

MANAGEMENT OF ONCOGENIC TRANSFORMATION BY INTERFERING WITH THE ACTION OF ACTIVATOR PROTEIN-1

AKTİVATOR PROTEİN-1'İN ETKİSİNİ KULLANARAK ONKOJENİK TRANSFORMASYONU YÖNLENDİRMEK

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ABSTRACT

Immediate Early Genes (IEGs) are the foremost genes to respond to any stimuli within the cell. This group of genes are in fact transcription factors which are associated with the growth, proliferation, differentiation and apoptosis of the cells. Fos proteins produced by c-fos gene, which is an IEG, and Jun proteins produced by c-jun gene, which is also an IEG, are the components of the transcription factor complex, namely the Activator Protein-1 (AP-1), and they act together. The members of the AP-1 complex modulate various gene expressions. All AP-1 proteins regulate certain aspects of the cellular responses to growth factors. These components are critically linked to many cellular processes including growth, proliferation, differentiation, apoptosis, and oncogenic transformation. Carcinogenesis resulting from the impairment in the cellular processes controlled by IEGs and AP-1 has been described. Besides the vital importance of their normal cellular expressions, the abnormal expressions of IEGs and AP-1 could cause serious problems such as oncogenic transformation. There are several ongoing studies about the substances and effectors causing overexpression or inhibition of AP-1. If the stages of oncogenic transformation and the role of AP-1 and IEGs in this transformation can be illuminated, carcinogenesis could be taken under control as well as some of the peculiarities of malignant cells could be beneficial for the treatments of various diseases.

Key words: IEGs, AP-1, Carcinogenesis, Proto-oncogenes, Oncoproteins, Oncogenic transformation.

ÖZET

Bir uyarıyla karşılaşan hücrelerde, uyarana ilk yanıt veren genler IEG (Immediate Early Gene) grubundaki genlerdir. Bu genler hücre büyümesi, çoğalması, farklılaşması ve hücrenin programlanmış ölümü (apoptozis) ile ilgili transkripsiyon faktörleridir. Bir IEG olan c-fos geninin ürettiği Fos proteinleri, yine bir IEG olan c-jun geninin ürettiği Jun proteinleri transkripsiyon faktör kompleksi Aktivator Protein-1 (AP-1)'in komponentleri olarak birlikte işlev görürler. AP-1 kompleksinin üyeleri farklı gen ekspresyonlarını ve büyüme faktörlerine hücre sel yanıtın bazı yönlerini düzenlerler. Bu komponentler büyüme, çoğalma, farklılaşma, programlanmış hücre ölümü ve onkojenik transformasyon gibi hücre sel süreçlerde kilit rolü oynarlar. Karsinogenezin, IEG ve AP-1 tarafından kontrol edilen hücre sel süreçlerdeki bozukluğun bir sonucu olduğu tanımlanmıştır. IEG ve AP-1'in hücrelerdeki normal ekspresyonlarının yaşamsal önemi vardır ancak anormal ekspresyonları, onkojenik transformasyon gibi ciddi sorunlar doğurur. AP-1'in ekspresyonunu artıran veya azaltan maddeler ve etkenler konusundaki çalışmalar devam etmektedir. Onkojenik transformasyonun aşamaları ve bu transformasyonda IEG ve AP-1'in rolü tam olarak aydınlatılabilirse karsinogenez kontrol edilebilir bir duruma gelebilecek hatta kanser hücrelerinin bazı özelliklerinden çeşitli hastalıkların tedavisinde yararlanılabilecektir.

Anahtar kelimeler : IEG, AP-1, Karsinogenez, Protoonkojenler, Onkoproteinler, Onkojenik transformasyon.

INTRODUCTION

Immediate Early Genes (IEGs) and Activator Protein -1 (AP-1) family proteins which contain their oncoprotein products, are required for the maintenance of the vitality

and regeneration of cells. Besides the vital importance of their normal cellular expressions, the abnormal expressions of IEGs and AP-1 could cause serious problems such as oncogenic transformation. If the role of AP-1 in onco-

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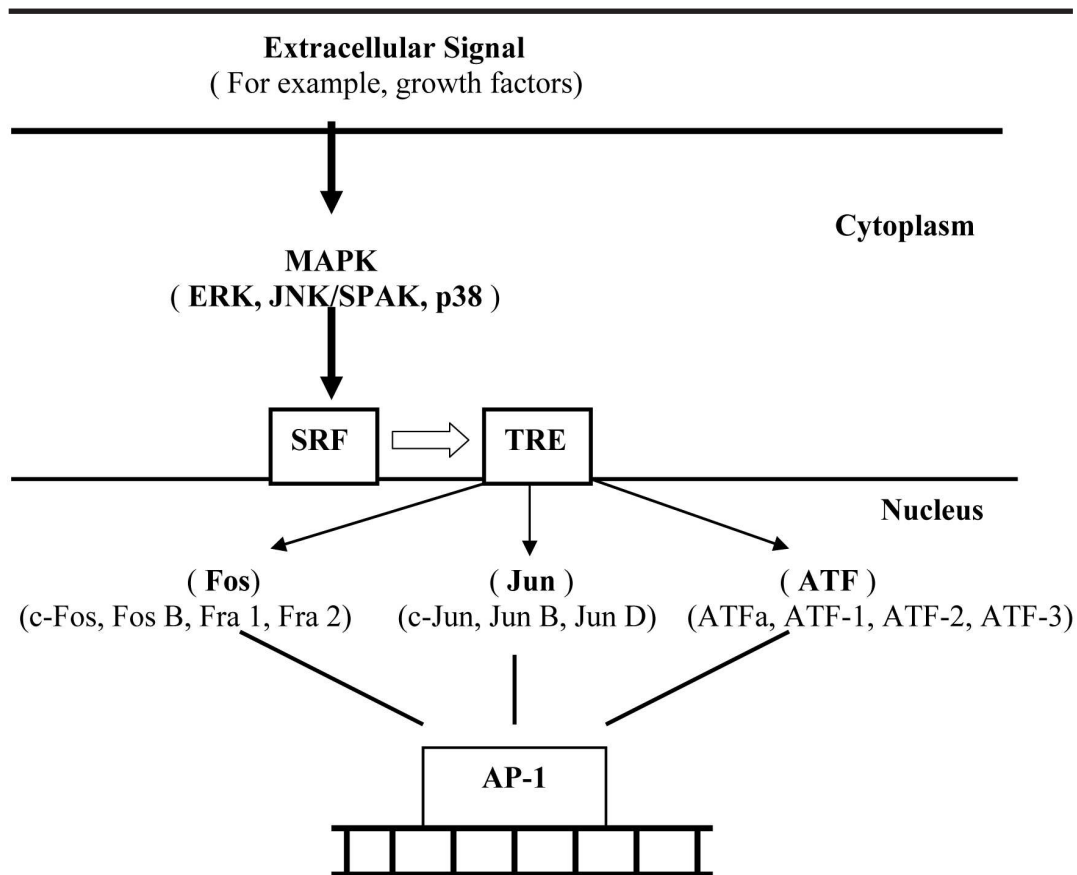


Figure 1. Signal transduction activation of Activator Protein-1 (AP-1)

genic transformation can be elucidated, characteristics of cancer cells could be utilized in the treatments of various disorders.

IEGs are potential activators of transcription and IEGs are the first genes to respond to any stimuli within the cell (7). IEGs and AP-1, play a very important role during cellular proliferation, differentiation, programmed cell death (apoptosis) and oncogenic transformation (4, 41). These proto-oncogenes and oncoproteins, being potential activators of transcription, are key elements to understand oncogenic transformation and normal development due to their relationship with biological processes. The pathways regulating different cell cycle phases are the central target for genetic alterations in cancer due to their interaction with various oncogenes and tumor suppressors (15). The transcription factors are fundamental to the progression of genetic and cellular changes which culminate in a malignant tumor (40). In some tumor types, c-fos and c-jun levels, both of which are IEGs, have been shown to increase, and it was suggested that this elevation may play an important role in tumorigenesis, since it is a sign of increased proliferation (14, 27). However, in addition to their role in malignancy, proto-oncogenes are also involved in the regulation of normal growth and differentiation. Many mitogens may stimulate IEGs, and therefore the protein product of these proto-oncogenes are referred to as

oncoproteins. These proteins are known to play a role in the development of cancer (46). Fos proteins produced by c-fos gene and Jun proteins produced by c-jun gene are the components of the transcription factor complex, namely the Activator Protein-1 (AP-1) (16). AP-1 consists of Fos proteins (c-Fos, Fos B, Fra 1, and Fra 2), Jun proteins (c-Jun, Jun B, and Jun D), and some activating transcription factor (ATF) proteins (ATFa, ATF-1, ATF-2, and ATF-3) (12, 25). Fos proteins form stable dimers with Jun proteins. On the other hand, Jun proteins form homodimers or heterodimers with Fos and ATF proteins (2, 14, 25). All AP-1 proteins are phosphoproteins and their DNA-binding properties and transactivation activities may be influenced by hyperphosphorylation and dephosphorylation (13). Each AP-1 dimer may be linked with various specific stages of cellular process, rather than the entire process (26).

The components of AP-1 complex bind to the promoter regions on DNA that contain 12-O-tetradecanoylphorbol-13-acetate (TPA) response elements (TRE) to modulate various gene expressions (2). AP-1 is crucial for cell adaptation to many environmental changes (5). All AP-1 proteins regulate certain aspects of the cellular response to growth factors and tumor promoting phorbol esters (2). These stimulants can stimulate AP-1 activity by activating mitogen-activated protein kinases (MAPK), such as extracellu-

lar signal-regulated kinase (ERK), c-Jun N-terminal kinase or stress-activated protein kinase (JNK/SAPK) and p38 kinase (19). Induced AP-1 activity is required for tumor promoter-induced transformation (10) (Figure 1).

It is known that IEGs and AP-1 are key factors in carcinogenesis (18, 37, 50). Carcinogenesis develops in three defined stages; initiation, promotion, and progression (36). Transactivation of AP-1 is important in traversing tumor promotion and/or progression stages of carcinogenesis (50). According to a claim, c-fos expression is involved in benign-to-malignant tumor progression (17).

It is possible to block carcinogenesis or inactivate cancer cells by inhibiting the transcriptional activity of AP-1 or AP-1 expression. Since AP-1 inhibitors respond to peptide growth factors like insulin-like growth factor-1 (IGF-1), epidermal growth factor (EGF), heregulin-beta and basic fibroblast growth factor (bFGF) by completely blocking proliferation, AP-1 blockade suppresses mitogenic signal from multiple different peptide growth factors (31). The incidence of cancer increases with age (3). A possible contributing factor may be that the level of AP-1 activity varies throughout the life time of both a cell and an individual. It has been suggested that IEG and AP-1 activity, which are high during embryonic development, may be altered by ageing. Cellular ageing results in significant changes in the composition and DNA-binding capacity of AP-1 transcription factor (43). Cellular ageing is characterized by many phenotypic changes such as the alteration in the proliferative capacity of gene expression, impairment in the stimulation of c-fos by serum, and alterations in the binding activity of Serum Response Factor (SRF). These changes are associated with decrease in c-fos expression in the older cells (32, 47).

According to the results of some studies, AP-1 proteins can substitute each others antagonistic functions in biological processes such as oncogenic transformation and cell proliferation and each of AP-1 proteins may have different individual functions (23, 26, 44). There are some different implications for these transcription factors according to tumour type, for example, Fra-1 overexpression enhances the motility and invasion of breast and colorectal cancer cells, but inhibits the tumorigenicity of cervical carcinoma cell lines (35). It is also claimed that some proteins belonging to Jun and Fos families, like Jun B and c-Fos, have tumour-suppressor activity and can suppress tumour formation. The decision as to whether AP-1 is oncogenic or anti-oncogenic depends on the cell type, differentiation state, tumour stage and the genetic background of the tumour (11).

The genes some of which have a potential to mediate neoplastic transformation, are regulated by AP-1 (1). Therefore the studies to determine substances and mechanisms which are able to inhibit AP-1 activation are crucial steps in the progress of controlling carcinogenesis (21, 29, 31, 52). There are ongoing studies pointing that the biologic mechanisms or curative substances inhibit growth or inva-

sion in cancer cells through repression or blocking of AP-1 activity (6, 20, 22, 34, 39, 49). It is known that dominant-negative cJun mutant (TAM67) (18, 31, 34) and Jun dimerization protein 2 (JDP2) (32) are specific inhibitors of AP-1. It has been reported that TAM67 inhibits breast cancer growth by inducing inhibitors of cyclin-dependent kinases (such as p27) and by reducing the expression of the cyclins involved in transitioning from G1 into S phase of the cell cycle (30). It has been shown that protein kinase C (PKC) inhibitors like Calphostin C and bisindolymaleimide I also inhibit AP-1 activation and phosphorylation of MAPKs (ERKs and p38 kinases) (9).

TRIM45 one of the tripartite motif (TRIM) proteins (48), Costunolide, a sesquiterpene lactone isolated from the root of *Saussurea lapa* Clarke [24], Gabexate mesilate, a synthetic protease inhibitor (51), Rhein (4,5-Dihydroxyanthraquinone-2-carboxylic acid), a constituent enriched in the rhizome of rhubarb (*R. palmatum* L. or *R. tanguticum* Maxim) (29), inhibit the activity of AP-1 transcription factor.

According to the result of a previously performed study; inhibition of AP-1 transcription factor causes blockade of multiple signal transduction pathways and inhibits breast cancer growth (31). Moreover, different cases about blocking AP-1 activity have also been reported in another studies, including blocking AP-1 activation using Ursodeoxycholic acid (UDCA) in order to block colonic carcinogenesis (42), inhibition of breast cancer cell growth by means of using overexpression of TAM67 (a dominant-negative form of cJun) (33) and inhibition of both AP-1 activation and translation initiation by programmed cell death 4 (PDCD4) while decreasing benign tumor development and malignant progression (21).

By AP-1 inhibition, it is possible to inhibit matrix metalloproteinases (MMPs) which are important factors in tumor invasion and metastasis. Treatment of human fibrosarcoma cells with Carboxylated chitoooligosaccharides (CCOS) leads to down-regulation of AP-1, which results in inhibition of matrix metalloproteinase-9 (MMP-9) (38). Moreover, treatment of human breast carcinoma cells with silibinin, a flavonoid antioxidant from milk thistle (*Silybum marianum* L.) suppresses AP-1 dependent MMP-9 gene expression by blocking the activation of AP-1 via MAPK signaling pathways (28).

Carcinogenesis resulting from the impairment in the cellular processes controlled by IEGs and AP-1 has been described. The abnormal expressions of oncogenes, oncoproteins and tumor suppressors disorder normal cell cycle. This incident brings new characteristics to these cells. The ability of a tumor cell to avoid programmed cell death (apoptosis) is crucial in the development of cancer (8). The acquisition of cellular immortality is a crucial step in human tumorigenesis (45).

Systemic activation or inactivation of IEGs and AP-1 may help to control the carcinogenesis invoked by inadequate or over-activation of IEGs and AP-1. The carcinogenesis progress can also be taken under control by analyzing and

fully revealing cancer cell characteristics such as immortality-evasion from apoptosis, metastasis, continuous division- proliferation and unaging. By controlling this process, mentioned peculiarities of cancer cells can be utilized to discover new treatment approaches or develop current treatment procedures. Therefore it may be possible to prevent cell and tissue based disorders such as cell-ageing, growth retardation and it may be also possible to compensate loss of tissue integrity due to several reasons.

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