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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

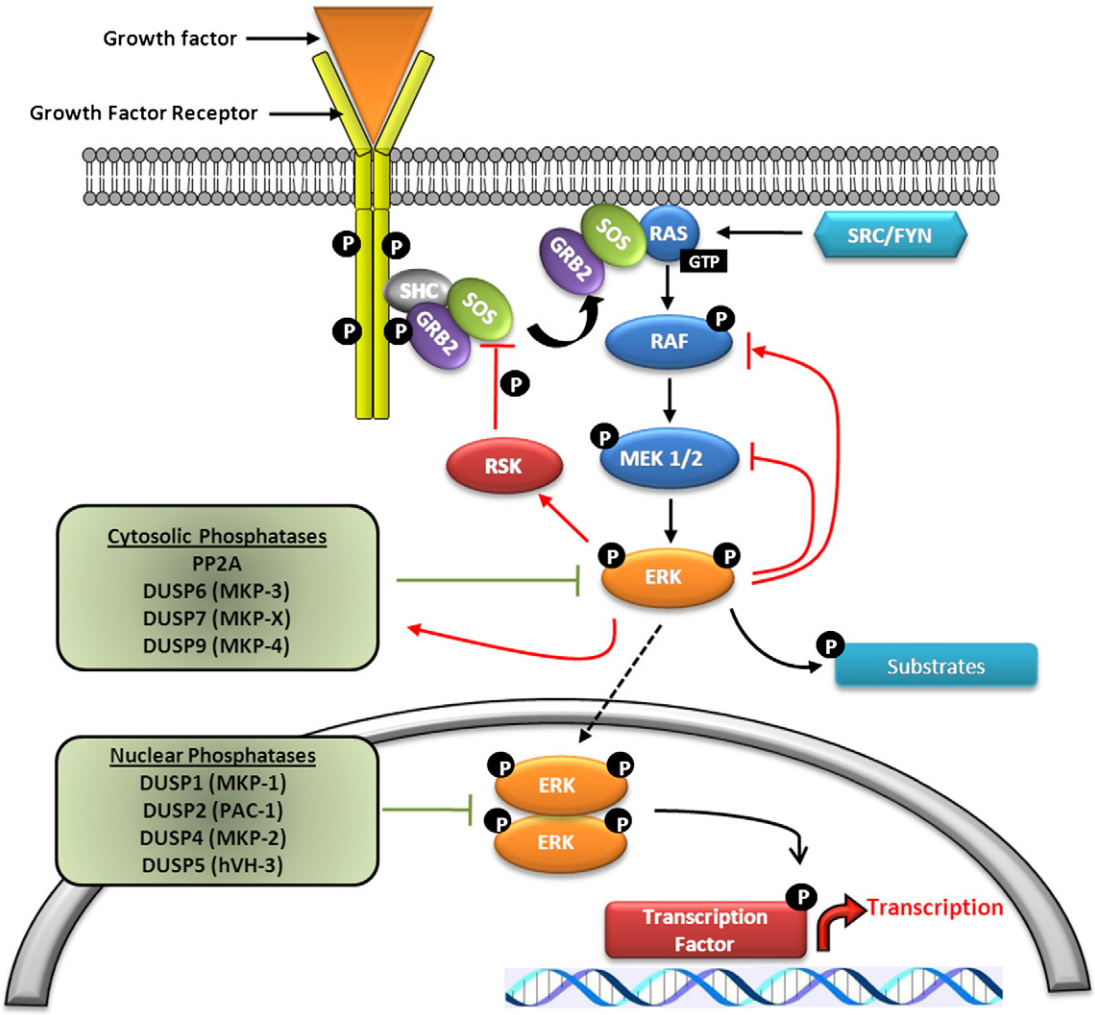


Fig. 1. Intracellular signaling through the ERK1/2 MAPKinase pathway (example of a growth factor receptor). The SHC/GRB2/SOS complex is recruited by the phosphorylated tyrosines of the intracellular domain of the receptor. Then SOS activates RAS and RAS/GTP recruits RAF which initiates the MAPKinase cascade leading to the phosphorylation of ERK1/2 by MEK1/2. Several negative controls are activated which are indicated in red lines. DUSP: dual specificity protein phosphatase; GRB2: growth factor receptor-bound protein 2; MKP: MAPK phosphatase; SHC: SRC homology 2 domain containing transforming protein 1; SOS: son of sevenless.

reproductive or metabolic disorders, and causes diseases such as cancer, infertility, obesity or diabetes.

3.1. Nuclear receptor classification

Since the late 1980s, it is known that nuclear receptors are a large family of molecules with similar structures and are capable of recognizing a wide range of ligands (or hormones). Thus, this "superfamily", which currently has 49 identified members, can be divided into four groups based on similarities of their ligands [46].

Group 1 includes steroid receptors such as the estrogen (ER), androgen (AR), mineralocorticoid (MR), glucocorticoid (GR) and progesterone (PR) receptors. These nuclear receptors are found only in vertebrates and act as homodimers. Group 2 is formed by the receptors that heterodimerize with the retinoic X receptor (RXR), including thyroid hormone (TR), vitamin D3 (VDR), retinoic acid (RAR), peroxisome proliferator-activated factor (PPAR), oxysterol (LXR) and farnesoid (FXR) receptors. Group 3 corresponds to the xenobiotic receptors (PXR and CAR). Finally, Group 4 brings together the so-called orphan receptors, for which ligands remain still unknown or may not exist (HNF4 (human nuclear factor 4) and COUP-TF (chicken ovalbumin upstream promoter-transcription factor)), or for which ligands have been recently identified such as ERR (estrogen receptor related) and ROR (RAR related orphan receptor).

3.2. Nuclear receptor structure

NRs exhibit a modular structure composed of 6 regions of homology (designated A to F, from the N-terminal to the C-terminal end) encompassing three main functional domains [42,47] (Fig. 2).

The DNA binding domain (DBD), which corresponds to region C, is the most conserved domain among all NRs. It is composed of approximately 70 amino acids and is well structured with two "zinc finger" motifs [48].

The ligand-binding domain (LBD), which corresponds to region E, is also conserved in most NRs. It is well structured with 12 alpha helices. This domain is functionally complex as it contains the ligand-binding pocket (LBP), the main dimerization domain and the ligand-dependent activation function-2 (AF-2) [49–51]. Ligand binding causes a conformational change of the AF-2, creating a new surface for the recruitment of co-activators or co-repressors, which serve as adaptors recruiting large complexes with different enzymatic activities such as histone acetyltransferases, histone deacetylases or histone methyl transferases. These complexes alter the chromatin structure surrounding the promoter of target genes and thus regulate their transcription [52] (Fig. 3).

The N-terminal domain (NTD) encompassing A and B regions contains the AF-1 domain, a ligand-independent transactivation domain. It is not conserved between NRs and is naturally unstructured [53].

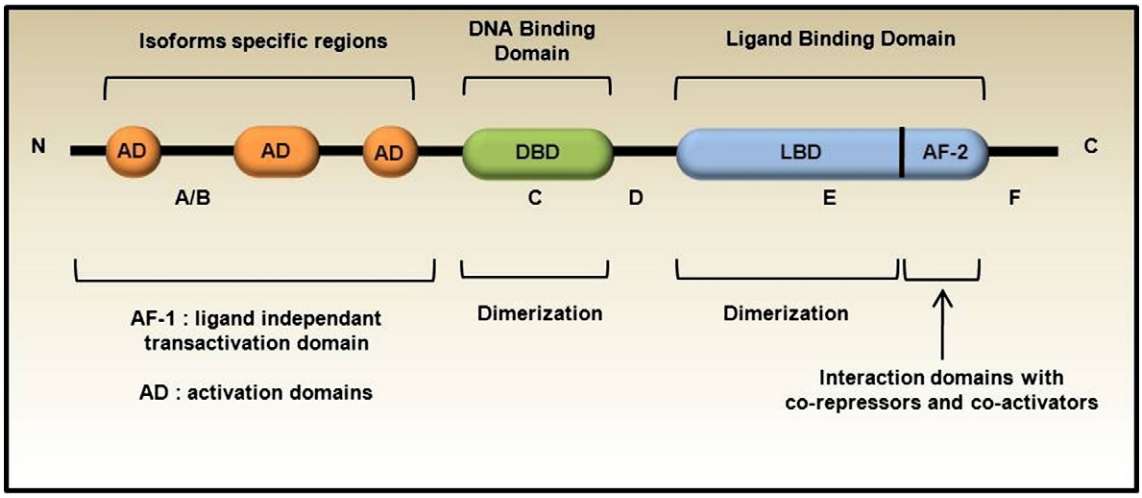


Fig. 2. Structural and functional organization of nuclear receptors. Evolutionary conserved regions C and E are represented in green and blue respectively. Variable regions A/B, D and F are indicated on the black line. Specific functions of the regions are indicated on the figure.

However, it contains several phosphorylation sites and interacts with co-regulators or proteins of the transcriptional machinery such as the RNA polymerase II (RNA Pol II), or TBP (TATA-binding protein) [54].

The D region is a hinge region between the DBD and the LBD and thus maintains the integrity of the NR structural configurations. It also intervenes in the nuclear localization of NRs [55].

The F region is not present in all NRs and its function is still ill-defined.

3.3. Classical model of the transcriptional activity of NRs

NRs bind specific DNA responsive elements (REs) located in the regulatory regions of target genes as monomers, homodimers or heterodimers with RXR [45,56]. REs are specific nucleotide sequences formed of two half-sites that are separated by variable spacing and can occur in different orientations. Half-sites have the consensus sequence AGGTCA, but considerable variation is tolerated. Combinations include the direct repeat (DR) AGGTCAn_xAGGTCA, the inverted repeat (IR) AGGTCAn_xTGACCT, and the everted repeat (ER) TGACCTn_x-AGGTCA, where the number of spacer nucleotides n_x can vary from zero to eight nucleotides.

Steroid hormone receptors bind their response elements as homodimers, whereas RAR, TR, PPAR and VDR bind REs as heterodimers with RXRs [48]. Heterodimerization increases the efficiency of DNA binding. It also increases the regulation possibilities of NRs via the creation of new sets of response elements and the addition of the signaling scheme of the RXR ligand.

Once attached at their response elements located in the promoter regions of their target genes, NRs recruit regulatory proteins associated to large complexes with enzymatic activities, which target chromatin through various epigenetic modifications such as histone acetylation/deacetylation. In the absence of ligand, NRs recruit complexes which compact chromatin and thus repress transcription. In contrast, liganded NRs bind other complexes, which remodel and decompact chromatin, paving the way for the recruitment of the transcription machinery [52] (Fig. 3).

Of note is that the transcriptional activity of a nuclear receptor can be "co-modulated" by another NR or by other transcription factors. For example, the simultaneous activation of the glucocorticoid receptor α (GRα) and the peroxisome proliferator-activated receptor α (PPARα), which are both involved in the immune response, cooperate for trans-repression of NF-κB driven genes, which play a key role in the proinflammatory response [57]. Moreover the transcriptional activity of the estrogen receptor was found recently to be dependent on FoxA1, also called HNF3a [58].

4. Novel regulation mechanisms of NRS via kinase signaling

To address their multiple and tissue-specific functions, especially during development, NRs integrate not only their specific ligand and the recruitment of batteries of coregulators but also several other processes including non genomic effects and post-translational modifications. Currently, these new aspects are the subject of an increasing number of studies.

4.1. NRs have non genomic effects

Recent studies highlighted that in response to their cognate ligand, NRs activate signaling pathways such as the MAPK pathway, independently of DNA binding and transcriptional effects, thus resulting in "non-genomic effects" [59]. These non-genomic effects involve the rapid and transient activation of several kinase cascades mediated by a subpopulation of NRs anchored at the cytoplasmic side of the cell membrane. Indeed, most of the classical steroid receptors (ER, PR, GR, AR) as well as non steroid receptors (RAR, VDR) have been found in specialized plasma membrane structures such as caveolae and lipid rafts [59–63] where they are part of membrane complexes containing several proteins involved in signal transduction. In response to the hormone, the membrane pool of NRs interacts with c-Src or G proteins [59,63–66], which then rapidly activate the MAPK pathways (Fig. 4). For nearly one third of NRs, the different steps downstream of the src and G proteins and involved in the activation cascade of ERKs have been described.

4.2. NR phosphorylation by ERKs

The main consequence of the non genomic effects of NRs, i.e., the activation of the MAPK pathway, is the phosphorylation by the activated kinases of several targets, including NRs themselves, their coregulators and histones (Fig. 4). Indeed, subsequent to the activation of the MAPK pathway by their cognate hormone, nuclear receptors have been shown to be rapidly phosphorylated by ERKs (this is the subject of this review) or by the p38MAPK/MSK1 pathway, which has been the subject of recent literature [59,67]. Note however, that NRs exemplified by PPARs can be also phosphorylated by ERKs in the absence of hormone, in response to other physiologic signals such as insulin signaling [68]. Moreover, several steroid NRs can be hyperphosphorylated by ERKs in several cancers characterized by aberrant MAPK signaling (see below, Section 5).

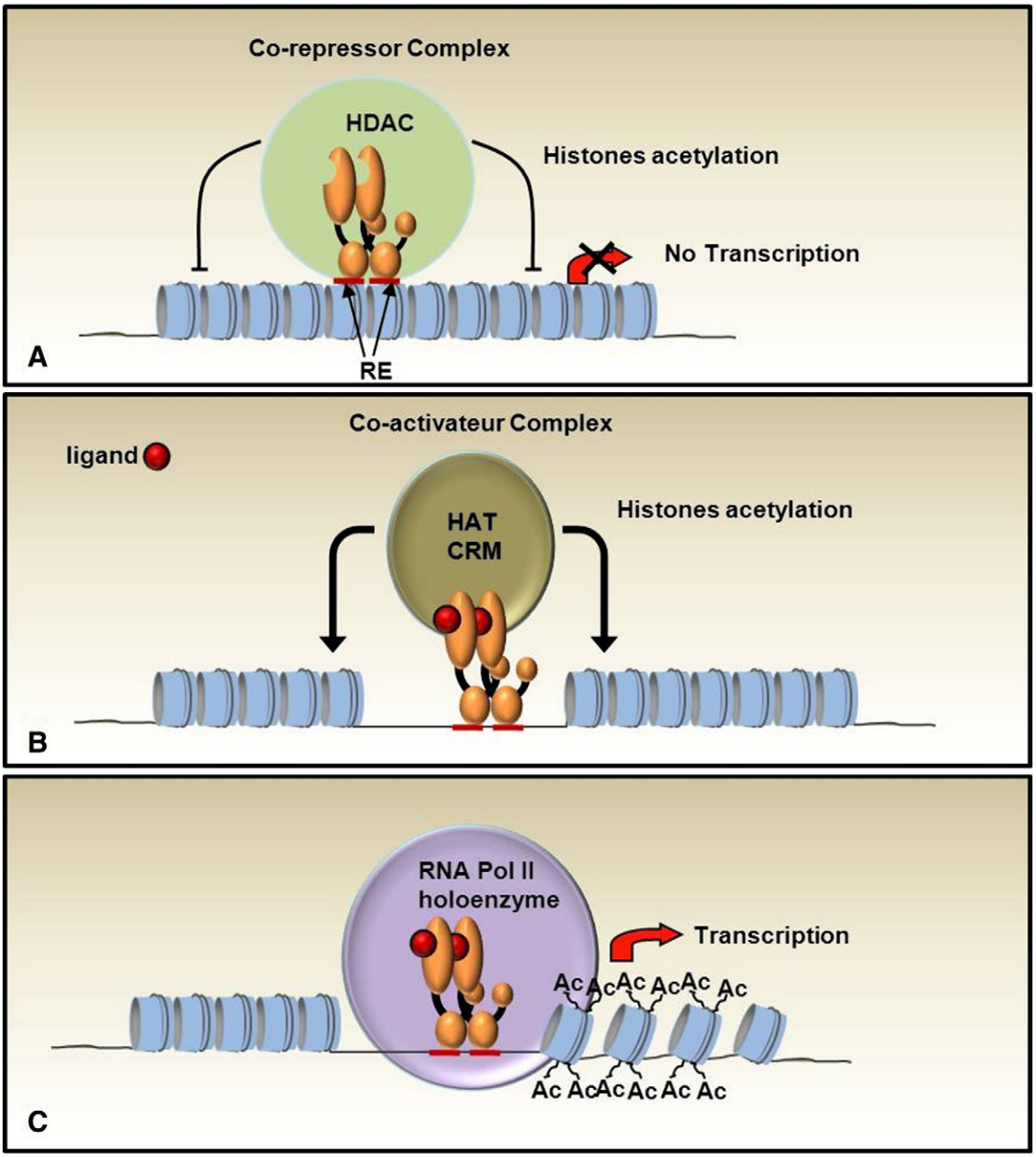


Fig. 3. Mechanism of nuclear receptor activity. (A) Nuclear receptors (NR), when located on their DNA response elements (RE) in the promoter regions of target genes are usually associated with co-repressor complexes with histone deacetylase activity (HDAC). (B) After the ligand interacts with its NR the co-repressor complex is replaced by a co-activator complex with histone acetyltransferase activity (HAT) which allows chromatin decompaction by the chromatin remodeling complex (CRM). (C) The transcription machinery is then recruited on the promoter to start the gene transcription.

The NR amino acid residues that are phosphorylated by ERKs have been characterized. In general, it concerns serine or threonine residues, which are surrounded by prolines and located in exposed and naturally unstructured domains [69]. Accordingly, most NRs are phosphorylated by ERKs at serine or threonine residues located in the NTD (Table 1) [70]. This is the case for steroid receptors including AR [71], ERα [72–74], ERβ [75] and PR [76], as well as PPARs [77–80], and RARs [81]. However residues located in flexible loops of the LBD (such as the omega loop) have been also shown to be phosphorylated by ERKs. This is the case of RXRα [82].

Note however that TRβ is phosphorylated by ERK1/2 in its DBD [37] and the orphan NRs such as RORα, LRH1 and the testicular receptor TR2 in the hinge region [83,84].

4.3. Regulation of NR transcriptional activity by MAPKs

After the ligand, the MAPK signaling pathway is the second major pathway involved in the regulation of NR transcriptional activity. For many NRs, phosphorylation by ERKs generally regulates positively their transcriptional activity [70]. Indeed, phosphorylation of the NTD of the estrogen receptors [85,86], AR [87] and PPARα [88], and of the DBD of TRβ [37] helps the dissociation of corepressors and/or the recruitment of coactivators thereby facilitating the recruitment of chromatin remodelers and modifiers and increasing the efficiency of recruitment of the transcriptional machinery. Phosphorylation of the NTD also increases the transcriptional activity of PR but through the reversal of its sumoylation, which has a repressive effect through the recruitment of HDAC-like corepressors [89].

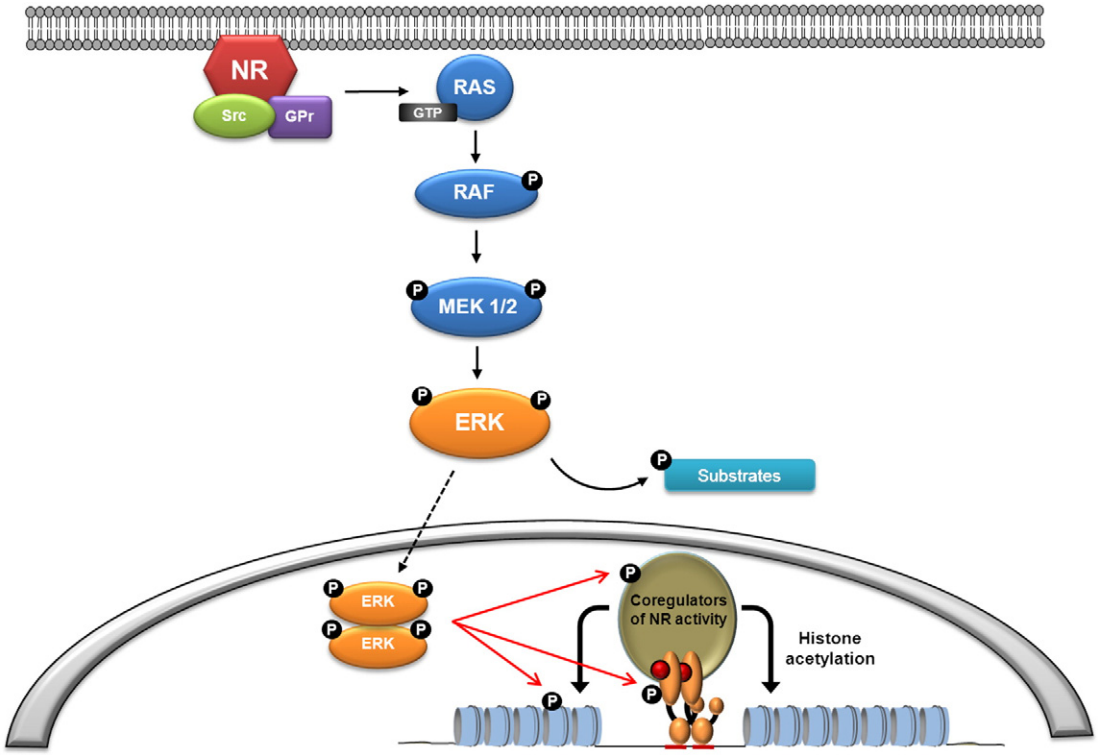


Fig. 4. Activation of the ERK1/2 pathway by non-genomic effects of nuclear receptor ligands. In response to hormones, nuclear receptors located in the plasma membrane activate intracellular signaling such as MAPKinases.

However phosphorylation by ERKs can also regulate negatively the transcriptional activity of other NRs. Indeed phosphorylation of the NTD of PPARγ has been shown to reduce ligand binding affinity through interdomain communication between the phosphorylated NTD and the ligand-binding pocket [90]. According to other studies, phosphorylation of the NTD rather promotes the degradation of PPARγ or GR by the ubiquitin–proteasome system and thus provides a mechanism to stop the response to the ligand [91,92]. It is interesting to note that PPARγ can interact directly with MEK1 (the serine/threonine kinase located immediately upstream of ERK1/2 in the cascade) [93] and that this interaction contributes to the inhibition of its activity via its export to the cytosol and its sequestration away from target genes.

Phosphorylation of the LBD also has negative effects. Indeed, phosphorylation of the RXR LBD creates conformational changes within the LBD disrupting interactions with coregulators and therefore decreasing the transcriptional activity of RXR/VDR heterodimers in response to vitamin D3 [94,95]. Finally, phosphorylation of the hinge region has been recently shown to repress the transcriptional activity of the orphan receptors RORα4 [83] and TR2 [96]. The mechanism is still ill-defined for RORα4. However, in the case of TR2, phosphorylation has been shown to promote the sumoylation and the strong interaction of the receptor with the RIP140 co-repressor.

4.4. Regulation of NRs by MAPKs via the phosphorylation of their coregulators and histones

Another manner by which the MEK/ERK1/2 pathway is capable of regulating NR function is through the phosphorylation of their coactivators and corepressors. This has been shown for the CBP/P300 factor, a critical element of the histone acetyl transferase (HAT) complexes [97–99], the RIP140 negative coregulator, the SMRT and NCoR corepressors and TRAP220 [100,101], a component of the mediator complex.

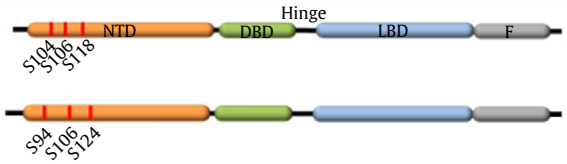
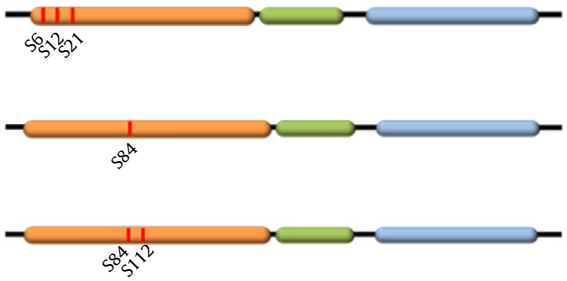
Phosphorylation of CBP/P300 enhances the NR transcriptional activity via increasing its HAT activity. Phosphorylation of TRAP22O has the same effect [101] but via the stabilization of its ability to bridge NRs and RNA polymerase II. Concerning the corepressors SMRT and NCoR, phosphorylation overcomes their repressive activity through promoting their dissociation from NRs [102,103]. Conversely, phosphorylation of RIP140 increases its repressive activity via enhancing its ability to recruit P300 and therefore to be acetylated [104].

Finally it must be noted that ERKs also phosphorylate and activate downstream kinases such as MSK1, which is well known to phosphorylate histones and to participate to the remodeling of the chromatin environment of NR-target gene promoters [59,105].

5. Deregulation of NR functions in cancer cells with aberrant ERK1/2 activity (Fig. 5)

Remarkably, the MAPK pathways are often aberrantly active in several cancers. Indeed, *RAS*, which is one element of the MAPK activation cascade (Fig. 1), is one of the most frequently mutated oncogene in cancer. Moreover the membrane receptor tyrosine kinases, which are the upstream factors of the ERK1/2 pathway are often deregulated due to mutations (*c-KIT*, *FLT3*, *EGFR*, *MET*) or overexpression (*HER2*, *MET*) [106]. The paradigms of these cancers are the breast mammary and prostate cancers characterized by the hyperexpression and/or hyperactivity of the erbB-2 receptor tyrosine kinase and the aberrant activity of the downstream kinases including ERKs [107]. Consequently, the phosphorylation of several ERK targets including NRs is increased independently of the hormone. This is exemplified by the androgen receptor, the estrogen receptors (ERα and ERβ), and the progesterone receptor, which are hyperphosphorylated at their NTD in prostate [71,108] and breast cancer cells [72,73,75,76,99,109]. Consequently, AR, PR and ERα are constitutively transcriptionally active, even in the absence of ligand, and such cancers are characterized by the failure of antiandrogenic and tamoxifen therapy. Note that in such cancers, the activation–degradation cycles of PR and ERβ are also exacerbated [110,111], adding more complexity to the intricate regulatory mechanisms involved in the control of nuclear receptor function by kinase signaling pathways.

Table 1
Nuclear receptors phosphorylated by the ERK1/2 kinases.

Category	Name	Avvreviations	Ligand	Residues phosphorylated by ERKs
Group 1: steroid receptors	Estrogen receptors	Erα Erβ	Estradiol, Estrogens	
	Glucocorticoid receptor	GR	Cortisol, glucocorticoïds	
	Progesterone receptor	PR	Progestérone, progestine	
	Androgen receptor	AR	Testostérone, androgens	
Group 2: receptors heterodimerizing with RXRs	Thyroid hormone receptor	TRα TRβ	Thyroid hormone	
	Peroxisome proliferator-actived receptor	PPARα PPARγ1 PPARγ2	Fatty acids linoleic acid	
	Retinoic acid receptors	RARα RARγ	Retinoic acid	
	Retinoid-X receptor	RXR	Retinoic acid	
Group 4 : Orphan Receptors	RAR-related orphan receptor	RORα	Unknown	
	Testicular receptor	TR2	Unknown	
	Liver receptor homologous protein 1	LRH1	Unknown	

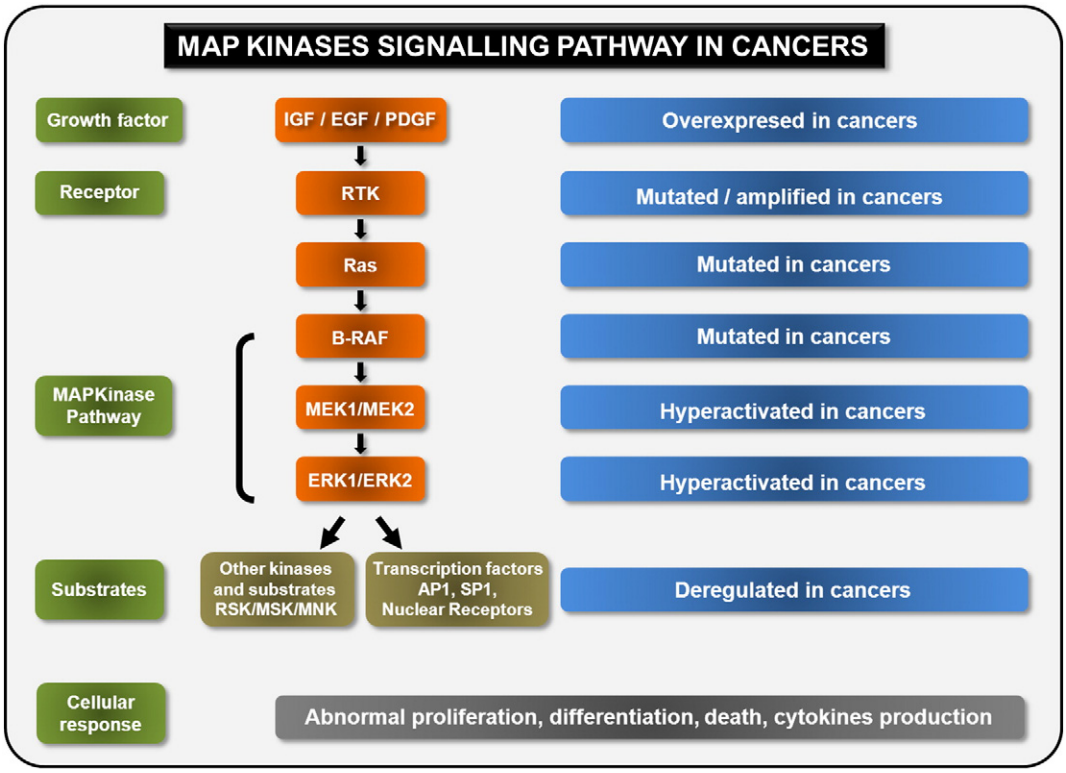


Fig. 5. Deregulation of the MAPKinase pathway in cancer cells. Many of the molecular abnormalities found in cancer cells contribute to abnormal regulation of the Ras–MAPKinase pathway.

6. Activation of the ERK1/2 pathway by cytokines restores RAR activity in retinoic acid resistant leukemic cells

RARs are well known to become rapidly phosphorylated in response to retinoic acid [67]. However, up to now, RAR phosphorylation appears to rather involve MSK1 and the cdk7/cyclin H subcomplex of the general transcription factor TFIIH. However, it has recently been shown that ERK1/2 participates in the restoration of the transactivating activity of RARα in leukemic cells that have become resistant to the action of retinoic acid. Indeed, in these cells, the activation of the MEK/ERK1/2 pathway by a cytokine such as G-CSF restored terminal differentiation to granulocytes, via reinduction of the expression of retinoic acid target genes. This phenomenon does not seem to occur through RARα phosphorylation, but rather through histone phosphorylation and CBP recruitment at the level of the promoters of retinoic acid target genes [112]. It is likely that this mechanism, as demonstrated in a model of leukemic cells, is in fact a physiological mechanism of regulation of granulopoiesis, by cooperation between the retinoic acid and G-CSF pathways.

7. Conclusion

Schematically, 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. This is particularly true for the MAPK pathway, and nuclear receptors. The role of the MEK/ERK1/2 pathway in the regulation of NR functions has been demonstrated for several members of this family and involves the phosphorylation of NRs themselves as well as that of other actors involved in NR functions, such as histones, and co-activator and co-repressor complex proteins (Fig. 4). Consequently the MEK/ERK1/2 pathway affects the nucleo-cytoplasmic localization of NRs, their degradation and their interactions with co-activators or co-repressors. In fine it influences various physiological processes, such as adipogenesis and granulopoiesis. Aberrant MAPK pathways contribute to carcinogenesis, but also to the lack of response to treatment, making them potential candidates for targeted therapies.

References

[1] R.J. Davis, Cell 103 (2000) 239–252.
[2] C. Dong, R.J. Davis, R.A. Flavell, Annual Review of Immunology 20 (2002) 55–72.
[3] M. Rincon, R.J. Davis, Immunological Reviews 228 (2009) 212–224.
[4] H.J. Schaeffer, M.J. Weber, Molecular and Cellular Biology 19 (1999) 2435–2444.
[5] T. Wada, J.M. Penninger, Oncogene 23 (2004) 2838–2849.
[6] E.F. Wagner, A.R. Nebreda, Nature Reviews. Cancer 9 (2009) 537–549.
[7] C.R. Weston, R.J. Davis, Current Opinion in Cell Biology 19 (2007) 142–149.
[8] T. Zarubin, J. Han, Cell Research 15 (2005) 11–18.
[9] M.H. Cobb, E.J. Goldsmith, Journal of Biological Chemistry 270 (1995) 14843–14846.
[10] G. Pearson, F. Robinson, T. Beers Gibson, B.E. Xu, M. Karandikar, K. Berman, M.H. Cobb, Endocrine Reviews 22 (2001) 153–183.
[11] L. Chang, M. Karin, Nature 410 (2001) 37–40.
[12] G.L. Johnson, R. Lapadat, Science 298 (2002) 1911–1912.
[13] R. Seger, E.G. Krebs, The FASEB Journal 9 (1995) 726–735.
[14] L.A. Tibbles, J.R. Woodgett, Cellular and Molecular Life Sciences 55 (1999) 1230–1254.
[15] C. Widmann, S. Gibson, M.B. Jarpe, G.L. Johnson, Physiological Reviews 79 (1999) 143–180.
[16] M. Cheng, T.G. Boulton, M.H. Cobb, Journal of Biological Chemistry 271 (1996) 8951–8958.
[17] F.A. Gonzalez, D.L. Raden, M.R. Rigby, R.J. Davis, FEBS Letters 304 (1992) 170–178.
[18] J.D. Lee, R.J. Ulevitch, J. Han, Biochemical and Biophysical Research Communications 213 (1995) 715–724.
[19] G. Zhou, Z.Q. Bao, J.E. Dixon, Journal of Biological Chemistry 270 (1995) 12665–12669.
[20] M.K. Abe, W.L. Kuo, M.B. Hershenson, M.R. Rosner, Molecular and Cellular Biology 19 (1999) 1301–1312.
[21] M.K. Abe, M.P. Saelzler, R. Espinosa III, K.T. Kahle, M.B. Hershenson, M.M. Le Beau, M.R. Rosner, Journal of Biological Chemistry 277 (2002) 16733–16743.
[22] S.J. Lee, T. Zhou, E.J. Goldsmith, Methods 40 (2006) 224–233.
[23] Z. Chen, T.B. Gibson, F. Robinson, L. Silvestro, G. Pearson, B. Xu, A. Wright, C. Vanderbilt, M.H. Cobb, Chemical Reviews 101 (2001) 2449–2476.
[24] R.M. Biondi, A.R. Nebreda, Biochemical Journal 372 (2003) 1–13.
[25] C.A. Dimitri, W. Dowdle, J.P. MacKeigan, J. Blenis, L.O. Murphy, Current Biology 15 (2005) 1319–1324.
[26] D.T. Ho, A.J. Bardwell, S. Grewal, C. Iverson, L. Bardwell, Journal of Biological Chemistry 281 (2006) 13169–13179.
[27] T. Tanoue, E. Nishida, Cellular Signalling 15 (2003) 455–462.

[28] A.C. Lloyd, Journal of Biology 5 (2006) 13.
[29] N. Hatano, Y. Mori, M. Oh-hora, A. Kosugi, T. Fujikawa, N. Nakai, H. Niwa, J. Miyazaki, T. Hamaoka, M. Ogata, Genes to Cells 8 (2003) 847–856.
[30] M.K. Saba-El-Leil, F.D. Vella, B. Vernay, L. Voisin, L. Chen, N. Labrecque, S.L. Ang, S. Meloche, EMBO Reports 4 (2003) 964–968.
[31] T. Nekrasova, C. Shive, Y. Gao, K. Kawamura, R. Guardia, G. Landreth, T.G. Forsthuber, Journal of Immunology 175 (2005) 2374–2380.
[32] G. Pages, S. Guerin, D. Grall, F. Bonino, A. Smith, F. Anjuere, P. Auberger, J. Pouyssegur, Science 286 (1999) 1374–1377.
[33] J. Schlessinger, A. Ullrich, Neuron 9 (1992) 383–391.
[34] S. Yoon, R. Seger, Growth Factors 24 (2006) 21–44.
[35] Y. Zhang, C. Dong, Cellular and Molecular Life Sciences 64 (2007) 2771–2789.
[36] T. Kallunki, B. Su, I. Tsigelny, H.K. Sluss, B. Derijard, G. Moore, R. Davis, M. Karin, Genes & Development 8 (1994) 2996–3007.
[37] H.Y. Lin, S. Zhang, B.L. West, H.Y. Tang, T. Passaretti, F.B. Davis, P.J. Davis, Biochemistry 42 (2003) 7571–7579.
[38] S.H. Yang, P.R. Yates, A.J. Whitmarsh, R.J. Davis, A.D. Sharrocks, Molecular and Cellular Biology 18 (1998) 710–720.
[39] D.N. Dhanasekaran, K. Kashef, C.M. Lee, H. Xu, E.P. Reddy, Oncogene 26 (2007) 3185–3202.
[40] H. Vaidyanathan, J. Opoku-Ansah, S. Pastorino, H. Renganathan, M.L. Matter, J.W. Ramos, Proceedings of the National Academy of Sciences of the United States of America 104 (2007) 19837–19842.
[41] E. Formstecher, J.W. Ramos, M. Fauquet, D.A. Calderwood, J.C. Hsieh, B. Canton, X.T. Nguyen, J.V. Barnier, J. Camonis, M.H. Ginsberg, H. Chneiweiss, Developmental Cell 1 (2001) 239–250.
[42] P. Germain, P. Chambon, G. Eichele, R.M. Evans, M.A. Lazar, M. Leid, A.R. De Lera, R. Lotan, D.J. Mangelsdorf, H. Gronemeyer, Pharmacological Reviews 58 (2006) 712–725.
[43] A. Chawla, J.J. Repa, R.M. Evans, D.J. Mangelsdorf, Science 294 (2001) 1866–1870.
[44] G.A. Francis, E. Fayard, F. Picard, J. Auwerx, Annual Review of Physiology 65 (2003) 261–311.
[45] D.J. Mangelsdorf, C. Thummel, M. Beato, P. Herrlich, G. Schutz, K. Umesono, B. Blumberg, P. Kastner, M. Mark, P. Chambon, R.M. Evans, Cell 83 (1995) 835–839.
[46] J.T. Moore, J.L. Collins, K.H. Pearce, ChemMedChem 1 (2006) 504–523.
[47] V. Laudet, H. Gronemeyer, Nuclear Receptor Factsbook, Academic Press, London, 2001.
[48] S. Khorasanizadeh, F. Rastinejad, Trends in Biochemical Sciences 26 (2001) 384–390.
[49] B.D. Darimont, R.L. Wagner, J.W. Apriletti, M.R. Stallcup, P.J. Kushner, J.D. Baxter, R.J. Fletterick, K.R. Yamamoto, Genes & Development 12 (1998) 3343–3356.
[50] R.T. Gampe Jr., V.G. Montana, M.H. Lambert, A.B. Miller, R.K. Bledsoe, M.V. Milburn, S.A. Kliewer, T.M. Willson, H.E. Xu, Molecular Cell 5 (2000) 545–555.
[51] A.K. Shiau, D. Barstad, P.M. Loria, L. Cheng, P.J. Kushner, D.A. Agard, G.L. Greene, Cell 95 (1998) 927–937.
[52] C. Rochette-Egly, Journal of Biological Chemistry 280 (2005) 32565–32568.
[53] A. Warnmark, E. Treuter, A.P. Wright, J.A. Gustafsson, Molecular Endocrinology 17 (2003) 1901–1909.
[54] D.N. Lavery, I.J. McEwan, Biochemical Journal 391 (2005) 449–464.
[55] T. Ylikomi, M.T. Bocquel, M. Berry, H. Gronemeyer, P. Chambon, EMBO Journal 11 (1992) 3681–3694.
[56] H.P. Harding, M.A. Lazar, Molecular and Cellular Biology 15 (1995) 4791–4802.
[57] N. Bougarne, R. Paumelle, S. Caron, N. Hennuyer, R. Mansouri, P. Gervois, B. Staels, G. Haegeman, K. De Bosscher, Proceedings of the National Academy of Sciences of the United States of America 106 (2009) 7397–7402.
[58] A. Hurtado, K.A. Holmes, C.S. Ross-Innes, D. Schmidt, J.S. Carroll, Nature Genetics 43 (2011) 27–33.
[59] Piskunov A, Rochette Egly C, MSK1 and nuclear receptors signaling. In *MSKs* J.S.C. Arthur Austin 2012.
[60] A.W. Norman, M.T. Mizwicki, D.P. Norman, Nature Reviews. Drug Discovery 3 (2004) 27–41.
[61] D.C. Marquez, H.W. Chen, E.M. Curran, W.V. Welshons, R.J. Pietras, Molecular and Cellular Endocrinology 246 (2006) 91–100.
[62] L. Matthews, A. Berry, V. Ohanian, J. Ohanian, H. Garside, D. Ray, Molecular Endocrinology 22 (2008) 1320–1330.
[63] A. Piskunov, C. Rochette-Egly, Oncogene 31 (2012) 3333–3345.
[64] J.J. Bergh, H.Y. Lin, L. Lansing, S.N. Mohamed, F.B. Davis, S. Mousa, P.J. Davis, Endocrinology 146 (2005) 2864–2871.
[65] A. Migliaccio, D. Piccolo, G. Castoria, M. Di Domenico, A. Bilancio, M. Lombardi, W. Gong, M. Beato, F. Auricchio, EMBO Journal 17 (1998) 2008–2018.
[66] D.W. Singleton, Y. Feng, C.J. Burd, S.A. Khan, Endocrinology 144 (2003) 121–128.
[67] N. Bruck, D. Vitoux, C. Ferry, V. Duong, A. Bauer, H. de The, C. Rochette-Egly, EMBO Journal 28 (2009) 34–47.
[68] A. Shalev, C.A. Siegrist-Kaiser, P.M. Yen, W. Wahli, A.G. Burger, W.W. Chin, C.A. Meier, Endocrinology 137 (1996) 4499–4502.
[69] C. Rochette-Egly, Germain P, Nuclear Receptor Signaling 7 (2009) e005.
[70] C. Rochette-Egly, Cellular Signalling 15 (2003) 355–366.
[71] L.A. Ponguta, C.W. Gregory, F.S. French, E.M. Wilson, Journal of Biological Chemistry 283 (2008) 20989–21001.
[72] G. Bunone, P.A. Briand, R.J. Miksicek, D. Picard, EMBO Journal 15 (1996) 2174–2183.
[73] S. Kato, H. Endoh, Y. Masuhiro, T. Kitamoto, S. Uchiyama, H. Sasaki, S. Masushige, Y. Gotoh, E. Nishida, H. Kawashima, D. Metzger, P. Chambon, Science 270 (1995) 1491–1494.
[74] R.S. Thomas, N. Sarwar, F. Phoenix, R.C. Coombes, S. Ali, Journal of Molecular Endocrinology 40 (2008) 173–184.
[75] M. Sanchez, N. Picard, K. Sauve, A. Tremblay, Trends in Endocrinology and Metabolism 21 (2010) 104–110.
[76] T. Shen, K.B. Horwitz, C.A. Lange, Molecular and Cellular Biology 21 (2001) 6122–6131.
[77] K.A. Burns, J.P. Vanden Heuvel, Biochimica et Biophysica Acta 1771 (2007) 952–960.
[78] M. Adams, M.J. Reginato, D. Shao, M.A. Lazar, V.K. Chatterjee, Journal of Biological Chemistry 272 (1997) 5128–5132.
[79] J. Han, D.P. Hajjar, J.M. Tauras, J. Feng, A.M. Gotto Jr., A.C. Nicholson, Journal of Biological Chemistry 275 (2000) 1241–1246.
[80] C.E. Juge-Aubry, E. Hammar, C. Siegrist-Kaiser, A. Pernin, A. Takeshita, W.W. Chin, A.G. Burger, C.A. Meier, Journal of Biological Chemistry 274 (1999) 10505–10510.
[81] C. Rochette-Egly, S. Adam, M. Rossignol, J.M. Egly, P. Chambon, Cell 90 (1997) 97–107.
[82] C. Solomon, J.H. White, R. Kremer, The Journal of Clinical Investigation 103 (1999) 1729–1735.
[83] A. Lechtken, M. Hornig, O. Werz, N. Corvey, I. Zundorf, T. Dingermann, R. Brandes, D. Steinhilber, Biochemical and Biophysical Research Communications 358 (2007) 890–896.
[84] Y.K. Lee, Y.H. Choi, S. Chua, Y.J. Park, D.D. Moore, Journal of Biological Chemistry 281 (2006) 7850–7855.
[85] H. Endoh, K. Maruyama, Y. Masuhiro, Y. Kobayashi, M. Goto, H. Tai, J. Yanagisawa, D. Metzger, S. Hashimoto, S. Kato, Molecular and Cellular Biology 19 (1999) 5363–5372.
[86] A. Tremblay, G.B. Tremblay, F. Labrie, V. Giguere, Molecular Cell 3 (1999) 513–519.
[87] S. Yeh, H.K. Lin, H.Y. Kang, T.H. Thin, M.F. Lin, C. Chang, Proceedings of the National Academy of Sciences of the United States of America 96 (1999) 5458–5463.
[88] P.M. Barger, A.C. Browning, A.N. Garner, D.P. Kelly, Journal of Biological Chemistry 276 (2001) 44495–44501.
[89] A.R. Daniel, E.J. Faivre, C.A. Lange, Molecular Endocrinology 21 (2007) 2890–2906.
[90] D. Shao, S.M. Rangwala, S.T. Bailey, S.L. Krakow, M.J. Reginato, M.A. Lazar, Nature 396 (1998) 377–380.
[91] Z.E. Floyd, J.M. Stephens, Journal of Biological Chemistry 277 (2002) 4062–4068.
[92] A.D. Wallace, J.A. Cidlowski, Journal of Biological Chemistry 276 (2001) 42714–42721.
[93] E. Burgermeister, D. Chuderland, T. Hanoch, M. Meyer, M. Liscovitch, R. Seger, Molecular and Cellular Biology 27 (2007) 803–817.
[94] H.Y. Lee, Y.A. Suh, M.J. Robinson, J.L. Clifford, W.K. Hong, J.R. Woodgett, M.H. Cobb, D.J. Mangelsdorf, J.M. Kurie, Journal of Biological Chemistry 275 (2000) 32193–32199.
[95] M. Macoritto, L. Nguyen-Yamamoto, D.C. Huang, S. Samuel, X.F. Yang, T.T. Wang, J.H. White, R. Kremer, Journal of Biological Chemistry 283 (2008) 4943–4956.
[96] P. Gupta, P.C. Ho, M.M. Huq, S.G. Ha, S.W. Park, A.A. Khan, N.P. Tsai, L.N. Wei, Proceedings of the National Academy of Sciences of the United States of America 105 (2008) 11424–11429.
[97] Y.J. Chen, Y.N. Wang, W.C. Chang, Journal of Biological Chemistry 282 (2007) 27215–27228.
[98] R. Gusterson, B. Brar, D. Faulkes, A. Giordano, J. Chrivia, D. Latchman, Journal of Biological Chemistry 277 (2002) 2517–2524.
[99] J.D. Meissner, R. Freund, D. Krone, P.K. Umeda, K.C. Chang, G. Gros, R.J. Scheibe, Nucleic Acids Research 39 (2011) 5907–5925.
[100] M. Cui, Y. Zhao, K.W. Hance, A. Shao, R.J. Wood, J.C. Fleet, Journal of Cellular Physiology 219 (2009) 132–142.
[101] P.K. Pandey, T.S. Udayakumar, X. Lin, D. Sharma, P.S. Shapiro, J.D. Fondell, Molecular and Cellular Biology 25 (2005) 10695–10710.
[102] S.H. Hong, M.L. Privalsky, Molecular and Cellular Biology 20 (2000) 6612–6625.
[103] V. Perissi, C. Scafoglio, J. Zhang, K.A. Ohgi, D.W. Rose, C.K. Glass, M.G. Rosenfeld, Molecular Cell 29 (2008) 755–766.
[104] P.C. Ho, P. Gupta, Y.C. Tsui, S.G. Ha, M. Huq, L.N. Wei, Cellular Signalling 20 (2008) 1911–1919.
[105] G.P. Vicent, C. Ballare, A.S. Nacht, J. Clausell, A. Subtil-Rodriguez, I. Quiles, A. Jordan, M. Beato, Molecular Cell 24 (2006) 367–381.
[106] P. Blume-Jensen, T. Hunter, Nature 411 (2001) 355–365.
[107] Y. Yarden, M.X. Sliwkowski, Nature Reviews Molecular Cell Biology 2 (2001) 127–137.
[108] R.E. Bakin, D. Gioeli, R.A. Sikes, E.A. Bissonette, M.J. Weber, Cancer Research 63 (2003) 1981–1989.
[109] A.R. Daniel, C.A. Lange, Proceedings of the National Academy of Sciences of the United States of America 106 (2009) 14287–14292.
[110] C.A. Lange, T. Shen, K.B. Horwitz, Proceedings of the National Academy of Sciences of the United States of America 97 (2000) 1032–1037.
[111] N. Picard, C. Charbonneau, M. Sanchez, A. Licznar, M. Busson, G. Lazennec, A. Tremblay, Molecular Endocrinology 22 (2008) 317–330.
[112] B. Cassinat, F. Zassadowski, C. Ferry, L. Llopis, N. Bruck, E. Lainey, V. Duong, A. Cras, G. Despouy, O. Chourbagi, G. Beinse, P. Fenaux, C. Rochette Egly, C. Chomienne, Molecular and Cellular Biology 31 (2011) 1409–1418.