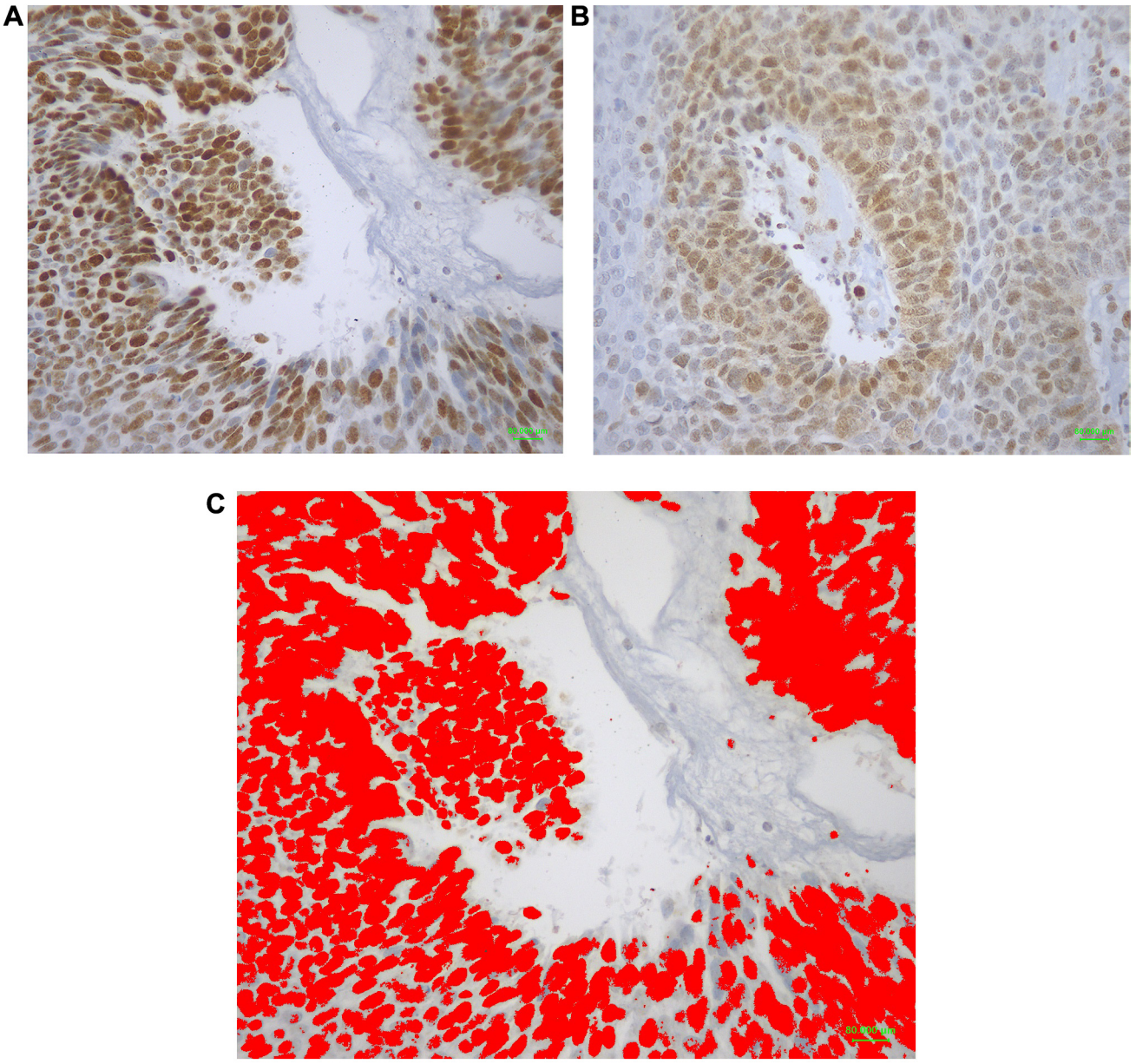

Figure 1. *c-FOS high expression (a), and c-JUN moderate expression (b) patterns in a case of non-squamous cell carcinoma (NSCLC). Note the nuclear and cytoplasmic dense dark staining pattern (high expression). (c) Digital image analysis procedure for c-FOS protein expression measurement in the current immune-stained slide. After the microscopic image capture process, detection of the stained cells (red color), and bio informative-based digital measurements of the corresponding staining intensity levels are implemented (DAB chromogen, original magnification 400×).*

characteristics respectively. All demographic and clinical variables in unifactorial analyses were included in a multiple linear regression model, using firstly the enter method to determine the significant independent factors associated with the outcome variables and secondly the stepwise method to determine the most significant factors associated with c-FOS and c-JUN respectively. All assumptions of linear regression analysis (homoscedasticity, linearity, normality and independence of error terms, as well as multicollinearity of independent variables) were examined. All tests are two-sided, statistical significance was set at $p<0.05$.

Results

According to the digitized IHC results, the examined cases demonstrated differences regarding their protein expression levels. High staining intensity levels were detected in 34/50 (68%) and 24/50 (48%), respectively. C-FOS over expression was statistically significant correlated to the stage ($p=0.033$) of the examined malignancies, whereas C-JUN over expression demonstrated a borderline association with the

Table II. *Statistical analysis of c-FOS variable.*

		Mean±SD	*p*-Value
Sex	Male	125.17±17.00	0.933
	Female	125.60±14.35	
Type	SCC	125.08±20.00	0.930
	ADC	125.49±11.54	
Localization	Left	126.44±16.25	0.550
	Right	123.68±15.34	
Grade	Low	124.76±17.26	0.972
	Moderate	125.70±14.34	
	High	126.29±20.79	
p-Stage	IA	116.18±13.88	**0.033**
	IB	132.37±15.14	
	IIA	125.07±15.75	
	IIB	132.57±13.96	
	IIIA	121.65±15.35	
Age		r=–0.257	0.071
Maximum diameter		r=–0.007	0.963

SCC: Squamous cell carcinoma; ADC: adenocarcinoma. Statistically significant *p*-values are shown in bold.

Table III. *Statistical analysis of c-JUN variable.*

		Mean±SD	*p*-Value
Sex	Male	144.05±14.32	0.664
	Female	142.14±12.64	
Type	SCC	139.79±6.54	**0.050**
	ADC	147.25±17.76	
Localization	Left	143.32±11.08	0.837
	Right	144.09±14.87	
Grade	Low	143.38±12.98	0.691
	Moderate	142.46±15.10	
	High	148.46±13.93	
p-Stage	IA	146.97±17.36	0.774
	IB	143.22±14.59	
	IIA	140.03±4.43	
	IIB	143.20±7.15	
	IIIA	140.13±5.27	
Age		r=–0.063	0.667
Maximum diameter		r=–0.284	**0.046**

SCC: Squamous cell carcinoma; ADC: adenocarcinoma. Statistically significant *p*-values are shown in bold.

NSCLC histotype (p=0.05) and also with the maximum tumor diameter (p=0.046). Table II and Table III present c-FOS and c-JUN numerical results and also statistical associations (p-values in bold indicate statistical significances).

c-JUN expression analysis. More specifically, maximum diameter was low to moderate negatively correlated with c-JUN (r=-0.284, p=0.046) and patients with ADC presented higher values of c-JUN compared with those with SCC, However, there were not any statistically significant associations between c-JUN and all other variables. The initial regression model presented co linearity between maximum diameter and p-stage something that leads us to exclude the variable maximum diameter. After the exclusion our model satisfied all assumptions of linear regression analysis. Additionally, regression analysis with enter method accounting for 26% of the variance in c-FOS [R2=0.257; F (6,41)=2.36, p=0.047].

c-FOS expression analysis. Concerning c-FOS results, only p-Stage (R2=15.2%, p=0.0033) was statistically significant (patients with IA p-stage presented lower values of c-FOS compared with those with other p-stage). Stepwise method confirmed the results of enter method. Only p-Stage (R2=13.3%, p=0.006) was the strongest predictor of c-FOS. The initial regression model presented colinearity between maximum diameter and p-stage something that leads us to exclude the variable maximum diameter. After the exclusion our model satisfied all assumptions of linear regression analysis. Regression analysis with enter method accounted for 13.7% of the variance in c-JUN [R2=0.257; F(6,41)=1.09, p=0.385]. According to these results, only the histotype of the examined malignancies (R2=10.2%, p=0.046) was statistically significant associated with c-JUN variable (patients with type SCC presented lower values of c-JUN compared with those with ADC). Stepwise method confirmed the results of enter method. Again, only the histotype (R2=8.2%, p=0.027) was the strongest predictor of c-JUN but with small contribution in explaining outcome variable.

Discussion

C-FOS/c-JUN complex of transcriptional factors demonstrate an oncogenic over activation in a variety of solid malignancies, including the main pathological entities of the NSCLC: SCC and ADC, respectively. Concerning the mechanisms that induce their activity, extensive genetic analyses show that novel genes and molecular pathways are involved in this process. A study group focused on the role of the epidermal growth factor-like domain multiple 6 (EGFL6) gene. Its protein expression seems to be negatively related to the progression and an aggressive biological behavior (increased TNM-stage/distant-bone metastases) in the corresponding ADC patients. Using *in vitro* ADC cell cultures, they observed that EGFL6 induced the osteoclast differentiation and bone resorption (destruction) by enhancing the oncogenic activity of specific signaling pathways including the c-FOS/NFATc1, Wnt/β-catenin and PI3K/AKT/mTOR, respectively (14). Similarly, another study explored the role of 27-Hydroxycholesterol (27-HC) expression in lung adenocarcinoma and its potential relation with the c-FOS gene. They reported a direct influence of the 27-HC protein in the activation of the STAT3/c-FOS/NFATc1 pathway

leading to elevated osteoclastogenesis in the corresponding analyzed malignant tissue sections (15). Another gene expression profiling interactive m-RNA based analysis explored the differences in the expression levels of the SMADs. These proteins act as genes' transcription regulators and they are involved in the signal transduction to the nucleus interacting negatively also with the c-FOS gene. The researchers reported low mRNA expression levels of SMAD-6/7/9 in the examined SCC and ADC patients with increased c-FOS expression (16). Interestingly, molecules that are involved in the tumor immune escape, such as programmed cell death (PD-L1) and the ligand 2 (PD-L2) seem to interact with transcription factors including the c-FOS. A molecular study based on a combination of reverse transcription/real-time polymerase chain reaction analyses and flow cytometry revealed that c-FOS/STAT genes were over activated implicated also both of them to the PD-L2 elevated expression. Additionally, interferon gamma (IFN-γ) is a potential inductor of c-FOS over expression in the corresponding pathways (17).

Concerning the role of specific microRNAs (MiRs) in the regulation of c-FOS/c-JUN expression in lung carcinoma, some studies have reported interesting data. In one of them, the researchers observed that miR-744 over activated c-FOS increasing also the metastatic potential in the corresponding examined NSCLC patients (18). In contrast, miR-345/miR-498 expression induces the oncogenic activity of the MAPK/c-Fos and AKT/Bcl-2 signaling transduction pathways (19). For this reason, these micro-markers inhibit proliferation of the malignant cells, leading also to elevated apoptosis. Another miR, the miR-147b upregulates the MAPK pathway activating also the c-JUN by over expressing the dual-specificity phosphatase 8 (DUSP8) (20). This molecule acts as a selective c-JUN oncogenic promoter.

In the current experimental study, we reported C-FOS/C-JUN co- or single over activation in NSCLC tissues. The majority of them demonstrated an aggressive patient phenotype (advanced stage, increased metastatic potential). Novel agents that target these transcription factors is a very promising approach for applying targeted therapeutic strategies in NSCC patients with specific genetic signatures and protein profiles. A G-quadruplex ligand BMVC-8C3O which enhances the activity of a monoclonal antibody –the osimertinib– in patients with lung cancer suppresses the oncogenic potential of c-FOS (21). Similarly, echinacoside, a natural substance inhibits the Raf/MEK/ERK/c-FOS signaling transduction pathway preventing malignant cell proliferation by providing mitochondria-mediated pyroptosis (22). Concerning the selective inhibition of c-JUN activity in NSCLC patients, dihydroartemisinin, huaier (Trametes robiniophila Murr) fungus, and claudin-6 seem to be effective by targeting the c-JUN N-terminal kinase (JNK) axis (23-25). Furthermore, anaplastic lymphoma kinase (ALK) inhibitors and also sorafebin – a monoclonal antibody- reduce the JNK activity by degrading it even in lung epithelia pre-cancerous lesions (26, 27).

In conclusion, c-FOS/c-JUN oncogenic activation is a crucial event n NSCLC patients potentially correlated to an aggressive phenotype (advanced stage). Although a variety of molecular mechanisms regarding their deregulation have been already discovered, there is still a pool of genes and pathways under investigation (28-30). Besides c-FOS/C-JUN complex, other transcriptional factors such as NFATc2 and Sp1 are over activated in solid malignancies, including NSCLC and pancreatic adenocarcinoma (31). Interestingly, in a variety of solid malignancies, activation of c-JUN N- terminal kinase leads to an increased apoptotic potential due to tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL) motivation (32). Defining the genetic imbalances that are responsible for the over expression of these two important transcriptional factors is essential for an optimal oncological management of the corresponding patients by producing new anti- c-FOS/c-JUN targeted agents and reducing the resistance to them.

Conflicts of Interest

The Authors declare no conflicts of interest regarding this study.

Authors' Contributions

All Authors contributed to the study conception and design. KM, AC, VP, ET: Draft writing, MA, AS, KV, SP, PP: data collection, references detection and analysis, GA, ACL, EK, PT, NK: academic advisors. All Authors read and approved the final manuscript.

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