JBUON 2020; 25(1): 582-587
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
Email: editorial_office@jbuon.com

LETTERS TO THE EDITOR

Physical activity and breast cancer: Role of inhibition of Wnt signaling in triple negative breast cancer

Dear Editor,

Breast cancer is the most common cancer in women. This common cancer can be prevented by an active lifestyle. Physical activity can reduce the risk of breast cancer, reduce the rate of recurrence, and increase the survival rate of patients with breast cancer. de Boer and colleagues in their review article [1] summarized the mechanisms and effects of physical activity on breast cancer. They investigated 5 possible underlying mechanisms through which physical activity has an influence on breast cancer. Another possible new mechanism was also defined. Wingless and integration site growth factor (Wnt) signaling is a tumorigenesis-related signaling pathway, also active especially in triple negative breast cancer [2]. Dickkpof-1 (DKK1) and secreted frizzled-related protein-1 (SFRP1) are endogenous regulators of Wnt/β-catenin signaling. One study investigated the effects of exercise training on circulating levels of DKK1 and SFRP1 in breast cancer survivors in a pilot single-blind randomized controlled trial [3]. They reported that the levels of DKK1 and SFRP1 were also significantly decreased by exercise training in breast cancer survivors (all $p<0.01$). Therefore, it is assumed that physical activity may inhibit Wnt/β-catenin signaling through inhibition of DKK1 and SFRP1 in triple negative breast cancer.

References

1. de Boer MC, Wörner EA, Verlaan D, van Leeuwen PA. The Mechanisms and Effects of Physical Activity on Breast Cancer. Clin Breast Cancer 2017;17:272-8.
2. Jamdade VS, Sethi N, Mundhe NA, Kumar P, Lahkar M, Sinha N. Therapeutic targets of triple-negative breast cancer: a review. Br J Pharmacol 2015;172:4228-37.
3. Kim TH, Chang JS, Park KS et al. Effects of exercise training on circulating levels of Dickkpof-1 and secreted frizzled-related protein-1 in breast cancer survivors: A pilot single-blind randomized controlled trial. PLoS One 2017;12:e0171771.

Kadri Altundag

MKA Breast Cancer Clinic, Tepe Prime, Ankara, Turkey

Corresponding author: Kadri Altundag, MD.
Email: altundag66@yahoo.com

Enhancing PTEN suppressor gene expression in pancreatic carcinoma

Dear Editor,

Pancreatic cancer is one of the most lethal gastrointestinal malignancies and the fourth leading cause of cancer-associated mortality worldwide. The main cause is late detection - called "silent killer" - and a lack of methods for proper evaluation of response to the therapeutic regimens. Combined k-ras oncogene overactivation and suppressor genes downregulation frequently are observed in pancreatic carcinogenesis [1]. The PI3K/AKT/PTEN/mTOR signaling transduction pathway regulates many critical cell functions including cell proliferation, protein synthesis and survival. Concerning carcinogenesis, gene imbalances lead to tumor growth and angiogenesis by deregulating VEGF and hypoxia-inducible factor-1 expression [2]. PTEN (gene locus: 10q23.3-phosphatase and tensin homolog deleted in chromosome 10) is a tumor suppressor gene that is deleted, mutated or epigenetically hyper-methylated in a variety of human malignancies. PTEN acts as a negative regulator of this specific pathway. Normal expression of PTEN induces growth suppression by promoting cell cycle arrest. It is also correlated with decreased levels and nuclear localization of cyclin D1 regulated by AKT that positively induces cell cycle [3].

PTEN downregulation in pancreatic carcinoma seems to be a significant genetic event inducing the aggressiveness of the malignancy such as proliferation and invasion. Novel therapeutic molecular approaches are based on specific agents that target critical proteins including PTEN. Enhancement of molecules' expression stabilizes the corresponding signaling transduction pathways. Two recent studies analyzed the effects of epigallocatechin 3 gallate and nimesulide on the inhibition of proliferation and induction of apoptosis of pancreatic cancer cells [4,5]. Both molecules were shown to have promising positive effects on pancreatic cancer by enhancing expression of PTEN and by suppressing the expression of AKt/mTOR and therefore limiting the proliferation of the cancer cells. Interestingly, nimesulide acts as a proliferation inhibitor and apoptosis inducer by cleaved caspase-3/Bax over expression and bcl-2 down regulation. Concerning its exact role at gene expression balance, the molecule acts as a selective COX-2 inhibitor and also as a PTEN enhancer. Similarly, epigallocatechin 3 gallate suppresses the expression of p-Akt and p-mTOR proteins in the corresponding pathway.

References

1. Sohn TA, Yeo CJ. The molecular genetics of pancreatic ductal carcinoma: a review. Surg Oncol 2000;9:95-101.
2. Schlessinger J. Cell Signaling by Receptor Tyrosine Kinases. Cell 2000;103:211-25.
3. Chu EC, Tarnawski AS. PTEN regulatory functions in tumor suppression and cell biology. Med Sci Monit 2004;10:235-41.
4. Liu S, Xu ZL, Sun L et al. Epigallocatechin-3-gallate induces apoptosis in human pancreatic cancer cells via PTEN. Mol Med Rep 2016;14:599-605.
5. Chu M, Wang T, Sun A, Chen Y. Nimesulide inhibits proliferation and induces apoptosis of pancreatic cancer cells by enhancing expression of PTEN. Exp Ther Med 2018;16:370-6.

Leonidas Petrogiannopoulos[1], Athanasios Niotis[2], Theodoros Niotis[2], Evangelos Tsiambas[3]

[1]Department of Gastroenterology, 417 VA Hospital, Athens, Greece; [2]2nd Department of Surgery, National and Kapodistrian University of Athens, School of Medicine, Aretaieion University Hospital, Athens, Greece; [3]Department of Pathology-Cytology, 401 GAH, Athens, Greece

Corresponding author: Evangelos Tsiambas, MD, MSc (ip), PhD.
Email: tsiambasecyto@yahoo.gr

Outcome of small node-negative ER+/HER2+ and ER–/HER2+ breast cancers might be different

Dear Editor,

Analysis of HER2+ metastatic breast cancer has often been performed disregarding the ER status of the disease. A recent study examined the metastatic pattern and prognosis of both ER+/HER2+ and ER-/HER2+ in 86,093 breast cancer patients [1]. This large study showed that patients with ER+/HER2+ and ER–/HER2+ breast cancers had different metastatic patterns and patients with ER–/HER2+ breast cancer had worse prognosis.Furthermore, neoadjuvant trials of chemotherapy plus anti-HER2 treatment consistently showed lower pathologic complete response (pCR) rates in patients with hormone receptor-positive compared to hormone receptor-negative tumors [2]. Furthermore, Bao and colleagues [3] compared survival and recurrence rates (RR) in patients with T1mi,a,bN0M0 breast cancer by tumor type. They identified 71 patients with HER2+ tumors, 545 with hormone receptor (HR)+ /HER2- tumors, and 45 with triple negative breast cancers (TNBC) diagnosed between January 1, 2000 through December 31, 2013 and they found that patients with T1mi,a,bN0M0 invasive breast cancer had an excellent prognosis. The authors concluded that chemotherapy was not associated with improved survival and tumor subtype may not influence recurrence and survival in such small early stage tumors. Interestingly, when patients with HER2+ breast cancer and TNBC who received chemotherapy were compared to those who did not, there was no difference in death rates (p=0.3). However, the authors did not consider ER+/HER2+ and ER-/HER2+ as a different molecular subtypes. As a whole, ER+/HER2+ and ER–/HER2+ breast cancers should be accepted as different subtypes. Survival benefit in small node-negative invasive breast cancers might be expected to be different whether they received chemotherapy plus anti-HER2 targeted therapy or not.

References

1. Arciero CA, Guo Y, Jiang R et al. ER(+)/HER2(+) Breast cancer has different metastatic patterns and better survival than ER-/HER2(+) breast cancer. Clin Breast Cancer 2019 Feb 14. pii: S1526-8209(18)30792-4. doi: 10.1016/j.clbc.2019.02.001. [Epub ahead of print]
2. Cortazar P, Zhang L, Untch M et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. Lancet 2014;384:164-72.
3. Bao J, Donovan C, Amersi F, Zhang X, Giuliano AE, Chung A. Outcomes in patients with small node-negative invasive breast cancer. Breast J 2019 May 12. doi: 10.1111/tbj.13288. [Epub ahead of print]

Kadri Altundag

MKA Breast Cancer Clinic, Tepe Prime, Ankara, Turkey

Corresponding author: Kadri Altundag, MD.
Email: altundag66@yahoo.com

Targeting caspase - dependent apoptosis in hepatocellular carcinoma

Dear Editor,

Apoptosis is the term that refers to the genetically programmed cell death mediated by a complex of proteins which influence positively or negatively intrinsic and extrinsic pathways. Among the proteins that are involved in apoptosis, caspases are critical molecules acting as inducers of it. Caspases (cysteine-aspartic proteases) represent a family of enzymes that influence several functions crucial for cell homeostasis such as inflammation, pyroptosis (a distinct aspect of programmed cell death mediated by microbial infection that triggers also an immune response), necroptosis, tissue differentiation and development in the embryonic early stages of life [1]. According to their impli-

cation in the apoptotic pathways, caspases are characterized as initiators and executioners, respectively. In the first group inserted have been caspase-2,-8,-9, and -10, whereas caspase-3,-6, and-7 belong to the second category [2]. All of these normal actions of the caspase complex that induce apoptosis are altered in carcinoma progression and establishment. In cancer tissues, programmed cell death is inhibited due to a deregulation in expression of pro- and anti-apoptotic proteins. This genetic imbalance drives the cancerous cell to immortalization which reflects the aberrant tissue proliferation.

Hepatocellular carcinoma (HCC) is one of the leading causes of malignancy-mediated deaths worldwide characterized by very low response rates to targeted therapeutic strategies and increased metastatic potential that reduce dramatically survival in the corresponding patients. Concerning deregulation in apoptotic pathways, recently published studies have shown that specific molecules play a critical role in activating specially caspase functions. A study group explored the influence of four-and-a-half LIM protein 1 (FHL1) in chemoresistance of paclitaxel - based therapy in HCC cells [3]. They observed that inactivation of FHL1 induced caspase-3 and caspase-9 promoting apoptosis, concluding also that FHL1 should be a promising protein target for modifying positively chemo resistance in HCC patients with specific genetic signatures. Similarly, another study group analyzed experimentally the role of vitamin D (Vit D) alone and in combination with 5-fluorouracil (5-FU) in rats. They reported that combined Vit D/5-FU therapeutic application in HCC-induced experimental animal-based model led to increased apoptotic rates due to caspase-3 overactivation [4]. Another protein that seems to be critical for modifying apoptotic activity in HCC cells is alpha-fetoprotein (AFP). Normally, AFP plays a pivotal role in regulating foetal liver formation and development as a growth factor. Concerning HCC, a study group concluded that AFP overactivation negatively affects apoptotic mechanism by inhibiting caspase-3, but not caspase-8 [5]. In fact, they found that this interaction is provided by specific amino acids, including loop-4 residues Glu-248, Asp-253 and His-257.

References

1. Leone G, Anja P, Anahid J, Janko K. Cysteine cathepsins: Their biological and molecular significance in cancer stem cells. Semin Cancer Biol 2018;S 30028-2.
2. Wilson CH, Kumar S. Caspases in metabolic disease and their therapeutic potential. Cell Death Differ 2018;25:1010-24.
3. Zhou L, Ding L, Liu J et al. Four-and-a-half LIM protein 1 promotes paclitaxel resistance in hepatic carcinoma cells through the regulation of caspase-3 activation. J Cancer Res Ther 2018;14:S767-S73.
4. Ebrahim A, El-Mesery M, El-Karef A, Eissa LA. Vitamin D potentiates anti-tumor activity of 5-fluorouracil via modulating caspase-3 and TGF-β1 expression in hepatocellular carcinoma-induced in rats. Can J Physiol Pharmacol 2018;96:1218-25.
5. Lin B, Zhu M, Wang W et al. Structural basis for alpha fetoprotein-mediated inhibition of caspase-3 activity in hepatocellular carcinoma cells. Int J Cancer 2017;141:1413-21.

Athanasios Niotis[1], Leonidas Petrogiannopoulos[2], Theodoros Niotis[1], Evangelos Tsiambas[3]

[1]Department of Surgery, National and Kapodistrian University of Athens, School of Medicine, Aretaieion University Hospital, Athens, Greece; [2]Department of Gastroenterology, 417 VA Hospital, Athens, Greece and 22nd Department of Surgery, National and Kapodistrian University of Athens, School of Medicine, Aretaieion University Hospital, Athens, Greece; [3]Department of Pathology-Cytology, 401 GAH, Athens, Greece.

Corresponding author: Evangelos Tsiambas, MD, MSc, PhD. Email: tsiambasecyto@yahoo.gr

Weighted Hula-Hooping may decrease breast cancer recurrence by decreasing abdominal fat and increasing trunk muscularity in obese postmenopausal breast cancer survivors

Dear Editor,

Exercise during and following treatment has been associated with reductions in breast cancer recurrence and disease-specific mortality rates of 30-60% [1]. Furthermore, regular exercise by itself increases skeletal muscle volume in the body, leading to increased skeletal muscle mass index [2]. Hula-hooping is an ancient type of dance, which has recently experienced a comeback in the form of aerobic core training. Beneficial metabolic effects in obese subjects is unknown. One study compared the effects of weighted hula-hooping and walking in obese subjects. They found that 6 weeks of hula-hooping for an average duration of 13 min per day significantly decreased waist circumference and body fat in the android region and increased trunk muscularity compared to a period of walking in a group of overweight subjects [3]. Furthermore, excess total body fat and abdominal adipose tissue are recognized risk factors for metabolic diseases but also for some types of cancers, including breast cancer. Obesity stimulates cancer progression through chronic, low-grade inflammation in white adipose tissue. One study showed that a 16-week aerobic and resistance exercise intervention attenuates adipose tissue inflammation in obese postmenopausal breast cancer survivors [4]. In conclusion, weighted Hula-Hooping as an exercise type may decrease breast cancer recurrence by decreasing abdominal fat and increasing trunk muscularity in obese postmenopausal breast cancer survivors. This issue merits further investigation.

References

1. Irwin ML, McTiernan A, Manson JE et al. Physical activity and survival in postmenopausal women with breast cancer: results from the Women's Health Initiative. Cancer Prev Res (Phila) 2011;4: 522-9.
2. Kida K, Osada N, Akashi YJ, Sekizuka H, Omiya K, Miyake F. The exercise training effects of skeletal muscle strength and muscle volume to improve functional capacity in patients with myocardial infarction. Int J Cardiol 2008;129:180-6.
3. Lahelma M, Sädevirta S, Lallukka-Brück S et al. Effects of Weighted Hula-Hooping Compared to Walking on Abdominal Fat, Trunk Muscularity, and Metabolic Parameters in Overweight Subjects: A Randomized Controlled Study. Obes Facts 2019;12: 385-96.
4. Dieli-Conwright CM, Parmentier JH, Sami N et al. Adipose tissue inflammation in breast cancer survivors: effects of a 16-week combined aerobic and resistance exercise training intervention. Breast Cancer Res Treat 2018;168: 147-57.

Kadri Altundag

MKA Breast Cancer Clinic, Tepe Prime, Ankara, Turkey

Corresponding author: Kadri Altundag, MD.
Email: altundag66@yahoo.com

HPV-mediated carcinogenesis: the role of k-ras mutations

Dear Editor,

Human papillomavirus (HPV) - especially high risk (HR) persistent infection- has emerged as a significant etiologic factor implicated in viral-mediated carcinogenesis in a variety of epithelial malignancies. HPV particle formations consist of capsids containing a circular double DNA molecule of approximately 8 kb. Eight reading open frames and a non-coding region compose HPV genome. At the molecular level, HPV oncogenic activity is released by E6/E7 oncoproteins overactivation. In fact, HPV E7 oncoprotein deregulates RB/E2F pathway leading to an aberrant $p16^{INK4A}$ overexpression, combined also by p53 inactivation due to HPV E6 oncogene overactivation, respectively [1]. Additionally, HR HPV-depended cervical or Head and Neck Squamous Cell Carcinoma (HNSCC) are characterized by the disorganization of specific signaling pathways, including mainly the PI3K-AKT-PTEN-mTOR, the RAS-(B) RAF-MEK-ERK/MAPK and also the IL6-JAK1/2-STAT3. In them, the Kirsten ras oncogene homolog (KRAS, Cytogenetic Location: 12p12.1) represents an important family of genes (proto-oncogenes) - including also HRAS and NRAS - that encode proteins acting as hydrolase enzymes, especially hydrolyzing guanosine triphosphate (GTPases) [2]. They promote cell division, cell differentiation, and also indirectly programmed cell death (apoptosis). Deregulation of KRAS is detected frequently in solid malignancies as a result of point mutations. Concerning cervical carcinogenesis, there are important but controversial findings regarding mutational KRAS activity. A study group analyzing benign and pre/ malignant tissues identified different incidence of KRAS codon 12 point mutations in them, but the presence of KRAS mutations in cervicitis is considered as an early genetic event [3]. In another genetic analysis, researchers showed that HR HPV persistent infection (especially HPV 16, HPV 18 types) was correlated with KRAS codon 12 point mutations in a subset of pre/malignant tissues with none of the cases showing a KRAS codon 13 point mutation. Furthermore, grade of differentiation in squamous carcinomas was associated with KRAS exon 2 gene alterations. In contrast to the previous referred molecular studies, a study group did not detect any point mutation in codons 12 and 13 of KRAS oncogene in HPV-associated high grade dysplasia and squamous cell cervical carcinoma [4]. Interestingly, KRAS mutations act as part of specific genetic signatures in cases of unusual mucinous neoplasms including gastric-type papillary mucinous adenocarcinoma. Genetic studies in these malignancies identified a combination of deregulated molecules such as p16, p53, muc-6 and k-ras in analyzed cases of Peutz-Jeghers syndrome [5]. In these neoplasms, HR HPV persistent infection seems to be not implicated in its development and progression, but the role of somatic KRAS mutation combined with defective function of p16 is the prominent molecular event.

References

1. Gustinucci D, Giorgi Rossi P, Cesarini E et al. Use of Cytology, E6/E7 mRNA, and p16INK4a-Ki-67 to define the Management of Human Papillomavirus (HPV)-Positive Women in Cervical Cancer Screening. Am J Clin Pathol 2016;145:35-45.
2. Van Damme N, Deron P, Van Roy N et al. Epidermal growth factor receptor and K-RAS status in two cohorts of squamous cell carcinomas. BMC Cancer 2010;10:189-93.
3. Prokopakis P, Sourvinos G, Koumantaki Y, Koumantakis E, Spandidos DA. K-ras mutations and HPV infection in cervicitis and intraepithelial neoplasias of the cervix. Oncol Rep 2002;9:129-33.
4. Pochylski T, Kwaśniewska A. Absence of point mutation in codons 12 and 13 of K-RAS oncogene in HPV-associated high grade dysplasia and squamous cell cervical carcinoma. Eur J Obstet Gynecol Reprod Biol 2003;111:68-73.
5. Ito S, Tase T, Satoh K, Ueki M, Sato I, Sasano H. Gastric-type endocervical glandular neoplasms associated with aberrant p16 expression and K-RAS gene mutation in Peutz-Jeghers syndrome. Pathol Int 2014;64:283-8.

Ilianna E Armata[1], Nicholas Mastronikolis[2], Evangelos Tsiambas[3], Vasileios Ragos[4]

[1]*Medical School, Cambridge University Hospital, Cambridge, UK;* [2]*ENT Department, Medical School, University of Patras, Patras, Greece;* [3]*Department of IHC & Mol. Biology, 401 GAH, Athens, Greece;* [4]*Department of Maxillofacial Surgery, Medical School, University of Ioannina, Ioannina, Greece*

Corresponding author: Evangelos Tsiambas, MD, MSc, PhD.
Email: tsiambasecyto@yahoo.gr

Optimum timing of primary tumor resection on outcome in patients with stage IV breast cancer: is it worth mentioning?

Dear Editor,

In common practice, surgery for the primary tumor is generally performed after systemic treatment given for reducing the metastatic burden in stage IV breast cancer patients. Lim and colleagues [1] investigated the effect of primary tumor resection on overall survival in stage IV breast cancer patients and they found that surgical resection of primary tumors tended to be associated with improved overall survival (HR=0.67, p=0.055). The authors concluded that surgical resection of the primary tumor may be a treatment option for patients with stage IV disease and may not have a negative effect on overall survival. The authors did not mention timing for surgery in this patient population. However, most similar studies did not reveal optimum timing for primary surgery in patients who present with stage IV breast cancer. Rao et al [2] evaluated the optimum timing for primary surgery in stage IV breast cancer patients and they reported that patients who underwent surgery in 3-8.9 months or later had improved metastatic progression-free survival. In conclusion, it would be rationale to recommend surgery for the primary tumor site in metastatic breast cancer patients who have responded well to systemic treatment.

References

1. Lim SM, Kim JY, Park HS et al. Effect of primary tumor resection on overall survival in patients with stage IV breast cancer. Breast J 2019;25:908-15.
2. Rao R, Feng L, Kuerer HM et al. Timing of surgical intervention for the intact primary in stage IV breast cancer patients. Ann Surg Oncol 2008;15:1696-702.

Kadri Altundag

MKA Breast Cancer Clinic, Tepe Prime, Ankara, Turkey

Corresponding author: Kadri Altundag, MD.
Email: altundag66@yahoo.com

c-Fos in oral squamous cell carcinoma

Dear Editor,

Malignant cell transformation is mediated by an aberrant gene expression, including predominantly oncogenes' upregulation combined with suppressor genes' downregulation that lead to cell cycle deregulation. Cancer genome consists of all genetic alterations that modify the normal DNA/mRNA sequences, triggering a cataract of molecular reactions inside and outside the nucleus microenvironment. Furthermore, malignancies are characterized by an inner clonal rise, intra-tumor heterogeneity and dormancy. Among oncogenes, Fos Proto-Oncogene or AP-1 Transcription Factor Subunit (c-Fos) represent well analyzed genes involved in solid malignancies' development and progression. The Fos superfamily includes c-Fos, FosB, FosL1, and FosL2 genes. c-Fos is a proto-oncogene 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 [1]. The gene encodes a 62 kDa protein (380 amino acids), forming heterodimer with c-jun, a strong transcription factors), 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.

Concerning oral squamous cell carcinoma (OSCC), c-fos aberrant expression seems to be critical for the biological behaviour of the malignancy. A combined protein and molecular study showed that c-fos is downregulated (reduced or loss of its expression) in OSCC mucosa in contrast to its expression in normal oral tissues. Interestingly, c-Fos expression levels - provided by immunostaining techniques - were associated with the grade of the examined tumors. A progressive loss of c-Fos expression is demonstrated in higher grades [2]. Controversial results of c-Fos expression patterns have been reported in other protein expression analysis studies. In one of them, c-Fos overexpression - at protein and also mRNA level- was estimated in different stages of oral carcinogenesis. The study group showed that in precancerous tissues and in carcinomas c-Fos/JunD complex was found to be overactivated, an evidence of early genetic imbalance [3]. Another co-analysis of c-Fos/c-Jun, and also p53 immunohistochemistry led to a significant correlation with lymph node metastasis, poor differentiation and clinical stage of the examined OSCC tissues. The study group suggested this co-expression as a potential independent prognostic factor for overall survival in the corresponding patients [4]. In conjunction to the previously described results, another study detected overactivation of c-Fos in invasive OSCC compared to adjacent non-malignant epithelia. A combination of nuclear and peri-nuclear cytoplasmic diffuse immunostaining was observed, especially in cases demonstrating lymph node metastasis, implicating also CD44-depended signal transduction pathway [5].

References

1. 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.
2. Krishna A, Bhatt MLB, Singh V et al. Differential Expression of c-fos Proto-Oncogene in Normal Oral Mu-

cosa versus Squamous Cell Carcinoma. Asian Pac J Cancer Prev 2018;19:867-74.

3. Mishra A, Bharti AC, Saluja D, Das BC. Transactivation and expression patterns of Jun and Fos/AP-1 superfamily proteins in human oral cancer. Int J Cancer 2010;126:819-29.
4. Wang S, Xu X, Xu F et al. Combined Expression of c-jun, c-fos, and p53 Improves Estimation of Prognosis in Oral Squamous Cell Carcinoma. Cancer Invest 2016;34:393-400.
5. Dong C, Ye DX, Zhang WB, Pan HY, Zhang ZY, Zhang L. Overexpression of c-fos promotes cell invasion and migration via CD44 pathway in oralsquamous cell carcinoma. J Oral Pathol Med 2015;44:353-60.

Efthymios Kyrodimos[1], Aristeidis Chrysovergis[1], Evangelos Tsiambas[2], Vasileios S.Papanikolaou[1]

[1]*1st ENT Department, Hippocration Hospital, University of Athens, Athens, Greece;* [2]*Department of Pathology-Cytology, 401 GAH, Athens, Greece.*

Corresponding author: Evangelos Tsiambas, MD, MSc, PhD. Email: tsiambasecyto@yahoo.gr