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Signalling networks in focus

Jun signalling in the epidermis: From developmental defects to psoriasis and skin tumors

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Abstract

The Jun proteins Jun, JunB and JunD are core members of activator protein-1 (AP-1), a dimeric transcription factor complex consisting of homo- and heterodimers of the Jun, Fos, activating transcription factor (ATF) and musculoaponeurotic fibrosarcoma (Maf) families. Growth factors, hormones and a variety of environmental stresses activate mitogen activated protein kinase (MAPK) cascades that enhance Jun/AP-1 activity, e.g. through phosphorylation thereby regulating cell proliferation, differentiation, transformation and/or apoptosis. Embryonic lethality of various AP-1 knock-outs, e.g. for Jun, JunB, Fra-1 and Fra-2 largely prevented functional studies in vivo. Therefore, conditional knock-out strategies, in particular for the epidermis, have become an important model to study the regulation and function of AP-1 subunits in physiological and pathological processes in vivo. Jun is regarded as a positive regulator of keratinocyte proliferation/differentiation during development and in skin cancer through its direct transcriptional effect on epidermal growth factor receptor (EGFR) expression. In contrast, JunB can antagonize proliferation of keratinocytes and hematopoietic stem cells. Furthermore, it has been demonstrated in patient's samples and an inducible mouse model that downregulation of JunB/AP-1 in keratinocytes is one initiating event in the aetiology of psoriasis which is characterized by increased cell proliferation and deregulated cytokine expression.

Keywords: Jun; AP-1; Skin; Epidermis; Keratinocyte; Conditional; Inducible; Knock-out; EOB; Papilloma; Cancer; EGFR; Psoriasis; S100a8; S100a9; T cell; TNF signalling

Signalling network facts

- Jun, Fos, ATF and Maf proteins form the core family of the dimeric AP-1 transcription factor.
- AP-1 can be regulated by dimer composition, transcription, post-translational modification and interaction with other proteins.

Abbreviations: bZip, basic leucine zipper; EGFR, epidermal growth factor receptor; EGF, epidermal growth factor; GM-CSF, granulocyte-macrophage colony stimulating factor; G-CSF, granulocyte colony stimulating factor; HB-EGF, heparin-binding epidermal growth factor; JNKs, Jun N-terminal kinases, JNK1, JNK2 and JNK3; KGF, keratinocyte growth factor; LPS, lipopolysaccharide; RTK, receptor tyrosine kinase; Rag2, recombination activating gene 2; Ref-1, redox factor 1 (also AP endonuclease; a DNA repair enzyme); SOS, son of sevenless; TGF-α, transforming growth factor α; TCFs, ternary complex factors, a subgroup of the ETS protein family; TGF-β, transforming growth factor β; VEGF, vascular endothial growth factor

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- Different AP-1 dimers control transcriptional activation or suppression of a variety of genes involved in the regulation of proliferation, differentiation, apoptosis and transformation.
- An auto-regulatory loop from EGF/-R to Jun-dependent EGFR expression is important for keratinocyte differentiation and skin tumor development.
- MAPK/RTK (receptor tyrosine kinase) regulates Fos/AP-1 activity via ERK1,2 and Jun/AP-1 activity via JNK.

1. Introduction

Activator protein-1 (AP-1) is a dimeric transcription factor complex that comprises members of the Jun, Fos, activating transcription factor (ATF) and musculoaponeurotic fibrosarcoma (Maf) protein families (Eferl & Wagner, 2003). Fos and Jun family proteins function as dimeric transcription factors that bind to AP-1 binding sites in the promoter and enhancer regions of numerous mammalian genes (Curran & Franza, 1988). Jun proteins form both homodimers and heterodimers with Fos proteins, whereas Fos proteins require heterodimerization to bind DNA (Chinenov & Kerppola, 2001). Despite the high degree of structural homology, the different members of the Jun and Fos families exhibit significant differences in DNA-binding and transcriptional activation suggesting specific functions in gene regulation for individual AP-1 dimers (Shaulian & Karin, 2002). AP-1 acting downstream of evolutionarily conserved signalling pathways, such as MAPK, TGF-β and Wnt, is one of the key factors that translate external stimuli both into short- and long-term changes of gene expression. AP-1 activity is induced by a myriad of agents from growth factors, neurotransmitters, polypeptide hormones to bacterial and viral infections as well as by a variety of physical and chemical stresses. These stimuli activate mitogen activated protein kinase (MAPK) cascades that enhance AP-1 activity, e.g. through phosphorylation of distinct substrates (Chang & Karin, 2001).

A functional role for AP-1 components in the epidermis of the skin has been suggested for differentiation, carcinogenesis, UV-response, photo-aging and wound repair (Angel, Szabowski, & Schorpp-Kistner, 2001). Here, we will discuss recent discoveries regarding the functions of Jun proteins, in particular in skin biology. These experiments demonstrate that Jun proteins are important regulators of keratinocyte proliferation/differentiation and cytokine production, which play important roles not only in inflammatory diseases such as psoriasis but also in skin tumor formation.

2. Cascades

In a given cell, AP-1 activity is regulated by a broad range of physiological and pathological stimuli, including cytokines, growth factors, stress signals as well as oncogenic stimuli, which lead to activation of MAPK signalling. Regulation of AP-1 can be achieved at different levels by changes in transcription of genes encoding AP-1 subunits, by controlling the stability of the mRNAs, by post-translational processing, turnover and modification by phosphorylation of AP-1 proteins, and by specific interaction between AP-1 proteins and other transcription factors and cofactors (Hess, Angel, & Schorpp-Kistner, 2004). The expression of Fos is induced by ternary complex factors (TCFs), which are activated by the extracellular-signalling-regulated kinase (ERK) MAPKs. Subsequently, Fos and myocyte-enhancer factor 2 (MEF2) transcription factors induce Jun expression. Once the AP-1 complexes are present in larger amounts, JNK and p38 kinases increase the transactivation potential of Jun and ATF proteins by phosphorylation. The mechanism of post-translational control is extensively documented in the case of mitogen- and cellular-stress-induced hyperphosphorylation of Jun through the Jun N-terminal kinase (JNK) cascade (Karin, Liu, & Zandi, 1997). Activated by a MAPK cascade, JNKs translocate to the nucleus, where they phosphorylate Jun within its N-terminal transactivation domain (residues Ser63 and Ser73) and thereby enhance its transactivation potential (reviewed in (Hess et al., 2004). The JNKs also phosphorylate and potentiate the activity of JunD and ATF-2. In contrast, the kinases that regulate the activity of Fos are less well defined. Potential candidates are a poorly defined Fos-related kinase (FRK) (Deng & Karin, 1993) and ERK (Chen, Abate, & Blenis, 1993). Additional kinases such as casein kinase II, glycogen synthase kinase 3β or RSK2 can phosphorylate Fos and Jun proteins thereby regulating their transactivation potential and DNA-binding activity (Eferl & Wagner, 2003). Importantly, RSK2 is essential for efficient c-Fos dependent osteosarcoma development (David et al., 2005). DNA-binding of the Jun–Fos heterodimer is also modulated by reduction–oxidation of a single conserved cysteine residue in the DNA-binding domains of the two proteins (Abate, Patel, Rauscher, & Curran, 1990). Reduction of oxidized Jun and Fos by redox factor 1 (Ref-1) stimulates sequence-specific AP-1 DNA-binding activity (Xanthoudakis & Curran, 1996).