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Review

Signal-dependent Elk-1 target genes involved in transcript processing and cell migration

Aneta Kasza *

Department of Cell Biochemistry, Faculty of Biochemistry, Biophysics and Biotechnology, Jagiellonian University, Gronostajowa 7, 30-387 Kraków, Poland

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ABSTRACT

Elk-1 was regarded as a transcription factor engaged mainly in the regulation of cell growth, differentiation, and survival. Recent findings show the engagement of Elk-1 in the control of expression of genes encoding proteins involved in transcript turnover, such as MCPIP1/ZC3H12A and tristetraprolin (TTP/ZFP36). Thus, Elk-1 plays an important role in the control of gene expression not only through the stimulation of expression of transcription factors, but also through regulation of transcript half-live. Moreover, Elk-1 is engaged in the regulation of expression of genes encoding proteins that control proteolytic activity, such as inhibitor of plasminogen activator-1 (PAI-1) and metalloproteinases-2 and -9 (MMP-2 and MMP-9). This review summarizes the biological roles of proteins with expression regulated by Elk-1, involved in transcripts turnover or in cell migration. The broad range of function of these proteins illustrates the complex role of Elk-1 in the regulation of cancer and inflammation.

1. Trancription factor Elk-1 and its activation

Elk-1 belongs to the ternary complex factor (TCF) subfamily, part of a large family of ETS-domain transcription factors. TCFs are named for their ability to form ternary complexes on target DNA sequences termed serum response elements (SREs). TCFs bind to these motifs along with a second transcription factor, serum response factor (SRF) [1]. Besides Elk-1 the TCF subfamily includes SAP-1 and SAP-2/Net. Each TCF contains three conserved domains: the N-terminal Ets domain, which binds DNA, B-box region engaged in the interaction with SRF, and C-terminal transcriptional activation domain containing multiple sites for MAPK phosphorylation. Elk-1 also has a repression domain, which can be modified by SUMO. Such modification of Elk-1 is required for its repression of transcriptional activity via SUMO-dependent recruitment of histone deacetylases. Activation of the ERK pathway causes de-SUMOylation and phosphorylation of Elk-1, which permits Elk-1 to go from a transcriptionally repressive to a transcriptionally active form [2]. All of the ETS-domain transcription factors bind to DNA sequences containing a central GGAA/T motif. The residues flanking this core sequence determine whether a specific ETS-domain protein will be able to bind [3]. However, functional redundancy of ETS-domain protein binding, where alternative factors from this family might substitute each other in target gene regulation, has been described [4,5]. Mice deficient for Elk-1 develop normally and are phenotypically indistinguishable from wild-type mice. Also, histological analysis of various tissues does not reveal any differences between Elk-1 mutants and wild-type mice. Thus compensatory activities of other TCFs substitute the lack of Elk-1 [6]. Recent studies reveal that many Elk-1 target genes are SRF-independent [4].

The main pathway leading to Elk-1 activation requires the stimulation of cells by mitogen or growth factors, including EGF. EGF binds to its receptor, EGFR/HER1/c-erbB-1, which belongs to the family of c-erbB receptors. Binding of ligands to c-erbB receptors results in their dimerization and leads to activation of the intrinsic kinase domain and phosphorylation of specific tyrosine residues within the cytoplasmic tail. The pathway responsible for the activation of Elk-1 is triggered by relocation of the Grb2/Sos complex from the cytoplasm to the cell membrane where Grb2 is recruited to phosphorylated residues of EGFR. Translocation of the Grb2/Sos complex facilitates the interaction of membrane-associated Ras with Sos. This results in Ras activation via exchange of Ras-bound GDP for GTP. Activated Ras activates Raf-1 (MAP3K), which phosphorylates MEK1/2 (MAP2Ks), which in turn phosphorylate extracellular signal-regulated kinases 1 and 2 (ERK1/2, (MAPKs)). ERK1/2 catalyzes the phosphorylation of several transcription factors, including Elk-1 [7,8].

EGFR activation can also activate PLCγ. This results in the activation of protein kinase C (PKC) and subsequent activation of ERK1/2. Binding of bradykinin to its cell surface G protein coupled receptor B2 can also result in PKC-ERK1/2-Elk-1 activation [9].

* Tel.: +48 12 664 6521; fax: +48 12 664 6902.
E-mail address: aneta.kasza@uj.edu.pl.

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However, Elk-1 can be also phosphorylated after IL-1 stimulation. Binding of IL-1 to IL-1 receptor (IL-1RI) results in its dimerization with IL-1 receptor accessory protein (IL-1RAcP). Signaling from IL-1RI/IL-1RAcP is initiated by the recruitment of MyD88 to the TIR domain of IL-1RI/IL-1RAcP. This is followed by phosphorylation of IL-1R-associated kinases (IRAKs), activation of TRAF6, activation of a complex containing the kinase TAK1 and TAK1-binding proteins (TAB1, TAB2, and TAB3), and activation of an IKK complex, composed of IKKα, IKKβ, and NEMO. The IKK complex phosphorylates the NFκB inhibitory protein, IκBα, which is followed by its ubiquitination and degradation. Free NFκB translocates to the nucleus and activates gene transcription [10,11]. Binding of IL-1 to IL-1 receptors can activate other than NFκB transcription factors. The kinase TAK1 activates mitogen-activated protein kinases kinases (MAP2Ks), which in turn phosphorylate c-Jun N-terminal kinase (JNK) and p38 MAPKs [12,13]. In cells stimulated by IL-1, ERK1/2 can be activated in addition to JNK and MAPKs. The NFκB pathway controls activation of ERK1/2 by tumor progression locus-2 (TPL-2). TPL-2 can phosphorylate and activate the MAP2Ks, MEK1 and MEK2, whose only known substrates are ERK1/2 [14,15]. Activation of ERK1/2, JNK, and p38 leads to the activation of many transcription factors, including Elk-1.

2. Elk-1 regulates expression of RNA-interacting proteins

The first discovered Elk-regulated genes encode proteins involved in transcriptional control. Elk-1/SRF complex controls expression of *FOS*, *EGR-1*, and *NUR77*. All of them are immediate-early (IE) genes, which means that they have rapid activation kinetics. Many IE genes encode transcription factors or signaling pathway regulators that affect the cellular gene expression profile. However, recently it has turned out that Elk-1 is also engaged in the regulation of expression of IE genes that encode proteins important in transcript turnover, namely RNase MCPIP1/ZC3H12A and tristetraprolin (TTP/ZFP36). Thus Elk-1 plays an important role in the control of gene expression not only through the activation of promoters (stimulation of expression of transcription factors) but also through regulation of transcript half-lives (stimulation of expression of RNA-interacting proteins) (Fig. 1).

2.1. MCPIP1/ZC3H12A

MCPIP1/ZC3H12A is a key regulator of inflammation. The activity of MCPIP1/ZC3H12A is regulated by pro-inflammatory cytokines (both at the transcriptional and post-transcriptional levels), and MCPIP1/ZC3H12A controls the level of IL-6, IL-1, IL12p40, and IL-2 transcripts by mediating their degradation [16–18]. MCPIP1/ZC3H12A is also involved in JNK and NFκB signaling by removing ubiquitin moieties from TRAF2, TRAF3, and TRAF6 [19]. MCPIP1/ZC3H12A is encoded by the *ZC3H12A* gene. *Zc3h12a* −/− mice spontaneously develop severe autoimmune inflammatory disease and most die within 12 weeks of birth [16]. MCPIP1/ZC3H12A is upregulated in cells stimulated by the chemo-attractant protein MCP-1, and this is the reason it was named as such. Investigations into the function and regulation of MCPIP1/ZC3H12A expression began only a few years ago, meaning the number of reports concerning MCPIP1/ZC3H12A is limited. MCPIP1/ZC3H12A was initially described by the Kolattukudy group as a transcription factor [20]. MCPIP1/ZC3H12A contains a single Cys–Cys–Cys–His (CCCH) zinc-binding domain that is typical of RNA- and ssDNA-binding proteins and a PIN domain that is characteristic of proteins with RNase activity. The presence of these structures indicates that MCPIP1/ZC3H12A may be involved in the turnover of transcripts. In 2009, two groups separately published that MCPIP1/ZC3H12A is a novel RNase that participates in the turnover of IL-6, IL12p40, IL-1β, and its own mRNAs [16,17]. The RNase properties of MCPIP1/ZC3H12A are also important for the antiviral role of this protein. MCPIP1/ZC3H12A degrades viral RNA and thus acts as a host innate defense (Fig. 2) [21]. Expression of MCPIP1/ZC3H12A is regulated by IL-1β, LPS, PMA, and TNF, although the molecular mechanisms underlying this regulation are not fully understood [17].

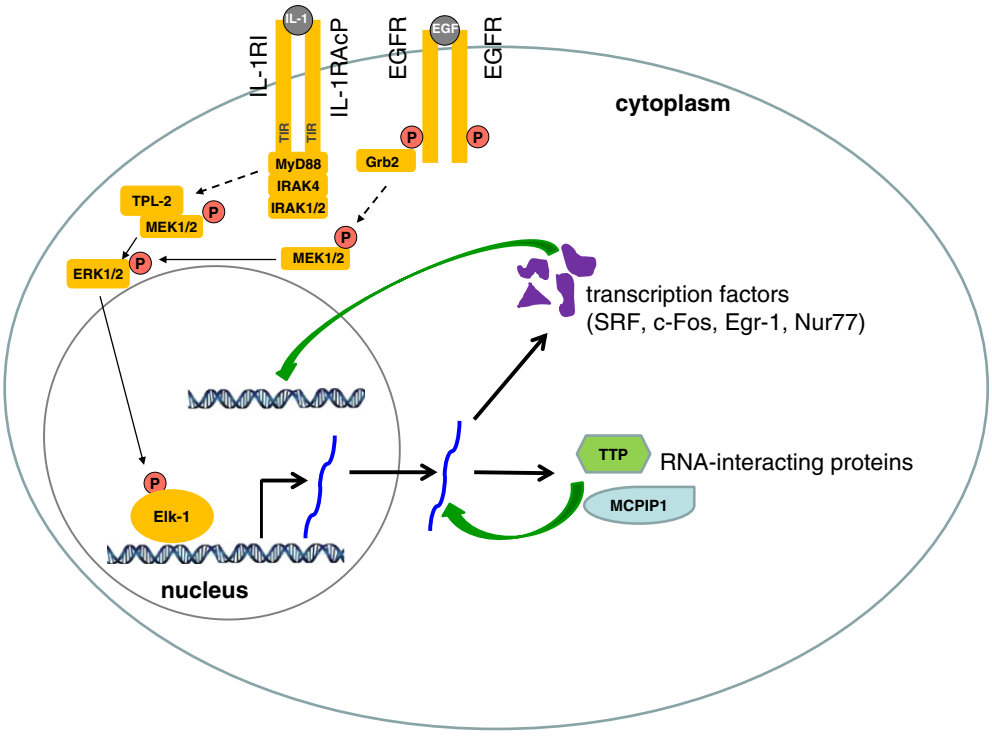

Fig. 1. Simplified scheme of the biological role of Elk-1-regulated genes following IL-1 or EGF stimulation. Activation of IL-1 receptor (IL-1RI/IL-1RAcP) or EGF receptor (EGFR) results in activation of ERK1/2 followed by phosphorylation of Elk-1. Elk-1 stimulates expression of genes encoding transcription factors such as SRF, c-Fos, Egr-1, and Nur77, and genes encoding RNA-interacting proteins such as TTP/ZFP36 and MCPIP1/ZC3H12A.