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SPECIAL MOLECULAR REVIEW

c-Fos/ c-Jun transcription factors in non-small cell lung carcinoma

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Summary

During lung carcinoma development, progression and metastasis, a variety of gross (chromosome) and specific (gene) genomic alterations are detected in dysplastic, neoplastic, and progressively malignant transformed epithelia as early or late genetic events. Oncogenes' overactivation combined with suppressor genes silence are crucial genetic events in malignant and pre-malignant epithelia. Especially, deregulation of crucial signalling transduction pathways that interact with strong transcription factors - such as c-Fos and c-Jun - leads to an aberrant expression of other critical genes responsible for cell homeostasis. Upregulation of c-Fos and c-Jun leading to other oncogenes overactivation seems to be correlated with aggressive biological behaviour in non-small cell lung carcinomas (NSCLCs). In the current special molecular article we explored the role of c-Fos/c-Jun complex deregulation in NSCLC based on their interactions with other genes that demonstrate modified expression profiles.

Key words: *lung, c-Fos, c-Jun, oncogene, carcinoma*

Introduction

Lung cancer exhibits an increasing incidence and a high mortality rate worldwide. According to 2015 WHO data and histo-genetic classification, lung cancer is the leading cause of death related to cancer and its incidence is still on the increase worldwide. Histo-pathologically, the former term ''Non-Small Cell Lung Carcinoma'' (NSCLC) constitutes the majority of patients suffered by lung cancer [1]. Specifically, NSCLC -including mainly adenocarcinoma and squamous cell carcinoma- constitutes the diagnosis attributed to the majority of patients suffering from lung cancer (about 85% of all pathologically defined lung cancer cases). A broad spectrum of genomic imbalances, including chromosome polysomy/aneuploidy, or specific gene deregulation mechanisms, such as point mutations, deletions and amplification in critical oncogenes such as Epidermal Growth Factor Receptor (EGFR) has been already identified in the corresponding patients modifying their response rates to novel targeted therapeutic regimens, and affecting also their lifespan [2,3]. Besides signaling transduction pathways, evolution of genetics and molecular biology have improved our knowledge and understanding of the structure, the functional roles and the mechanisms of deregulation in a variety of genes involved in cancer genome development, such as transcriptional factors [4,5].

The current review focused on the critical role of c-Fos/c-Jun complex in NSCLC, and especially in its interactions with other genes that experimentally co-analyzed and found to modify their expression profiles.

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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 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].

Besides 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 gene interactions in NSCLC

Recently published experimental molecular studies reported interesting data regarding to c-Fos/c-Jun expression profiles in NSCLC and their interactions with other genes. Co-analyzing by immunohistochemistry assay the expression levels of c-Fos/c-Jun, Cyclooxygenase-2 (COX-2) and also nuclear factor of activated T cells 3 (NFAT3) in NSCLC tissue microarray spots, a study group observed that the overexpression of c-Fos – but not of c-Jun – was significantly associated with the expressions of NFAT3 and COX-2 in the corresponding malignant tissues [12]. Interestingly, COX-2 was significantly higher in squamous cell carcinoma than that in adenocarcinoma, associated also with differentiation grade of the examined malignancies. Besides these molecules, interleukins that represent cytokines implicating in lymphocyte proliferation and growth induction in solid tumors seem to interact also with c-Fos/c-Jun complex in NSCLC. A study group focused on the interleukin-7 and its receptor role in lung carcinoma cell proliferation analyzing *in vitro* the previously referred molecules in conjunction to cyclin D1. They observed that interleukin-7/interleukin-7 receptor led to cyclin D1 overexpression due to increased oncogenic activity of c-Fos/c-Jun pathway providing aberrant cell proliferation in lung cancer cells [13]. Furthermore, molecules that are implicated in hypoxia regulation seem to interact with c-Fos/c-Jun complex in NSCLC. According to molecular analysis at genetic polymorphism level, a study detected a novel allelic modification on Hypoxia-inducible factor-2α (HIF-2α, or EPAS1) gene. They observed that this specific genetic imbalance (rs13419896 single nucleotide polymorphism-SNP) is correlated with overexpressed c-Fos or c-Jun molecules, leading also to NSCLC progression and should be potentially served as a prognostic micromolecular marker in the corresponding patients [14]. Similarly, in order to identify agents that could inhibit invasion and migration in NSCLC, a study group focused on the acacetin (5,7-dihydroxy-4'-methoxyflavone) - a flavonoid compound - influence in NSCLC cell cultures. The authors observed that the agent suppressed strongly the p38α MAPK signaling pathway and also decreased the nuclear expression levels and oncogenic activity of c-Fos/c-Jun complex [15]. Another study explored the efficacy of ursonic acid, a pentacyclic triterpenoid compound in NSCLC cell lines. The authors concluded that this agent led to decreased Matrix Metalloproteinase-1 (MMP-1) mRNA levels by suppressing ERK and c-fos dependent-signaling pathways [16]. Additionally, the role of programmed cell death ligand 2 (PD-L2) in NSCLC and its interaction with the c-Fos gene is also under investigation. A study based on combined reverse transcription, real-time polymerase chain reaction analysis and flow cytometry showed that c-fos overexpression mediated by interferon gamma (IFN-γ) leads to the extrinsic induction of PD-L2 activation [17]. Interestingly, overexpression of a calcium-binding protein, regucalcin encoded by RGN gene, seems to be also important for NSCLC oncogenes' inhibition. A molecular study based on *in vitro* cell lines analysis identified that regucalcin overactivation provides c-Fos and c-myc oncogene downregulation, decreasing its expression levels, and leading also to cancer cell proliferation suppression [18]. Additionally, the role of specific steroidal Na(+)/K(+) ATPase inhibitors in suppressing

oncogenes' activity inducing also apoptotic potential inside malignant tissues is under investigation. A study group explored the influence of the 3-[(R)-3-pyrrolidinyl]oxime derivative (3-R-POD) agent in lung carcinoma cell lines and observed a remarkable tumor growth inhibition in lung xenografts *in vivo*. The authors concluded that this inhibitor induced apoptosis by stimulating caspase-3 activity combined with modifications in BCL-2 and c-fos gene transcription [19]. Another recently cloned new oncogene that seems to be implicated in lung carcinoma progression is the CRLK. According to a study based on carcinoma cell lines analysis, its overexpression led to cell invasion by overactivating c-Fos - dependent Matrix Metalloproteinase- 9 (MMP-9) promoter expression [20].

In conclusion, overactivation of c-Fos/c-Jun complex is a frequent and crucial genetic event in NSCLC development and progression, which 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 oncoproteins' levels inhibiting their activity should be a very promising approach for applying targeted therapeutic strategies in selected groups of NSCC patients.

Conflict of interests

The authors declare no conflict of interests.

References

1. Travis WD, Brambilla E, Nicholson AG et al. The 2015 World Health Organization Classification of Lung Tumors. Impact of Genetic, Clinical and Radiologic Advances since the 2004 classification. J Thorac Oncol 2015; 10: 1243-60.
2. Richer AL, Friel JM, Carson VM, Inge LJ, Whitsett TG. Genomic profiling toward precision medicine in non-small cell lung cancer: getting beyond EGFR. Pharmgenomics Pers Med 2015;8:63-79.
3. Tsiambas E, Lefas AY, Georgiannos SN et al. EGFR gene deregulation mechanisms in lung adenocarcinoma: A molecular review. Pathol Res Pract 2016;212:672-7.
4. Hanahan D, Weinberg RA. Hallmarks of cancer: The next generation. Cell 2011;144:646-74.
5. Belluti S, Rigillo G, Imbriano C. Transcriptional factors in cancer: When alternative splicing determines opposite cell fates. Cells 2020;9:760-8.
6. Angel P, Allegretto EA, Okino ST et al. Oncogene jun encodes a sequence specific trans-activator similar to AP-1. Nature 1988;332:166-71.
7. Curran T, Peters G, Van Beveren C, Teich NM, Verma IM. FBJ murine osteosarcoma virus: identification and molecular cloning of biologically active proviral DNA. J Virol 1982;44:674-82.
8. Angel P, Karin M. The role of Jun, Fos and the AP-1 complex in cell-proliferation and transformation. Biochim Biophys Acta 1991;1072:129-57.
9. Adler V, Polotskaya A, Wagner F, Kraft AS. Affinity purified c-Jun amino-terminal protein kinase requires serine/threonine phosphorylation for activity. J Biol Chem 1992;267:17001-5.
10. Angel P, Hattori K, Smeal T, Karin M. The jun protooncogene is positively auto-regulated by its product, Jun/AP-1. Cell 1988;55:875-85.
11. Behrens A, Jochum W, Sibilia M, Wagner EF. Oncogenic transformation by ras and fos is mediated by c-Jun N terminal phosphorylation. Oncogene 2000;19:2657-63.
12. Zhao X, Chen Z, Zhao S, He J. Expression and significance of COX-2 and its transcription factors NFAT3 and c-jun in non-small cell lung cancer. ZhongguoFei Ai ZaZhi 2010;13:1035-40.
13. Ming J, Jiang G, Zhang Q, Qiu X, Wang E. Interleukin-7 up-regulates cyclin D1 via activator protein-1 to promote proliferation of cell in lung cancer. Cancer Immunol Immunother 2012;61:79-88.
14. Putra AC, Eguchi H, Lee KL et al. The A Allele at rs13419896 of EPAS1 Is Associated with Enhanced Expression and Poor Prognosis for Non-Small Cell Lung cancer. PLoS One 2015;10:e0134496-02.
15. Chien ST, Lin SS, Wang CK et al. Acacetin inhibits the invasion and migration of human non-small cell lung cancer A549 cells by suppressing the p38α MAPK signaling pathway. MolCellBiochem 2011;350:135-48.
16. Son J, Lee SY. Ursonic acid exerts inhibitory effects on matrix metalloproteinases via ERK signaling pathway. Chem Biol Interact 2020;315:108910-15.
17. Shibahara D, Tanaka K, Iwama E et al. Intrinsic and Extrinsic Regulation of PD-L2 Expression in Oncogene-Driven Non-Small Cell Lung cancer. J Thorac Oncol 2018;13:926-37.
18. Yamaguchi M, Osuka S, Shoji M, Weitzmann MN, Murata T. Survival of lung cancer patients is prolonged with higher regucalcin gene expression: suppressed proliferation of lung adenocarcinoma A549 cells in vitro. Mol Cell Biochem 2017;430:37-46.
19. Honisch S, Alkahtani S, Kounenidakis M et al. A steroidal Na+/K+ ATPase inhibitor triggers pro-apoptotic signaling and induces apoptosis in prostate and lung tumor cells. Anticancer Agents Med Chem 2014;14:1161-8.
20. Lin F, Chengyao X, Qingchang L, Qianze D, Enhua W, Yan W. CRKL promotes lung cancer cell invasion through ERK-MMP9 pathway. Mol Carcinog 2015; 54 (Suppl 1):E35-44.