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Review

Regulation of the transcriptional activity of nuclear receptors by the MEK/ERK1/2 pathway

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ABSTRACT

Cells undergo continuous and simultaneous external influences regulating their behavior. As an example, during differentiation, they go through different stages of maturation and gene expression is regulated by several simultaneous signaling pathways. We often tend at separating the nuclear pathways from the signaling ones initiated at membrane receptors. However, it is essential to keep in mind that all these pathways are interconnected to achieve a fine regulation of cell functions. The regulation of transcription by nuclear receptors has been thoroughly studied, but it now appears that a critical level of this regulation involves the action of several kinases that target the nuclear receptors themselves as well as their partners. The purpose of this review is to highlight the importance of one family of the mitogen-activated protein kinase (MAPK) superfamily, the MEK/ERK1/2 pathway, in the transcriptional activity of nuclear receptors.

Contents

1. Introduction

During their life, cells undergo continuous and simultaneous external influences. As an example, during differentiation, they go through different stages of maturation and gene expression is regulated by several simultaneous signaling pathways. However, the impact of an

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intracellular signaling pathway on a cell is often analyzed without taking into consideration the other pathways that occur simultaneously. The regulation of transcription by nuclear receptors has been thoroughly studied, but it now appears that a critical level of this regulation involves the action of several kinases that target the nuclear receptors themselves as well as their partners. The purpose of this review is to highlight the importance of one family of the mitogen-activated protein kinase (MAPK) superfamily, the MEK/ERK1/2 pathway, in the transcriptional activity of nuclear receptors.

2. Mitogen-activated protein kinases (MAPKs): the ERK1/2 pathway

Mitogen-activated protein kinases (MAPKs) are key players in the transduction of extracellular signals from activated receptors located in the plasma membrane, to various cellular compartments notably the nucleus. MAPKs are serine/threonine kinases, which regulate positively or negatively the activity of their substrates, thus leading to different cellular responses. Accordingly, they direct the execution of appropriate genetic programs, including activation of gene transcription, protein synthesis, cell cycle machinery, cell death, differentiation and even the immune response [1–8].

2.1. MAPK description

MAPKs operate in modules composed of three protein kinases that phosphorylate and activate each other sequentially: a MAP kinase kinase kinase (MAPKKK or MEKK or MAPK3) that activates a MAP kinase kinase (MAPKK or MEK or MAPK2), which in turn activates a MAPK. MAPKKKs and MAPKKs are threonine/tyrosine kinases, which activate their substrates by dual phosphorylation of conserved threonine and tyrosine residues separated by an amino acid (Thr-X-Tyr) [9,10].

In mammals, at least 14 MAPKKKs, 7 MAPKKs and 12 MAPKs have been identified. MAPKs are highly conserved along evolution and, to date, mammalian MAPKs can be classified in separate groups according to their sequence homology and the configuration of the Thr-X-Tyr peptide. The three main and most studied groups are: (i) extracellular signal-regulated protein kinases with ERK1 and ERK2; (ii) c-JUN N-terminal kinases with JNK1, JNK2 and JNK3; and (iii) p38MAPKs with p38 α–β–γ and δ [11–15]. More recently, three other groups with poorly known characteristics have been described: (iv) ERK3 with ERK3, p97 MAPK and ERK4 [16,17]; (v) ERK5 described as BMK1 (big mitogen-activated protein kinase) [18,19]; and (vi) ERK7 with ERK7 and ERK8 [20,21].

MAPKs have been extensively studied from a structural point of view and the ERK1/2, p38 and JNK group members have all been crystallized with or without their substrates, scaffolding co-proteins or inhibitors [22]. MAPKs are composed of two domains: an N-terminal domain and a C-terminal domain, each containing several residues involved in their catalytic activity [23]. The junction of these two domains constitutes the catalytic site, which is activated by the binding of ATP and two magnesium ions. MAPKs bind both their regulatory proteins and their targets, upstream and downstream of the signaling cascade, respectively, via specific recognition motifs located outside of the catalytic domain [24–27].

The ERK1 ($p44^{MAPK}$) and ERK2 ($p42^{MPAK}$) proteins are the central components and are typically designated under the name ERK1/2. Indeed, with 84% of sequence homology [28], they share many features. However there is compelling evidence that they are not redundant and that they have very different roles as the knockout phenotypes are very different: the ERK2 null mice die early in development, at E8.5 [29,30] while the ERK1 null mice are viable with only minor defects [31,32].

2.2. Regulation of the ERK1/2 pathway

MAPKs are activated by several signals including mainly growth factors that bind to membrane receptor tyrosine kinases (RTKs) (Fig. 1) and cytokines that bind to receptors linked to tyrosine kinases of the JAK family (Janus kinases). MAPKs are also activated through the upregulation of the Src family Fyn tyrosine kinase by integrin engagement or through activation of G protein coupled chemokine receptors (GPCRs) [33].

Once activated, ERK1/2 proteins can phosphorylate more than one hundred different substrates, and thus can generate a variety of different biological responses [34]. ERK1/2 proteins are kinases that generally phosphorylate serine/threonine residues followed by a proline (S/T–P). Phosphorylation by ERKs requires the docking of the kinase to very well-defined domains of the substrate: the D domain (also called DJEL motif) and the DEF domain (or FxFP motif) [24,35]. The D domain contains the Arg/Lys-x-x-Arg/Lys-x_{1-6}-Leu-x-Leu sequence [36], which can be found not only in ERK1/2 substrates, but also in the upstream kinases such as MEK1/2. The DEF domain contains a S/T–P phosphorylation site located near a Phe-x-Phe-Pro (FxFP) sequence, and is found in substrates such as the c-FOS transcription factor, the DUSP1 phosphatase (MKP-1) and the nuclear receptor TRβ [37]. Finally, some substrates such as ELK-1 contain both the D and DEF domains [38].

Remarkably, in a given cell, the biological response to the activation of the ERK pathway depends not only on the availability of the substrates but also on "context-specific" and "cell-specific" parameters. Indeed the ERK signaling pathway can be controlled by scaffold proteins, which form complexes with ERK1/2 and its upstream activators or its substrates, bringing them closer to facilitate their functional interactions [39]. As an example the PEA-15 protein interacts with ERK on one side and with RSK2 on the other, thus forming a three-element complex, which contributes to improve the ERK-dependent phosphorylation and kinase activity of RSK2 [40]. However in other contexts, scaffold proteins may also have negative effects. Indeed PEA-15, which contains a nuclear export domain, can sequestrate ERK1/2 in the cytoplasm resulting in a limitation of its function [41].

Finally, once activated, the ERK pathway has to be negatively controlled by feedback mechanisms targeting ERKs themselves or their upstream activators. Indeed ERK1/2 is inhibited through dephosphorylation by MAPK phosphatases (MKPs or DUSPS for dual specificity phosphatases on tyrosine and threonine residues) (Fig. 1), the expression of which is controlled by ERK1/2 or their substrates. The ERK1/2 pathway can be also inhibited subsequent to the phosphorylation and inhibition of SOS (one of the upstream proteins involved in the activation of the RAS–MAPK pathway) by RSK2, an ERK substrate (Fig. 1).

3. Nuclear receptors

Hormones constitute an elaborated communication system, which allows cells to be continuously informed about their environment and to adapt their functioning. Target cells recognize the presence of a hormone through specific receptors. There are two main response systems to hormones: (i) trans-membrane receptors, which recognize peptide hormones that cannot diffuse through cell membranes and (ii) nuclear receptors (NRs), which recognize lipid-soluble hormones that can diffuse through cell membranes.

NRs bind small hydrophobic and lipid-soluble molecules such as steroids, thyroid hormones, vitamin D3, retinoids, fatty acids or xenobiotics. They constitute a superfamily of ligand-dependent transcription regulators (encoded by 49 genes in the human genome) that function through gene regulation [42]. In the absence of hormone, NRs are inactive or repress target gene expression. However, once activated by the binding of their cognate ligand, NRs function as transcription regulators bound on very specific DNA sequences called "response elements" located in the promoters of their target genes. Therefore, due to their ability to control gene expression, NRs play essential roles in many processes such as embryonic development, cell differentiation, metabolism or cell death [43–45]. Consequently, a deregulation of the NR signaling system leads to proliferation, and