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Dialogue between estrogen receptor and E2F signaling pathways: The transcriptional coregulator RIP140 at the crossroads*

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ABSTRACT

Estrogen receptors and E2F transcription factors are the key players of two nuclear signaling pathways which exert a major role in oncogenesis, particularly in the mammary gland. Different levels of dialogue between these two pathways have been deciphered and deregulation of the E2F pathway has been shown to impact the response of breast cancer cells to endocrine therapies. The present review focuses on the transcriptional coregulator RIP140/NRIP1 which is involved in several regulatory feed-back loops and inhibitory cross-talks between different nuclear signaling pathways. RIP140 regulates the transactivation potential of estrogen receptors and E2Fs and is also a direct transcriptional target of these transcription factors. Published data highlight the complex regulation of RIP140 expression at the transcriptional level and its potential role in transcription cross-talks. Indeed, a subtle regulation of RIP140 expression levels has important consequences on other transcription networks targeted by this coregulator. Another level of regulation implies titration mechanisms by which activation of a pathway leads to sequestration of the RIP140 protein and thus impinges other gene regulatory circuitries. Altogether, RIP140 occupies a place of choice in the dialogue between nuclear receptors and E2Fs, which could be highly relevant in various human pathologies such as cancer or metabolic diseases.

Keywords: RIP140; E2F Transcription Factors; Estrogen Receptors; Gene Expression; Cell Proliferation; Breast Cancer; Endocrine Therapies

*Role of RIP140 in estrogen and E2F pathways.

1. ESTROGEN RECEPTOR AND E2F SIGNALING PATHWAYS

1.1. Estrogen Signaling in Breast Cancer Cells

Estrogens are steroid hormones that regulate growth and differentiation of a large number of target tissues such as the mammary gland, the reproductive tract and skeletal and cardiovascular systems [1]. Most of these events are mediated through two distinct intracellular receptors, ERα and ERβ, which belong to the superfamily of nuclear receptors. ERs bind as homo- or heterodimers to specific DNA response elements (EREs) located within the regulatory regions of target genes. Indirect recruitment on target promoters also occurs through protein-protein interaction with other transcription factors, such as Sp1 or AP-1. The ligand-dependent transcriptional activity of ERs is mediated by two distinct activation domains, a constitutive activation function-1 (AF-1) located within the N-terminus of the molecule and a hormone-dependent transactivation domain AF-2, associated with the ligand-binding domain. Depending on cell and promoter contexts, these two domains function independently or synergistically. Ligand binding induces a conformational change that facilitates the recruitment of a large set of coactivator proteins [2]. These transcription mediators act either by stabilizing the formation of a transcription preinitiation complex or by facilitating chromatin disruption through various enzymatic activities that target histone tails. On the other hand, ERα has been shown to in-

teract specifically with corepressors such as the MTA1/NuRD chromatin-remodeling complex or NCOR1 in the presence of partial antiestrogens such as 4-hydroxytamoxifen. Estrogens stimulate cell proliferation in normal developing breast tissues and in a large proportion of ERα-positive breast cancers. Endocrine therapies using selective estrogen receptor modulators or aromatase inhibitors have proven their efficacy in the prevention or treatment of breast cancer [3]. The role of estrogens in breast cancer cells appears more complex since in addition to its classical genomic actions, ERα also exerts rapid non-genomic effects, which involve interaction with different signal transduction proteins including the tyrosine kinase Src and the phosphatidylinositol 3-kinase (PI3K) [4]. In addition, the estrogen signaling pathway is finely regulated by multiple post-translational modifications which regulate its function and play important roles in physiopathology [5].

1.2. E2F Transcription Factors

E2Fs and their heterodimer partners, DPs, are central regulators of cell cycle progression and directly regulate the expression of a broad spectrum of genes involved in cell cycle regulation, DNA replication and repair, apoptosis, differentiation or development [6]. E2F1, discovered as a protein promoting the transition to S phase, was the founding member of the E2F family which comprises eight members in mammals. Among this family, some were initially presented as "activator E2Fs" (E2F1, 2 and 3) while the other members were mostly known as transcription repressors. E2F transcriptional activity was shown to be regulated by a large number of transcription coactivators or corepressors including the so-called pocket proteins which form the retinoblastoma tumor suppressor family (RB together with the related proteins p107 and p130) [7]. RB attenuates activator E2F action by recruiting transcriptional corepressors such as histone deacetylases (HDACs) to E2F-regulated promoters, thus mediating transcriptional repression of E2F-regulated genes. RB is a critical component of the cell cycle control machinery and as a consequence, its loss or inactivation is a major mechanism by which cancer cells attain a growth advantage during tumorigenesis [8].

1.3. Cross-Talks between ER and E2F Signalings

1.3.1. Regulation of ER Signaling by E2Fs and Pocket Proteins

A first dialogue between the two pathways deals with the regulation of ER and nuclear receptor coregulator expression by the E2F pathway. The ERα promoter contains two E2F binding sites in the proximal promoter region and it has been demonstrated that multimolecular complexes containing E2F4/5 are recruited on the ERα promoter in cycling MCF-7 and MDA-MB-231 breast cancer cell lines [9]. This suggests that the E2F pathway might be involved in the transcriptional repression of the ERα gene which occurs in up to one-third of breast cancers. Interestingly, a study on human breast cancer biopsies confirmed the overexpression of E2F5 in ERα-negative breast cancers and its association with a worse outcome [10]. Steroid receptor coactivator 3 (SRC3/NCOA3), a major transcriptional coactivator for estrogen receptors which is overexpressed in breast cancers, is also a transcriptional target of E2F transcription factors. In MCF-7 breast cancer cells, SRC3 expression is under the control of E2F1 (ectopic expression increases SRC3 levels whereas knockdown of E2F1 reduces SRC3 expression) [11]. The regulation operates at the transcriptional level and involves Sp1 response element in the proximal promoter region. At the transactivation level, RB has been shown to potentiate the enhancing effect of SRC2/NCOA2 on both ERα and ERβ activity [12] and an interaction between ERβ and p130 has been reported although the relevance of this interaction has not been investigated [13]. RB can also interact indirectly with ERα through the RIZ protein [14]. Finally, other members of the E2F pathway such as Cdc25B [15] or cyclin-cdk complexes [16] have also been described as modulators of ER activity.

1.3.2. Regulation of the E2F Pathway by Estrogens

A main level of cross-talk between ER and E2F signaling pathways resides in the regulation of E2F1 expression by estrogens. This regulation has been observed at the mRNA level in several breast cancer cell types such as MCF-7, ZR75-1 or T47D cells [17]. Recently, ChIP experiments confirmed the presence of ERα on the E2F1 promoter [18]. The regulation was also detected at the E2F1 protein level which was significantly increased upon E2 treatment [19]. The regulation of E2F1 levels appears critical for the mitogenic effect of estrogens since silencing of E2F1 expression in MCF-7 breast cancer cells resulted in a loss of estrogen regulation of cell proliferation [19]. Whereas E2F1 mRNA levels are strongly increased by estrogens in MCF-7 cells, the expression of E2F2 and E2F6 mRNA is only weakly increased and that of E2F3-5 not affected [19]. However, another study reported the regulation of E2F1, E2F2, E2F7 and E2F8 mRNA by E2 in MCF-7 cells, all being sensitive to protein synthesis inhibition [20]. It should be noted that the induction of E2F1 by estrogens is modulated by various factors such as SCFskp2 [18], the IκB kinase (IKKα) [21] or the transcription factor HES-1 [22]. Estrogens treatment also impacts the E2F signaling pathway at other levels by increasing the formation of active Cyclin D1-Cdk4 complexes in MCF-7 cells and increasing the phosphorylation of pRB or by regulating the expression

of other members of the pathway such as the Cdk-activating phosphatase Cdc25A [23-25]. Another point deals with the fact that nuclear receptor coregulators such as CBP [26], PCAF [27], ASC-2/ NCOA6 [28] or AIB1/ NCOA3 [29] interact with E2F and modulate its transcriptional activity. The specific role of the nuclear receptor corepressor RIP140 in the regulation of E2F activity is discussed below.

1.3.3. E2F Signaling and Regulation of Cell Proliferation by Estrogens and Antiestrogens

Approximately 70% of breast cancers are ER-positive tumors and patients bearing such tumors are treated with endocrine therapies which comprise selective ER modulators such as Tamoxifen, aromatase inhibitors which target estrogen synthesis such as Letrozole or pure ER antagonists such as Fulvestrant [30]. Although hormonal interventions have proven to be very effective in breast cancer treatment, many patients develop drug resistance which represents a major clinical problem [31]. The mechanisms by which tumors escape from endocrine therapies are not fully understood and several signaling pathways have been involved in the bypass of these treatments [30]. One mechanism by which cells overcome the inhibition of ER signaling is linked to the activation of the Cyclin/Cdk/RB/E2F. In MCF-7 breast cancer cells, antiestrogens reduce the level of Cdk2 activity and decrease the level of hyperphosphorylated RB [32,33]. Moreover, the group of E Knudsen demonstrated that silencing of RB expression or ectopic expression of E2F3 compromised the short-term cell-cycle inhibition by antiestrogen resulting in continued cell and tumor proliferation in the presence of Tamoxifen [34]. By reanalyzing microarray datasets, the deregulation of RB/E2F target gene expression was shown to be strongly associated with recurrence in patients treated with Tamoxifen. More recently, the perturbation of the transcriptional response to RB was confirmed in antiestrogen-resistant MCF7-derived cell models [35] and an estrogen-independent role for ERα demonstrated in driving an E2F transcriptional program [36]. This study also reported that an E2F activation gene signature correlates with a decrease in patient response to aromatase inhibitors. Altogether, these studies support the idea that hyperactivation of the E2F signaling pathway is a key determinant of the response to hormonal therapies [37].

2. REGULATION OF THE ER AND E2F SIGNALINGS BY RIP140

2.1. Introduction

Almost 20 years ago, one of the main goals in the field of nuclear receptor (NR) biology was to identify interacting partners acting as transcriptional coregulators. RIP140 (Receptor Interacting Protein of 140 kDa) also known as Nuclear receptor-interacting protein 1 (NRIP1), was one of the first NR coregulator to be isolated from human cancer cells by far-western blotting using the ligand binding domain of the mouse ERα as a radiolabeled probe [38,39]. Although RIP140 has been first described as a repressor of gene expression, it can also activate transcription depending on the target transcription factors and promoters considered (see below). The human RIP140 protein is a polypeptide of 1158 amino acids which is well conserved across species. It contains two putative nuclear localization signals and several other domains important for its biological activity as a transcription factor. Four repressive domains (RD) have been identified in the RIP140 molecule [40,41]. The RD1 acts mainly by recruiting class I and II histone deacetylases (HDACs) whereas the RD2 interacts with carboxyl-terminal-binding proteins (CtBP1 and CtBP2) through two conserved motifs (sequences PIDLS and PINLS) [42,43]. No downstream effectors have yet been identified for RD3 and RD4 which are located in the carboxyl-terminal region of the molecule (amino acid residues 753 - 804 and 1118 - 1158, respectively). Interestingly, two lysine residues located in these domains are conjugated to SUMO proteins and play an important role in controlling the repressive activity of RIP140 [44]. Extensive biochemical studies performed in the laboratory of L Wei have revealed a complex network of post-translational modifications (e.g. phosphorylation, acetylation or methylation) which target the RIP140 protein and affect various parameters such as its subcellular localization, interaction with partners and transcriptional regulation. Mainly as a consequence of some of these post-translational modifications, RIP140 could be delocalized in the cytoplasm where it exerts different functions. A first example deals with the regulation of glucose uptake through the control of glucose transporter type 4 (GLUT4) trafficking which involves interaction with the 160-KDa Akt substrate, AS160 [45]. Another effect of cytoplasmic RIP140 has been demonstrated in lipid metabolism of adipocytes with a positive regulation of lipolysis through its direct interaction of RIP140 with perilipin [46]. Besides its interaction with various members of the NR superfamily, RIP140 has also been evidenced as a regulator of other transcription factors like the aryl hydrocarbon receptor (AhR) [47]. More recently, it has been shown that, in murine macrophages, RIP140 positively controls the expression of proinflammatory genes such as *IL1β, IL6* or *TNFα* [48]. The ability of RIP140 to function as a transcriptional activator of cytokine gene transcription relies on direct protein-protein interactions with the NFκB subunit RelA and histone acetylase cAMP-responsive element binding protein (CREB)-binding protein (CBP). Using genetically manipulated mice (mainly constitutive gene knockout mice),

several laboratories have deciphered the physiological roles of RIP140, highlighting a wide spectrum of major phenotypes dealing for instance with metabolism, reproduction, heart and mammary gland physiology or behavior [49,50].

2.2. RIP140 as a Regulator of Estrogen Signaling

2.2.1. Interaction of RIP140 with ER*α*

RIP140 was originally identified as a repressor of the estrogen receptor ER*α* in human breast cancer cells [39]. As transcription coactivators, RIP140 is recruited to ER*α* in the presence of agonist by means of short helical motifs which exhibit the LXXLL consensus amino acid sequence. These motifs facilitate protein-protein interactions and docking on NR ligand-binding domains in their apo conformation. The RIP140 protein contains nine LxxLL motifs thus offering a great diversity in term of NR interaction [51]. Depending on the promoter context and post-translational modifications, this conformational adaptation allows RIP140 to function as a scaffold for the assembly of chromatin remodeling complexes. Several studies have demonstrated the ligand-dependent recruitment of RIP140 on target genes in intact cells using the chromatin immunoprecipitation technique. This was for instance described on the RAR*α* promoter in the presence of E2 [52]. A recent paper reported a ChIP-Seq analysis of RIP140 target genes in MCF-7 cells treated by 17*β*-estradiol [53]. Surprisingly, this whole-genome binding sites analysis revealed only 2000 binding sites for RIP140 representing less than 5% of the genes targeted by ER*α* in the same conditions.

2.2.2. Effect of RIP140 on ER*α* and ER*β*

One of the hypotheses to explain the inhibitory effect of ER*β* on E2 regulation of gene expression and cell proliferation implies a differential recruitment of transcriptional coregulators by the two ER subtypes. Previous studies have reported ER*β* [54,55] or ER*α* [56,57] specific interaction with different coregulators. A recent analysis of the nuclear interactomes of the two ER subtypes revealed only a small set of common proteins [58]. Interestingly, using various approaches (GST pull down, anisotropy measurements, FCCS and ChIP assays), we have recently demonstrated that RIP140 was preferentially interacting with ER*β* as compared with ER*α* [59]. Moreover, our results obtained after siRNA-mediated knockdown of RIP140 expression in BG1 ovarian cancer cells demonstrated the key role of RIP140 in the repressive effect exerted by activated ER*β* on the regulation of ERE-controlled transcription by estrogens. This preferential interaction of RIP140 with ER*β* was supported by global ChIP-Seq analysis showing that, in MCF-7 breast cancer cells, the number of RIP140-binding sites was increased by about 4-fold upon ER*β* expression [53].

2.2.3. Ternary Complex Involving ERs and RIP140

In addition to the ERE-mediated regulation of gene expression, ERs are involved in protein-protein interaction with other transcription factors such as Sp1 or AP1 [60, 61]. In some cases, it has been reported that such complex are also regulated by RIP140. For instance, AP1-mediated transcription is increased by ER*α* through a direct interaction with c-Jun and the recruitment of the coactivator GRIP1/NCOA2. This estradiol-induced AP-1-dependent transcription is inhibited by RIP140 in a dose-dependent manner [62]. In HepG2 cells, the inhibition of the *PROS*1 gene transcription by estrogen involves the interaction of ER with Sp proteins and the recruitment of RIP140 and a NCoR-SMRT-HDAC3 complex on the proximal region of the *PROS*1 promoter, as demonstrated by chromatin immunoprecipitation assays [63]. Another crosstalk involves the aryl hydrocarbon receptor (AhR) which interacts with ERα and inhibits E2 target genes when activated by ligands such as polycyclic aromatic or halogenated hydrocarbons. Different mechanisms have been reported involving proteasomal degradation of ER*α* [64] or squelching of common coactivators [65]. More recently, a new mechanism by which AhR regulates ER*α* action in breast cancer cells has been proposed. It involves the formation of a ternary complex with RIP140 on ER*α*-binding sites as demonstrated by ChIP-reChIP studies on the *LRRC*54 or *HSPB*8 gene promoters [66].

2.3. Effects of RIP140 on the E2F Pathway

2.3.1. Interaction of RIP140 with E2Fs

By means of various approaches, the interaction between RIP140 and E2F1 was clearly demonstrated [67]. Using *in vitro* GST pull-down assays, the respective binding sites on the two proteins were delineated. Two regions of the RIP140 molecule spanning from amino acids 119 to 199 and 916 to 1158 are involved in the interaction with the N-terminus of E2F1. Co-immunoprecipitation experiments and ChIP assays confirmed that the interaction between RIP140 and E2F1 occurs in intact cells.

2.3.2. RIP140 Inhibits E2F Target Gene Expression

In transiently transfected MCF-7 breast cancer cells, RIP140 ectopic expression resulted in a significant dose-dependent inhibition of E2F1 activity measured on different E2F reporter promoters such as the *CCNE* or *CDKN2A* promoters. This repressive activity of RIP140 was also observed in other human cancer cell lines and on the two other activator E2Fs, *i.e.* E2F2 and E2F3. Moreover, the expression of several E2F target genes (*CCNE*, *CCNB*2, *CDC*2 and *CDC*6) was strongly decreased in MCF-7 breast cancer cells overexpressing a chimaeric GFP-RIP140 protein. However, the negative regulation was not observed for all E2F-target genes

since for instance, the DHFR mRNA levels were not significantly affected. In agreement with the inhibition of E2F activity, RIP140 reduced the proportion of cells in S phase after ectopic expression in various human cell lines.

2.3.3. Inverse Correlation between RIP140 and E2F Target Gene Expression

To emphasize the biological significance of E2F inhibition by RIP140, the expression of RIP140 and E2F1-target genes were analyzed on a tumor microarray data set of 170 breast cancer samples [68]. A clustering analysis clearly showed that, in this cohort of human breast cancers, RIP140-deficiency is inversely correlated with the expression of several E2F1-target genes (*CCNE*1, *MYBL*2, *BIRC*5, *E2F*1, *CCNB*2 and *CDC*6). Moreover, variations of RIP140 expression discriminate between molecular subtypes, low RIP140 mRNA expression being associated with basal-like tumors.

3. REGULATION OF RIP140 EXPRESSION BY ESTROGENS AND E2FS

3.1. Structure and Regulation of the RIP140 Gene

The human RIP140 gene is located in a gene-poor region of chromosome 21 q11.2 [69]. Interestingly, the RIP140 coding sequence is comprised in a single large exon with several short non-coding exons which undergo alternative splicing placing the promoter about 100 kb upstream of the ATG [70]. RIP140 is a widely expressed gene and in the mouse, the mRNA is detected in all the tissues with a strong expression in the testis and in the brain [71]. The RIP140 mRNA is present in a large number of cancer cell lines where it appears regulated by various nuclear receptors [72].

3.2. RIP140 as an Estrogen Induced Gene

We initially reported that RIP140 gene expression was regulated by 17β-estradiol (E2) in MCF-7 human breast cancer cells [38]. Several studies using global gene expression profiling also identified RIP140 as an estrogen-induced gene in breast cancer MCF-7 cells [19]. More recently, using the Rank product method, a meta-analysis of several expression studies provided a list of genes differentially expressed upon E2 stimulation [73]. By analyzing 9 time-series data sets, the authors identified between 1000 and 2000 target genes mostly related to cell signaling and proliferation which exhibit an early regulation by estrogens (*i.e.* 3-4 hrs post E2 treatment). The *RIP*140 gene was well ranked in this list of early up-regulated genes. The regulation of RIP140 expression by estrogens is independent of protein synthesis [74], direct (*i.e.* it does not require synthesis of an intermediary protein as judged by the absence of effect of cycloheximide) and operates at the transcriptional level [70]. A consensus ERE (which binds the ERα in gel shift and ChIP experiments) has been mapped in the 5' proximal region of the gene [20,70,75] and it has been proposed that FoxA1 sites might function as an enhancer facilitating the recruitment of ERα on the *RIP*140 promoter [76]. In MCF-7 cells, the regulation was preferentially mediated by ERα as indicated by the use of the specific agonist ligand 4,4',4"-(4-propyl-[1H]-pyrazole-1,3,5-triyl) trisphenol (PPT). These results were confirmed using HeLa cells stably transfected with either ERα or ERβ expression vector [77] or MDA-MB 231 breast cancer cells infected with recombinant adenovirus expressing either variant of the ER. In MCF-7 cells, we showed that ER antagonist ligands such as 4-hydroxy Tamoxifen, Raloxifene or the pure antiestrogen ICI 182,780 did not increase the steady-state levels of RIP140 mRNA [70]. The regulation by estrogens was not restricted to mammary cancer cells since similar increase of RIP140 mRNA levels by estradiol was observed in human ovarian cancer cells [59]. In addition, transcriptional profilings of ER-regulated genes using stably transfected U2OS cells expressing either ERα or ERβ have also identified *RIP*140 as an E2-regulated gene although the relative induction by the two isoforms of ER varied according to the study [78,79].

3.3. E2Fs Control RIP140 Transcription

We recently published the identification and characterization of E2F binding sites in the proximal promoter region of the RIP140 gene [80]. Using gel shift experiments, we showed that E2F1 strongly interacts with oligonucleotides encompassing the putative binding sites. ChIP experiments demonstrate that the interaction of E2F1/DP1 with the proximal promoter region occurred in intact cells. Moreover, transient transfection experiments demonstrate a transcriptional regulation of the human and mouse *RIP*140 promoters by E2F1, E2F2 and E2F3 and promoter mutagenesis (deletion and point mutations) suggested a complex regulation of the *RIP*140 promoter by E2F1, involving a combination of direct and indirect recruitment through Sp1 similar to the regulation of SRC3 by E2F1 [11]. Interestingly, a significant increase in the levels of endogenous RIP140 mRNA was observed upon ectopic overexpression of E2F1 and DP1, thus confirming that RIP140 is a transcriptional target of E2F1 and could explain the variation in RIP140 expression observed after cell synchronization.

3.4. Nuclear Cross-Talks Involving RIP140

Auto-and cross-regulation between members of the nuclear receptor superfamily appear important for the coor-

dination of hormone action in a temporal and tissue-specific manner and for the regulation of hormonal signals through positive or negative feedbacks [81]. Several indirect transcriptional cross-talks involving the regulation of *RIP*140 gene expression have been reported. Treatment of MCF-7 cells with 2,3,7,8-tetrachlorodi-benzo-p-dioxin (TCDD), an agonist of the arylhydrocarbon receptor (AhR) induced a two-fold increase in RIP140 mRNA steady state level [70]. This TCDD-mediated increase in RIP140 expression could lead to a transrepression of ER activity and thus participate in the antiestrogenic effect of AhR [82,83]. RIP140 mRNA expression was also shown to be induced by all-trans retinoic acid in human embryonic carcinoma cells and in MCF-7 cells [84], suggesting that RIP140 might mediate some of the anti-estrogenic effects of retinoic acid [85]. Indeed, RIP140 knock-down using siRNA reverse the antiestrogenic effect of retinoic acid on an ERE-mediated transcriptional response. RIP140 appears to be a limiting factor in the estrogen signaling pathway since silencing its expression leads to an enhancement of the mitogenic effect of estrogens [85]. As a consequence, the nuclear receptors which positively regulate RIP140 expression (*i.e.* vitamin D [86], progestin [87], androgens [88] and ERRs [89]) have all the potential to inhibit estrogen-induced proliferation. It should be mentioned that this straightforward interference should be counterbalanced by the competition of the different nuclear receptors for a limiting pool of RIP140 protein. Interestingly, such interference should also exist with the other transcription factors targeted by RIP140 (E2F, NFkB…) and further work is necessary to decipher these different levels of cross-talk.

4. CONCLUSIONS-PERSPECTIVES

The interactions between transcription factors and their target genes play a key role in the regulation of cellular processes. These molecular circuitries which control the expression levels of genes are dialoguing with each other and deregulation of these cross-talks is responsible for a variety of pathological events such as cancer. The transcriptional coregulator RIP140 is engaged not only in regulatory feed-back loops but also in repressive cross-talks occurring between different nuclear signaling pathways. RIP140 regulates the transactivation potential of estrogen receptors and E2Fs and is a direct transcriptional target of these transcription factors. Due to rate-limiting cellular levels, a subtle regulation of RIP140 expression (through transcriptional regulation or protein titration) may have important consequences on the other transcription networks targeted by this coregulator. This could be relevant in the case of molecular circuitries involving estrogen receptors and E2F transcription factors such as resistance to endocrine therapies. Another cell parameter which could be impacted by such cross-talks is cell metabolism. RIP140 is a main regulator of cellular metabolic circuitries and some of these regulations may involve cross-talks between E2Fs and nuclear receptors.

The present review mainly focuses on dialogue within the nucleus. However, RIP140 and ERα are also cytoplasmic proteins and further work will be necessary to determine whether RIP140 participates in the regulation of non-genomic action of estrogens and the nature of cross-talks in this cellular compartment. Moreover, additional studies are required to fully decipher the role of the multiple post-translational modifications of the different partners in cross-talk settings. Finally, RIP140 may be involved in the regulation of other signaling pathways which are also interconnected with estrogen receptor pathways such as the Wnt or p53 signaling which have been shown to be important for the resistance to antiestrogens [90,91]. Further genome wide profiling of RIP140 binding sites in breast cancer cells is obviously needed to address these issues.

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