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Modulation of the composition of AP-1 complex and its impact on transcriptional activity

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Abstract. AP-1 transcription factor known to play a role in cell proliferation and neuronal activation, it is also involved in apoptosis of cells in response to stress, DNA damaging agents or lack of survival signals. AP-1 DNA binding complex is not a single transcritpion factor but a dimer consisting of members of Fos and Jun families. In this review, we discuss evidence that composition of the AP-1 complex is different under various physiological and pathophysiological conditions. Furthermore, we describe biochemical properties of Fos and Jun proteins that may explain the ability of this transcription factor to activate different sets of genes in response to different stimuli. We propose a hypothesis that AP-1 might contribute to distinct biological processes because an activation of specific signaling pathways results in changes of AP-1 composition and/or phosphorylation status and modulates its transactivating potential towards different promoters.

Key words: transcription factors, c-Jun protein, Jun proteins, ATF-2, protein phosphorylation, neurodegeneration, long-term responses

INTRODUCTION

The transcription factor AP-1 was first defined as a DNA binding activity specific for positive regulatory element in SV40 early promoter that is important for inducible gene expression in response to phorbol esters (TPA). Further studies revealed that AP-1 DNA binding activity is not a single transcritpion factor but a dimer consisting of various members of Fos and Jun families. Changes in AP-1 activity, due to changes in the expression of AP-1 family members and posttranslational modifications, occur in response to a wide variety of different events. Two decades of work have revealed the activation of some AP-1 components by an incredible number of diverse stimuli. Among those are: growth factors, antigen binding by B and T lymphocytes, neurotransmitters, cellular stress, ionizing and ultraviolet irradiation, cytoskeletal rearrangements, and variety of cytokines (for review see: Angel and Karin 1991, Curran and Morgan 1995, Kaczmarek and Chaudhuri 1997, Herdegen and Leah 1998, Kasibhatla et al. 1998).

COMPOSITION AND BIOCHEMICAL PROPERTIES OF AP-1

The molecular composition of the AP-1 complex is heterogeneous. Both the Fos and Jun families of nuclear phosphoproteins may participate in formation a homo- or heterodimeric complex that binds to the DNA consensus sequence TGAC/GTCA and modulates expression of the target genes (Hirai et al. 1989, Angel and Karin 1991, Morgan and Curran 1995). The Fos family contains 5 proteins (c-Fos, Fos B, ΔFosB, Fra-1, Fra-2) and Jun family includes 3 known members (c-Jun, JunB, JunD). Jun proteins, in contrast to Fos proteins, can form homo- and heterodimers. Although AP-1 complex consists of dimers formed between two Jun or between Jun and Fos molecules, other proteins such as ubiquitously expressed ATF/CREB, can interact with AP-1 components (Benbrook and Jones 1990, Hai and Curran 1991). In the brain, an activation of AP-1 complex is dependent on *de novo* synthesis of some of AP-1 components and their interactions with existing proteins. Recent studies established some signalling pathways critical for AP-1 complex activation. Of particular importance are protein kinases belonging to MAP kinase families: ERK, JNK, and p38 kinases which influence not only synthesis of Fos and Jun proteins but also regulate their trancritpional potential (Karin 1995, Karin et al. 1997). Phosphorylation of the serine residues 63 and 73 in c-Jun by c-Jun the N-terminal kinases (JNKs) increases its trans-activating potential (Hibi et al. 1993, Minden et al. 1994, Karin 1995, Kallunki et al. 1996). This phosphorylation results in a large increase in the ability of c-Jun to interact with the CBP/p300 family of general coactivators and affect transcritpion activation (Franklin et al. 1995).

Despite all combinations of Fos-Jun or Jun-Jun dimers bind the consensus AP-1 target element, functional assays revealed some differences in the ability to bind unique AP-1 sites in various promoters, stability of binding, and trancriptional activation. For example, binding of heterodimers of Fos-Jun to DNA is more stabile than binding of homodimers (Halazonetis et al. 1988, Abate et al. 1991). *In vitro* studies using recombinant proteins revealed that a stability of binding AP-1 complexes to DNA differs depending on the presence of particular proteins. The stability of binding for complexes containing c-Jun is higher than those containing JunD or JunB; heterodimers consisting of Fos B bind to DNA more stabily than heterodimers made of Fra-1 or c-Fos (Ryseck and Bravo 1991). Also transactivating potentials of various AP-1 components differ significantly showing for example opposing activities of c-Fos and Fra-2 (Yashioka et al. 1995, Ruthberg et al. 1997).

THE AP-1 TRANSCRIPTON FACTOR IS INVOLVED IN DIFFERENT BIOLOGICAL PHENOMENA

Since treatment of cultured cells with mitogenic agents results in a strong induction of AP-1 activity, it has been suggested that AP-1 transcription factor is primarily involved in transmitting growth promoting signals into the nucleus (Angel and Karin 1991, Kovary and Bravo 1992, Lallemand et al. 1997, Wisdom et al. 1999). Furthermore many studies, including ours, have shown that AP-1 complex is induced in the brain under physiological conditions (Takeuchi et al. 1993, Kaminska et al. 1995, 1996, Francois-Bellan et al. 1999, Herdegen and Leah 1999). In regenerating neurons c-Jun expression correlates with their ability to survive and regenerate (Herdegen et al. 1997). Recently AP-1 complex has been implicated in the regulation of apoptosis. The increased level of c-Jun and an induction of AP-1 transcription factor has been associated with apoptosis in central nervous system cells *in vivo* (Sonnenberg et al. 1989, Pennypacker et al. 1993, Kaminska et al. 1994, Dragunow et al. 1995, Kasof et al. 1995, Pennypacker 1998, Hughes et al.

TABLE I

Composition of AP-1 DNA binding activity under various conditions determined by supershift analysis with similar antibodies (Santa Cruz Biotechnology)

Extract source and biological phenomena		Jun proteins	Fos proteins	References
Rat sensory cortex:	naive	**JunD**	**FosB**	Kaminska et al. 1996,1999
	light deprived	**JunD**	**FosB**	
	light stimulation for 2h	**P-c-Jun, JunB**, JunD	**c-Fos**, FosB	
	light stimulation for 6h	**JunB, JunD**	**FosB**	
Rat sensory cortex at 21 postnatal day		**JunD**, JunB	FosB, **Fra-2**, c-Fos	Kaminska et al. 1995
Rat hippocampus after seizures induced by kainate:				
	Early phase- 2 h	**P-c-Jun, JunB**	**c-Fos**, FosB	Kaminska et al. 1994, 1997
	Late phase- 6 h	**JunB**	c-Fos, **Fra-2, FosB**	
	Neurodegeneration- 72h	JunD, P-c-Jun	FosB	
Rat hippocampus at 2 h after seizures induced by pentylenotrazole		**JunB**	**c-Fos,** FosB	Lukasiuk, Kaczmarek 1994
Rat suprachiasmatic nucleus:				
	Constant darkness	**JunD**	**Fra-2**	Francois-Bellan et al. 1999
	2h after light stimulation	**JunB**	**c-Fos**, Fra-2, FosB	
Rat visual cortex after learning session:				
	Not trained	**JunD**, c-Jun, JunB	**FosB**, Fra-2, c-Fos	Lukasiuk et al. 1999
	2 h after trening	**JunB**, c-Jun, JunD	**c-Fos**, FosB,	
Chronic electroconvulsive shock		FosB (ΔFosB)	JunD	Hiroi et al. 1998

1999). Many *in vitro* studies have indicated that induction of c-jun transcription and elevated c-Jun expression are associated with apoptosis in sympathetic neurons, differentiated PC12 cells, and central nervous system neurons (Estus et al. 1994, Ham et al. 1995, Eilers et al. 1998, Watson et al. 1998). Furthermore an interference with function of c-Jun either by expression of dominant-negative c-Jun mutants or microinjection of neutralizing c-Jun antibodies protect sympathetic neurons or postmitotic PC12 cells from apoptosis (Estus et al. 1994, Ham et al. 1995).

These results suggested that AP-1 may modulate cell function positively or negatively and raised an important issue where the specificity of response lies. Some aspects of specificity of AP-1 action may be revealed by further analysis of contribution of different Fos and Jun proteins to AP-1 DNA binding activity, and definition of activities specific to individual protein.

Expression of Fos and Jun, at both mRNA and protein levels, is sensitive to a number of different stimuli. The inductions, especially at the mRNA levels, are often large in magnitude but very transient. On the other hand, some AP-1 family members (often Fra-1, Fra-2, and JunD) are expressed under unstimulated conditions and in consequence the total increase in AP-1 DNA binding activity is less impressive than would be expected based on analysis of mRNA expression. The composition of AP-1 complex depends upon the relative proportions of different proteins present in cells at a given time. Studying expression of only one member of Fos or Jun

families brings a partial and inefficient information about AP-1 complex. To understand how could AP-1 mediate the cellular response to such a wide array of stimuli, it is necessary to establish precisely the composition of the complex and relative contribution of each protein.

The composition of AP-1 DNA binding complexes can be probed by addition of antibodies specific for each Fos and Jun protein. Addition of antibodies produces either a supershift due to decreased electrophoretic mobility of the IgG containing complexes or disappearance of the DNA-protein complex due to disruption of the complex. The last situation occurs when an antibody is directed against DNA binding or dimerization domain of Fos and Jun proteins. Using supershift analysis many studies demonstrated that the composition of AP-1 complex differs in various physiological situations and even closely related members of the same family might contribute to quite distinct biological phenomena. The Table I summerizes some data concerning the composition of AP-1 complex under physiological and patological conditions. To facilitate comparisons only supershift data employing similar antibodies were considered. The proteins more abundant in AP-1 complex are written in bold type. Although the data are not complete, one can see a tendency that in unstimulated brain there is AP-1 composed of **FosB** and **JunD**, while stimulation of neuronal activity is associated with the appearance of AP-1 complexes containing **c-Fos**, **c-Jun**, **JunB**. Prolonged AP-1 activity observed under conditions of chronic neuronal stimulation is associated with the presence of chronic **Fras** that appear to be a truncated form of FosB (ΔFosB) (Hiroi et al. 1998). A growing body of evidence suggests that neurodegeneration resulting from programmed cells death is associated with an accumulation of heterodimers composed of **FosB** and **Jun** proteins or **Jun** homodimers, with particular abundance of phosphorylated **c-Jun** and **JunD**.

The functional consequences of changes in subunit composition are poorly understood, although it is clear that the different Fos and Jun proteins are distinct in term of their ability to effect transcriptional control.

THE COMPOSITION AND PHOSPHORYLATION STATUS OF AP-1 COMPLEX MODULATES ITS TRANSACTIVATING POTENTIAL

The role of AP-1 in different cellular processes and pleiotropic nature of AP-1 inducers raise an issue how could AP-1 mediate such different, often contradictory processes. One possible explanation for this dilemma is that changes in the composition or phosphorylation status of AP-1 complex can modulate its transcriptional activity or modify a selection of target genes. We have set up a series of experiments to test this hypothesis and collected evidence supporting this notion.

We have previously reported that cyclosporin A induces apoptotic death of C6 glioma cells due to the inhibition of signaling pathway consisting of a calcium regulated protein phosphatase-calcineurin and transcription factor NFAT (Mosieniak et al. 1997, 1998). This apoptotic cell death was associated with the induction of AP-1 DNA binding activity before the onset of apoptosis (Mosieniak et al. 1997). Recently we found that the composition of AP-1 complex during apoptosis varies due to alterations in the levels of c-Jun, JunB proteins and participation of these proteins together with JunD in the AP-1 DNA binding activity. In addition we demostrated an activation of JNK signaling pathway associated with accumulation of phosphorylated c-Jun and ATF-2 proteins in apoptotic cells (Pyrzynska et al. 2000).

In order to determine the transactivating potential of AP-1 complexes, cells were transfected with the reporter genes under control of AP-1 containing promoters. We demonstrated that AP-1 complexes accumulated during apoptosis have different transactivating potential towards different promoters: they downregulate collagenase AP-1/TRE-dependent transcription but transactivate Fas ligand promoter. The transactivation of FasL promoter was dependent on the intact AP-1 site since mutation of the AP-1 site partially abolished this effect (Pyrzynska et al. 2000). The AP-1 ability to transactivate FasL promoter corresponded to upregulation of *fasL* mRNA level (unpublished). Upregulation of FasL expression can be considered as one pathway of transcription-dependent apoptosis in the brain.

THE ROLE OF C-JUN AND JNK SIGNALING PATHWAY IN NEURONAL APOPTOSIS

Elevated c-Jun expression and JNK activation have been shown to be tightly associated with the induction of neuronal apoptosis (Pombo et al. 1994, Xia et al. 1995, Eilers et al. 1998, Watson et al. 1998). Moreover, the recent findings suggest a direct link between the stimulation of JNK signaling and the activation of death-inducing systems. Colocalization and temporal

correlation of phospho-c-Jun and Fas ligand expression in the brain after kainate seizures and ischemia (Herdegen et al. 1998, Martin-Villalba et al. 1999) suggests that the phosphorylated c-Jun protein is a likely mediator of FasL induction in neuronal apoptosis. This possibility is supported by recent studies by Le-Nicolescu et al. (1999) showing the strong correlation between c-Jun N-terminal phosphorylation, Fas/FasL expression, and the onset of apoptosis in the three experimental systems of neuronal apoptosis. Furthermore the expression of a nonphosphorylable c-Jun mutant, c-Jun (A63/73), protects PC12 cells from apoptosis caused by activation of MAP kinase cascade (Le-Nicolescu et al.1999).

A growing evidence of the involvement and blameworthy role of c-Jun protein in apoptotic cell death can suggest that c-Jun is a critical component and its interaction with AP-1 DNA-binding partners may control the AP-1-dependent transcriptional activation. A key role of c-Jun may result from the fact that c-Jun can recruit JNK to phosphorylate its binding partner (Kallunki et al. 1996). JNKs phosphorylate c-Jun more efficiently than JunD and they do not phosphorylate JunB. Although JunB can bind JNK, is not phosphorylated due to the lack of phosphoacceptor site. JunD, in contrast, lacks a JNK docking site but is phosphorylated by JNK through interactions with docking competent partner such as: c-Jun, JunB or ATF-2 (Gupta et al. 1995).

Recently we performed a series of experiments that provides direct evidence that composition of the AP-1 complex modulates its transactivating potential. In transfection experiments we employed genetic constructs carrying on different AP-1 dimers. These constructs were developed and functionally tested in laboratory of Dr. M. Yaniv. Our preliminary data suggest that constructs encoding for c-Jun/ATF-2 dimer have a strong ability to transactivate human FasL promoter while constructs coding for JunB/JunD dimers do not transactivate FasL promoter. Results of more detailed studies of AP-1 transactivating potential towards collagenase AP-1/TRE driven promoter are demonstrated in Fig. 1. We tested constructs coding for dimers consisting of c-Jun and particular dimerization partner.

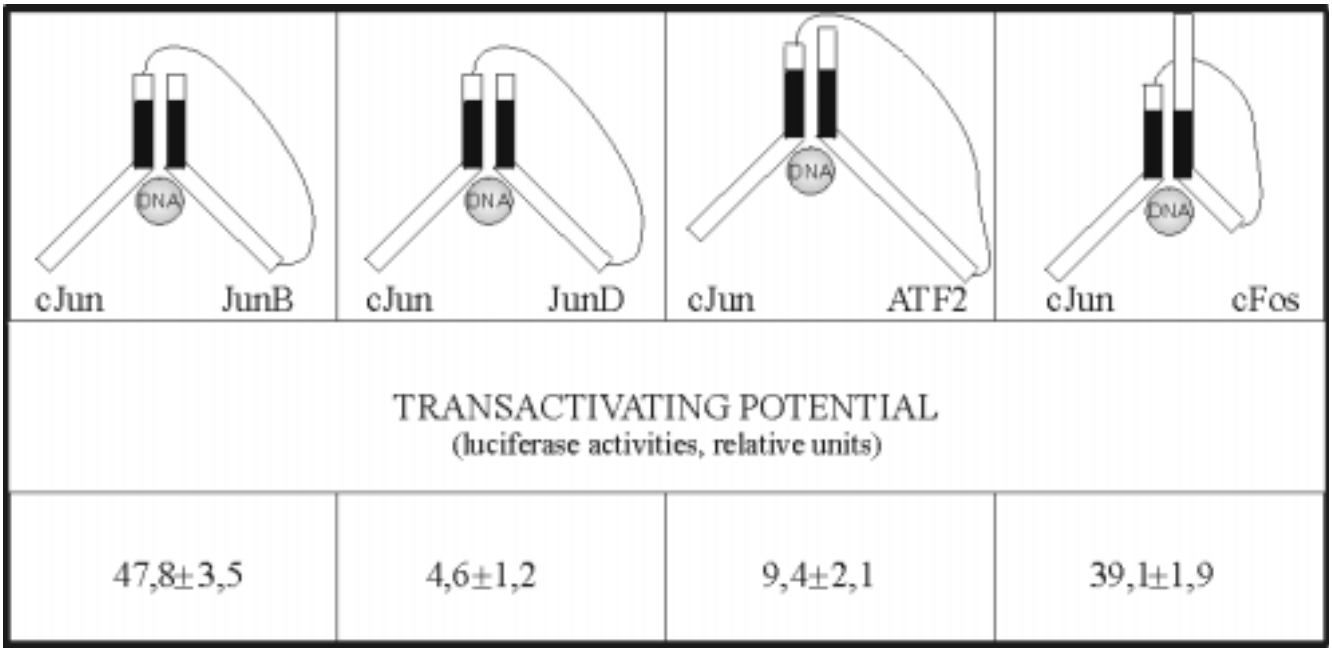

Fig. 1. Composition of AP-1 complex determines AP-1 transactivating potential. Glioma cells were transfected with reporter constructs (in which Firefly luciferase gene expression was controlled by the collagenase gene TRE/AP-1 sequence) and vectors encoding for specific AP-1 dimers. One day after transfection, cells were harvested by scraping cells in lysis buffer. The activities of Firefly luciferase in cell extracts were evaluated according to standard protocol for dual-luciferase reporter assay system (Promega) using a luminometer (Monolight 2010, Analytical Luminescence Laboratory, San Diego, CA). The results were given as average relative Firefly luciferase activity normalized to luciferase activity in cells cotransfected with BSK vector (empty vector lacking AP-1 dimer). The data represent means ± SEM from 3 independent experiments.

These data clearly indicate that the identity of c-Jun partner in AP-1 heterodimer determines ability of entire complex to transactivate AP-1 dependent transcription.

CONCLUDING REMARKS

As discussed above the available data reveal a "double face" of AP-1 transcription factor in the regulation of gene expression. Findings demonstrating that a diverse transcriptional activity is associated with particular combination of AP-1 transcription factor, enlarges on our understanding how apparently similar AP-1 complexes can play contradictory roles in cell growth, activation and apoptosis. The functional differences between the AP-1 complexes may explain how activation of different AP-1 components and signaling pathways can affect cell survival and lead to apoptosis. c-Jun appears to be a critical component of AP-1 because the identity of c-Jun partner in AP-1 heterodimer determines ability of entire complex to transactivate AP-1 dependent transcription. The crucial role of c-Jun in the formation and function of Jun/Jun dimers stems from the fact that c-Jun can recruit JNK to phosphorylate its binding partner. An activation of specific signaling pathways and cross-talk between them provide final inputs for specific changes of AP-1 composition and/or phosphorylation status that results in specific and discrete genomic responses.

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