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Non-genomic signaling of steroid receptors in cancer

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Abstract

Steroid receptors (SRs) are members of the nuclear receptor family, which are ligand-activated transcription factors. SRs regulate many physiological functions including development and reproduction, though they can also be involved in several pathologies, especially cancer. Highly controlled cellular responses to steroids involve transcriptional regulation (genomic activity) combined with direct activation of signaling cascades (non-genomic activity). Non-genomic signaling has been extensively studied in cancer, mainly in breast cancer for ER and PR, and prostate cancer for AR. Even though most of the studies have been conducted in cells, some of them have been confirmed *in vivo*, highlighting the relevance of this pathway in cancer. This review provides an overview of the current and emerging knowledge on non-genomic signaling with a focus on breast and prostate cancers and its clinical relevance. A thorough understanding of ER, PR, AR and GR non-genomic pathways may open new perspectives for the development of therapeutic strategies.

Keywords: Estrogen receptor, ER α , progesterone receptor, androgen receptor, glucocorticoid receptor, non-genomic signaling.

1. Introduction

According to the classical model of steroid receptor (SR) signaling, steroids enter in the cells through the plasma membrane, and bind to their receptors located in the cytoplasm. After dimerization and nuclear translocation, these receptors bind to specific binding sites on chromatin and recruit coregulator proteins to trigger the transcription of their target genes. This pathway is called the genomic signaling of SRs (Klinge, 2018).

Alternatively, rapid effects of steroids that cannot be mediated through their transcriptional regulation have been described even before the cloning of the first SRs. Indeed, the occurrence of rapid non-genomic effects of steroids was first mentioned in 1942 by Hans Selye who observed that an intraperitoneal injection of progesterone in rats induced rapid anesthesia (Selye, 1942). Similarly, it has been shown that E₂ induces an increase in cAMP synthesis in the uterus of an ovariectomized rat within 15 seconds (Szego and Davis, 1967) and calcium mobilization in murine endometrial cells within 2.5 minutes (Pietras and Szego, 1977). Several decades later, the deciphering of non-genomic SR signaling began in different physiopathological contexts. Notable works include those of Gametchu et al. which led to the identification of a particular form of the glucocorticoid receptor (GR) located at the cytoplasmic layer of the plasma membrane, mGR, that is involved in glucocorticoid-induced apoptosis in lymphoma and leukemia cell models (Gametchu, 1987; Gametchu et al., 1999).

Since then, numerous studies demonstrated the role of non-genomic signaling, initiated by a pool of SRs located at the plasma membrane or inside the cytoplasm, in various type of cancers. Indeed, extranuclear activities of SRs contribute to the regulation of different signaling pathways, notably MAPK (Mitogen-Activated Protein Kinases) and PI3K (Phosphatidylinositol 3-Kinase)/Akt pathways, well described for their involvement in tumorigenesis. SRs are activated upon recruitment of numerous adaptor proteins with or without enzymatic activities in order to transduce extracellular signals. It should be noted that

a cross-talk between genomic and non-genomic signaling exists (Wilkenfeld et al., 2018). We will herein focus on SRs for which non-genomic events have been reported in cancer, namely estrogen receptors (ER), androgen receptors (AR), progesterone receptors (PR) and glucocorticoid receptors (GR).

2. ER non-genomic signaling

Non-genomic effects of estrogens were shown to rely on several receptors such as ER α , its splice variant ER α 36 (Mahboobifard et al., 2021; Thiebaut et al., 2020), ER β , and a G protein-coupled receptor called GPER (Xu et al., 2019). However, in this latter case, the *in vivo* relevance of GPER on estrogen activation has not been fully demonstrated (Luo and Liu, 2020). In this review, we will thus focus on ER α , ER α 36 and ER β .

2.1. ER α

It has been extensively shown that a limited pool of ER α is located outside of the nucleus, at or close to the plasma membrane of tumoral cells (Levin, 2009). Without hormone stimulation, some reports demonstrated that a small fraction of ER α is palmitoylated at C447, located in the human ER α ligand-binding region (Acconcia et al., 2004). This palmitoylation triggers ER α signaling at the plasma membrane through its interaction with caveolin-1 and the caveolin-binding protein striatin (Lu et al., 2004) (**Figure 1**). Upon estrogen stimulation, ER α is depalmitoylated and triggers downstream phosphorylation cascades through direct interactions with several proteins including Src tyrosine kinases and PI3K (Castoria et al., 2001; Simoncini et al., 2000) (**Figure 1**). Migliaccio *et al.* demonstrated that ER α is phosphorylated on Y537 by Src tyrosine kinases (p56^{lck} and p60^{c-src}) allowing its association with the SH2 domain of Src (Migliaccio, 2000). A six-amino-acid peptide that mimics the sequence around the phosphorylated Y537 residue was shown to disrupt ER α /Src interaction in MCF-7 breast cancer (BC) cell line, inhibiting cyclin D1 expression and cell proliferation (Varricchio et al., 2007). Other regulatory

proteins have also been reported to be part of the non-genomic complex such as the adaptor protein p130^{Cas} (Crk-associated substrate) (Cabodi et al., 2004), and the focal adhesion kinase (FAK) (Le Romancer et al., 2008) (**Figure 1**).

This complex will activate two major pathways regulating cell proliferation and survival, namely Src/MAPK and PI3K/Akt pathways. Indeed, in BC cell lines, estrogen non-genomic signaling is well-known to regulate the expression of proliferative genes like Cyclin D1 (Castoria et al., 2001; Zassadowski et al., 2012) (**Figure 1**). In addition, after estrogen stimulation, Akt was shown to phosphorylate the pro-apoptotic protein BAD (BCL-2 Antagonist of cell Death) leading to its subsequent inactivation and to the release of the anti-apoptotic proteins Bcl-2 and Bcl-XL. By this mechanism, estrogens prevent apoptosis and subsequent cell death of BC cells (Fernando and Wimalasena, 2004) (**Figure 1**). After estrogen stimulation, activation of the PI3K/Akt pathway by ER α can also disrupt the management of DNA damage in BC cells. Akt-dependent phosphorylation of TopBP1 (Topoisomerase II Binding Protein 1), prevents its association with ATR (Ataxia-Telangiectasia Mutated and Rad3-related) and consequently inhibits cell cycle checkpoints and delays DNA repair (Pedram et al., 2009) (**Figure 1**). Additionally, using an ER α -construct devoid of its nuclear localization signal, Azuma *et al.* demonstrated that rapidly after estrogen stimulation, ER α interacts with HDAC6 (Histone DeAcetylase 6) at the plasma membrane. This event induces the rapid deacetylation of tubulin, contributing to cell migration and aggressiveness of BC cells (Azuma et al., 2009) (**Figure 1**). Interestingly, the knockdown of ER α prevents the HDAC6-dependent deacetylation of microtubules and consequently increases the sensitivity of MCF-7 cells to the microtubule-stabilizing agent paclitaxel (Tokuda et al., 2012). This suggest that ER α /HDAC6 interaction could also participates to the development of a paclitaxel resistance in BC cells.

Several years ago, our team identified that the arginine methyltransferase 1 (PRMT1) plays a key role in the formation of the ER α non-genomic complex, ER α /Src/PI3K in BC cells. Indeed,

118 PRMT1 dimethylates ER α on R260, located at the end of its DNA-binding domain. This event
119 is required for the interaction of ER α with Src and the regulatory subunit p85 of PI3K. It should
120 be noted that enzymatic activities of Src and PI3K are also important to maintain ER α
121 methylation and the formation of the complex (Le Romancer et al., 2008) (**Figure 1**).

122 In addition, estrogens trigger a rapid and transient methylation of ER α , suggesting the
123 involvement of a regulatory mechanism. However, having shown that ER α degradation did not
124 rely on its methylation, we hypothesized and demonstrated that the unique arginine
125 demethylase, called JMJD6, rapidly demethylated ER α (Poulard et al., 2014). This in turn led
126 to the disruption of the complex containing ER α /Src/PI3K, terminating downstream signaling
127 (Poulard et al., 2014). Our team also identified a new partner of the ER α non-genomic complex,
128 the serine/threonine kinase LKB1, which is a well-known tumor suppressive gene. When LKB1
129 is sequestered in the complex with methylated ER α /Src/PI3K, it loses its repressive role on the
130 mTor pathway (Bouchekioua-Bouzaghoul et al., 2014) (**Figure 1**).

131 More recently, we found that IGF-1 is also able to trigger ER α methylation *via* PRMT1.
132 Interestingly, PRMT1 constitutively binds to IGF-1R and methylates ER α in response to IGF-
133 1 treatment. This event favors the association between ER α and IGF-1R. Concomitantly, IGF-
134 1 induces an autophosphorylation of IGF-1R on Y1135, which leads to the subsequent
135 activation of adaptor proteins such as Shc and IRS1 that regulate ERK1/2 and Akt pathways,
136 respectively. The role of PRMT1 in the IGF-1 pathway is crucial as evidenced by PRMT1
137 knockdown which strongly diminishes downstream Akt and MAPK signaling. Hence, targeting
138 PRMT1 could represent a valuable strategy to concomitantly impact estrogen and IGF-1
139 pathways (Choucair et al., 2019) (**Figure 1**).

140 To establish whether ER α non-genomic pathways play a relevant role in cancer, we studied
141 ER α methylation (using an antibody that specifically recognizes metER α), as well as ER α /Src
142 and ER α /PI3K interactions, by proximity ligation assay in a cohort of 175 breast tumor samples.

Of interest, we found that the ER α /Src/PI3K complex occurs in normal breast and is highly expressed in a subset of breast tumors. In addition, the expression of the complex is correlated with activation of the downstream effector Akt. Survival analyses revealed that a high level of expression of this complex is an independent marker of poor prognosis associated with reduced-disease-free survival (Poulard et al., 2012). Then, as PI3K/Akt pathway has largely been associated with resistance to endocrine therapies notably in ER α + /HER2- BC (Araki and Miyoshi, 2018), we speculated that ER α non-genomic signaling could be implicated in this mechanism. Using both *in vitro* and *in vivo* models of endocrine resistance, we found that ER α /PI3K and ER α /Src expression significantly increased in models of resistance to tamoxifen. Of interest, targeting this complex partially restored tamoxifen sensitivity (Poulard et al., 2019). Lastly, we confirmed that ER α /PI3K was a marker of poor prognosis in BC and attempted to target the ER α non-genomic complex *in vivo* using several models of patient-derived breast cancer xenografts (PDXs). After treatment of PDXs with fulvestrant and/or the PI3K inhibitor BYL719 alone or in combination, we found that resistance to fulvestrant was not due to an inefficient targeting of nuclear ER α , but rather to a defect in disrupting ER α /PI3K interaction. However, BYL719 was not able to disrupt the ER α /PI3K interaction, highlighting the need for a better way to target the complex, possibly *via* PRMT1 inhibitors (Jacquemetton et al., 2021). Altogether, these results clearly show that ER α non-genomic signaling plays a crucial role in BC and thus factors involved in this cascade could constitute new biomarkers and targets to treat this pathology.

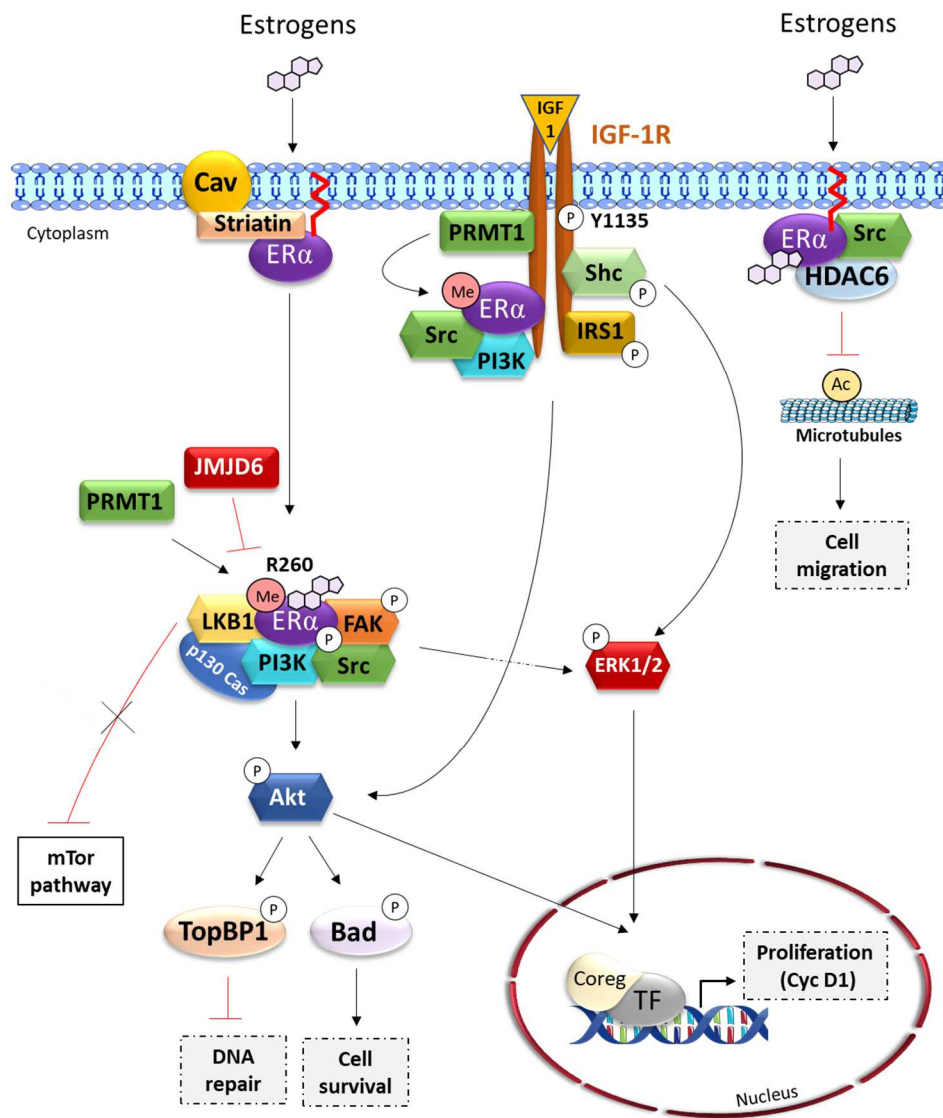


Fig. 1. Non-genomic signaling pathways mediated by ERα

The palmitoylated fraction of ERα is located close to the plasma membrane following its association with the caveolin-1/striatin complex. In response to estrogens, the submembrane form of ERα can be assembled into a complex containing the kinases PI3K and Src, the adaptor protein p130Cas, the focal adhesion kinase (FAK) and the serine/threonine kinase LKB1. This complex activates well-described Akt and MAPK pathways notably for their involvement in the regulation of cell survival, proliferation and DNA repair. Phosphorylation of ERα on Y537 by Src, as well as its dimethylation on R260 by PRMT1, play key roles to regulate the formation

of this non-genomic complex. IGF-1 through its receptor IGF-1R can also trigger ER α methylation *via* PRMT1 and consequently stimulate these pathways. Conversely the arginine demethylase JMJD6 which demethylates ER α disrupts the complex containing ER α /Src/PI3K. Finally, formation of the ER α /Src/HDAC6 complex induces the deacetylation of microtubules that enhances the migratory potential of cancer cells. Ac: acetylation, Cav: Caveolin-1, Coreg: Coregulators, Cyc D1: Cyclin D1, Me: Methylation, P: Phosphorylation, TF: Transcription factors.

2.2. ER α 36

In 2005, a new ER α splice variant, called ER α 36, was identified. This variant is transcribed from an alternative promoter located in the first intron of the *ESR1* gene and shortened by an alternative splicing. These events result in a shorter protein of 36 kDa lacking the transactivation domains AF1 and AF2, with a truncated ligand binding domain and a unique C-terminal region of 27 amino acids (Wang et al., 2005). ER α 36, which possesses three potential myristoylation sites in C and E domains is mainly located at the plasma membrane, where it acts as a key mediator of estrogen non-genomic signaling (Wang et al., 2006). It was demonstrated through *in vitro* (MCF-10A cell line) and *in vivo* (MMTV-ER α 36 mouse strain) models of healthy mammary gland that non-genomic activities of ER α 36 may support the development of a neoplastic phenotype and increase BC risk. Indeed, the expression of this variant is associated with an increase in the survival and the migratory potential of mammary epithelial cells which depends notably on the activation of signaling pathways involving JAK2 and STAT3 (Thiebaut et al., 2017).

ER α 36 is expressed in 40% of BCs independently of the presence of ER α in the nucleus (Shi et al., 2009). Moreover, its expression has been associated with poorer disease-free survival and metastasis-free survival in patients treated with tamoxifen (Shi et al., 2009; Wang et al., 2018).

More recently, a poor prognosis associated with membranous ER α 36 expression was unveiled exclusively in PR-positive BCs (Konan et al., 2020). The link between ER α 36 expression and resistance to tamoxifen is probably due to an agonistic effect leading to a mitogenic signaling that involves ERK1/2 (Zheng et al., 2007). In addition, tamoxifen induces ER α 36 localization in the nucleus where it increases aldehyde dehydrogenase 1A1 expression, a cancer stem cell marker, resulting in an increase in BC metastasis (Wang et al., 2018) (**Figure 2**). Interestingly, it was also demonstrated that the pure anti-estrogen fulvestrant fails to degrade ER α 36 and exerts an agonistic effect as opposed to its action on the canonical form of ER α (Zhang et al., 2012).

In triple-negative BC cells, ER α 36 activates MAPK/ERK by two different mechanisms. First, at the plasma membrane, the ER α 36/Src interaction activates ERK2 which triggers paxillin phosphorylation and nuclear translocation to activate the transcription of cyclin D1. Second, ER α 36 binds directly to phospho-ERK2 impeding its dephosphorylation by the phosphatase MKP3, sustaining ERK2 phosphorylation (Omarjee et al., 2017). Interestingly, the ER α 36/Src complex can also activate EGFR by phosphorylating Y845 and consequently stimulate the MAPK/ERK1/2 pathway (**Figure 2**). This mechanism contributes to the induction of cell proliferation at low E₂ concentrations (Zhang et al., 2011). In parallel, ER α 36 can mediate anti-apoptotic effects of E₂ by stimulating PLC (Phospholipase C)/PKC (Protein Kinase C) and PI3K/Akt pathways. More precisely, activated Akt promotes cell survival by inhibiting c-Jun kinase (JNK) and the subsequent pro-apoptotic signaling. This could notably participate to the development of a resistance to paclitaxel in BC cells (Chaudhri et al., 2014). The ER α 36-dependent activation of the PKC pathway also promotes the metastatic potential of tumor cells by inducing the expression of factors associated with the epithelial to mesenchymal transition, such as Snail1 (Chaudhri et al., 2012) (**Figure 2**).

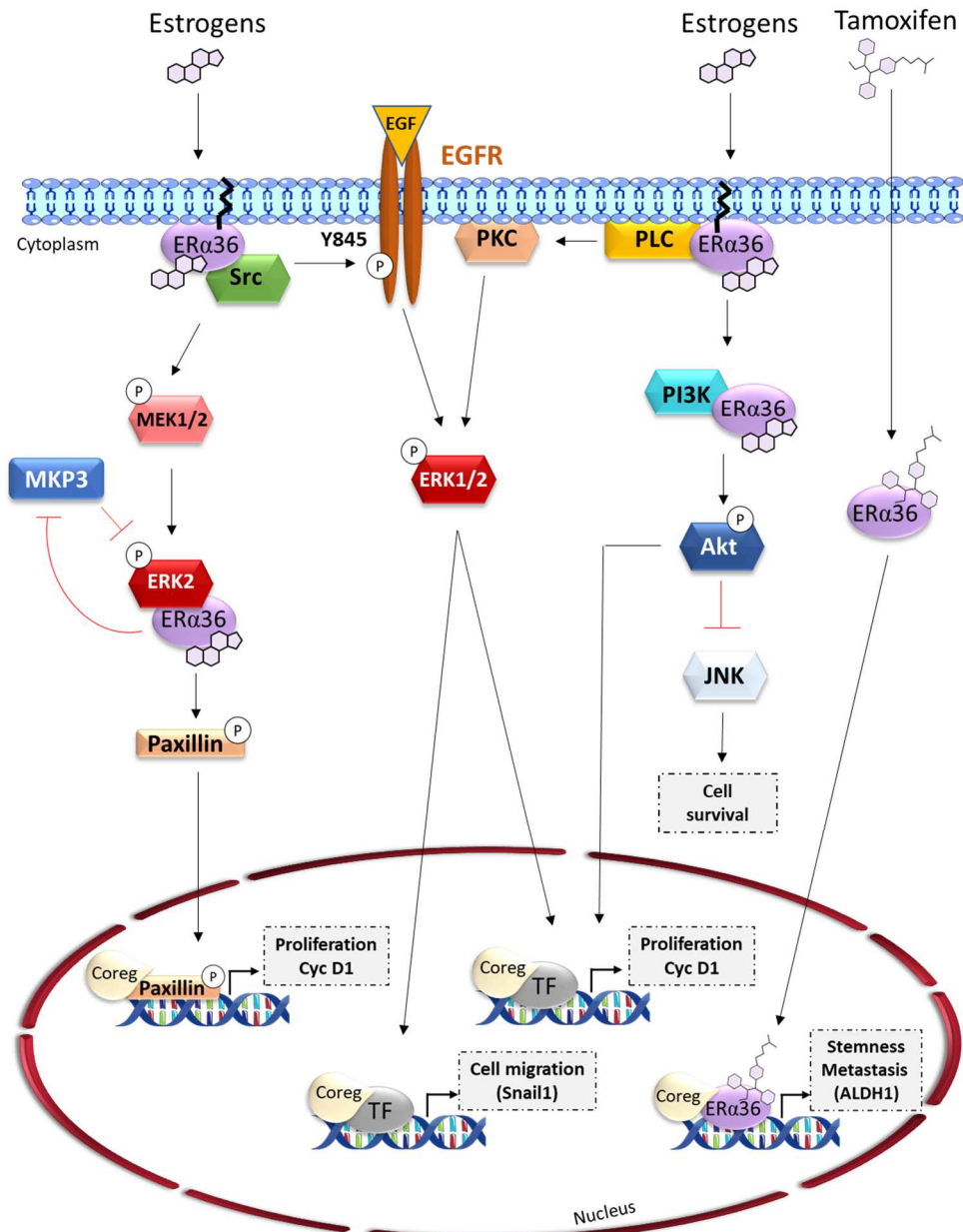


Fig. 2. Non-genomic signaling pathways mediated by ERα36

ERα36 is mainly located at the plasma membrane, owing to post-translational modifications such as myristoylation, and is the main mediator of non-genomic estrogen signaling. Firstly, the estrogen-induced interaction between ERα36 and Src activates ERK2 and triggers the paxillin-dependent transcription of cyclin D1. ERα36 can also interact directly with phosphorylated ERK2 and stabilize it by preventing its dephosphorylation by the phosphatase MKP3. In parallel, Src phosphorylates EGFR on Y845 and consequently induces the phosphorylation of

ERK1/2. Secondly, ER α 36 was described as an activator of PLC/PKC and PI3K/Akt pathways that control the proliferative, migratory and anti-apoptotic effects of this variant. Finally, the anti-estrogen, tamoxifen, can induce a nuclear relocalization of ER α 36 which is associated with an induction of aldehyde dehydrogenase 1A1 (ALDH1) expression, a cancer stem cell marker. Coreg: Coregulators, Cyc D1: Cyclin D1, P: Phosphorylation, TF: Transcription Factors.

2.3. ER β

ER β also acts through non-genomic signaling but its role as an onco-suppressor or as an oncogene is still pending in various types of cancer. Currently, five ER β isoforms (ER β 1-5) resulting from alternative splicing of exon 8, have been identified and differ by their ligand binding abilities (Leung et al., 2006).

In prostate cancer (PCa), although ER β declines with advancing carcinogenesis, its expression is elevated in bone metastasis and correlated with a poor prognosis. One hypothesis is that the ER β 2 isoform which is highly expressed in metastatic PCa acts as an oncogene by repressing the expression of the protective isoform ER β 1 (Nelson et al., 2014). These two isoforms are differentially regulated during cell cycle in LNCaP cells. Unlike ER β 2 which is predominantly expressed in G2/M phase, ER β 1 induces in response to E₂ a cell cycle arrest in early G1 phase through a non-genomic pathway involving JNK. More precisely, the interaction of ER β 1 with JNK is associated with a decreased c-Jun phosphorylation and consequently with an inhibition of the c-Jun/AP1 complex activity that regulates cyclin D1 expression (Hurtado et al., 2008). More recently, Zhao et al. also demonstrated that silencing of ER β in androgen-independent PCa cells, PC3, is associated with an increased ERK1/2 phosphorylation by MEK that promotes cell proliferation, migration, invasiveness as well as resistance to apoptosis (Zhao et al., 2017). In BC, despite a large number of studies listed in the review of Zhou and Liu, the prognostic value of ER β remains unclear even if the majority of the studies suggest that a high ER β

expression is rather associated with a better outcome (Zhou and Liu, 2020). A crosstalk between ER β and the EGFR, IGF-1R and JAK/STAT signaling pathways was described in MDA-MB-231 cells, however there is no clear evidence that it depends of a direct non-genomic effect of ER β (Piperigkou et al., 2016).

Finally, in non-small cell lung cancer, despite conflicting reports, ER β expression appears to be predominant over that of ER α defining ER β as the main mediator of E₂ effects in this model (Wu et al., 2005; Zhang et al., 2009). Although in clinic, ER β expression seems to be associated with a good prognosis as it positively correlates with a lower grade of differentiation and an absence of lymph node metastasis (Schwartz et al., 2005; Wu et al., 2005), various studies demonstrated that *in vitro* ER β stimulates the growth of different non-small lung cancer cells in response to estrogen or to the ER β -specific agonist 2,3-bis(4-hydroxyphenyl)propionitrile (DPN) through the activation of the cAMP, Akt and MAPK pathways (Hershberger et al., 2009; Zhang et al., 2009).

3. PR non-genomic signaling

For several decades numerous studies have reported that progestins stimulate non-genomic signaling pathways involved in the physiological function of the female reproductive tract but also in the progression of certain cancers, such as BC (Daniel et al., 2011; Gellersen et al., 2009). These non-nuclear actions of progestins are partly mediated by membrane progesterone receptors (mPRs) belonging to a family of 7-transmembrane proteins called ‘progesterin and adiponectin Q receptor family’ (PAQR) (Moussatche and Lyons, 2012; Smith et al., 2008). The 3 isoforms of mPRs (mPR α , mPR β , mPR γ) act predominantly as non-canonical G-protein coupled receptors (GPCRs) by activating inhibitory G-proteins and underlying signaling pathways (Dressing et al., 2011; Sleiter et al., 2009; Thomas et al., 2007). It was notably described that, this mPR-dependent signaling is associated with an increased survival of BC

cells (Dressing et al., 2012). In this review we will focus on another mediator of the non-genomic effects of progestins, the classical PR for which cytoplasmic and membrane-associated activities have been described. The non-genomic effects of PR described in the literature are mainly related to the full length isoform PR-B which has a higher cytoplasmic subcellular localization than the N-terminally truncated isoform PR-A (Lim et al., 1999).

In the context of human BC cells, the first described non-genomic effects of PR involved the activation of MAPK pathways and a cross-talk between PR and ER α . More precisely, the synthetic progestin R5020 stimulates in a rapid and transient way the oncogenic Src/p21^{ras}/ERK1/2 signaling pathway in T47D mammary tumor cells to a degree similar to that induced by growth factors such as EGF (Migliaccio et al., 1998). This induction, which also occurs in response to estrogens alone and is inhibited by both anti-estrogens and anti-progestins, relies on the formation of a complex between ER α , PR and Src (Migliaccio et al., 1996; Migliaccio et al., 1998) (**Figure 3**). Modalities that govern the formation of this complex have evolved over the years. Initially, it was described that PR was unable to interact directly with Src. Thus, it was accepted that PR formed a pre-complex *via* its N-terminal domain (NTD) with unliganded ER α and that under progestin treatment ER α could interact with the SH2 domain of Src (Migliaccio et al., 1998). This model was revisited following a study demonstrating the ability of PR to interact directly with the SH3 domain of Src through a polyproline motif in its NTD (Boonyaratanakornkit et al., 2001). However, a third study showed that this interaction between PR and Src (i) fails to activate the Src/Ras/ERK1/2 signaling pathway in the absence of ER α and (ii) is not necessary to activate this pathway in cells that express ER α (Ballaré et al., 2003).

This ability of PR to activate MAPK pathways enables the regulation of cell cycle in BC cells. More precisely, the expression of different cell cycle actors involved in S-phase entry, notably Cyclin D1, Cyclin E and Cdk2, is significantly upregulated in T47D cells after treatment with

306 R5020 and the subsequent activation of the Src/p42/p44 MAPK pathway (**Figure 3**). This effect
307 on proliferation, which is also observed with a transcriptionally-impaired PR (S294A) but
308 reversed with another mutant, PR-B_{mPro}, that is not able to interact with Src, appears to be
309 independent of the transcriptional activity of PR (Boonyaratanakornkit et al., 2001; Lange et
310 al., 1998; Skildum et al., 2005).

311 As described for other SRs, the transcriptional activity of PR differs during cell cycle
312 progression and peaks during the S-phase (Narayanan et al., 2005). Interestingly, in the same
313 study, the authors suggested that PR-dependent non-genomic signaling involving Src/p42/p44
314 MAPK may also be differentially regulated according to cell cycle phases. While in the S-
315 phase, treatment with R5020 induces a total relocalization of PR in the nucleus, in G1-phase,
316 most of the PR pool remains cytoplasmic. Therefore the non-genomic activity of PR-B could
317 rise to its maximum during the G1-phase and contribute to the control of the G1/S restriction
318 point in BC cells (Narayanan et al., 2005). This switch between genomic and non-genomic
319 effects of PR during the cell cycle could help explaining the biphasic effect of progesterone on
320 proliferation that has been observed in different models but for which the underlying
321 mechanisms remain unclear (Groshong et al., 1997; Skildum et al., 2005).

322 The lack of involvement of the PR-A isoform in the activation of this pathway in response to
323 progestin was demonstrated by Boonyaratanakornkit *et al.* This lack of effect was attributed to
324 its predominant nuclear localization and to the absence of the NTD domain necessary for its
325 interaction with both ER α and Src (Boonyaratanakornkit et al., 2007). Although most hormonal
326 treatments used in BC target ER α , Sartorius *et al.* demonstrated that the PR-A isoform increases
327 the sensitivity of T47D cells to tamoxifen, whereas PR-B is associated with a resistance to this
328 treatment, suggesting that non-genomic PR-B signaling may participate in the development of
329 resistance to endocrine therapies (Faivre et al., 2008; Sartorius et al., 2003).

In addition, other studies highlighted the involvement of the PI3K/Akt pathway in non-genomic effects of PR. For instance, the synthetic progestin medroxyprogesterone acetate, MPA, induces a rapid phosphorylation of Akt in various BC cell lines, notably in T47D cells (Carnevale et al., 2007; Saitoh et al., 2005; J. Wu et al., 2005). Interestingly, this effect has also been demonstrated in the LM3 murine metastatic mammary tumor cell line, which lacks ER α expression (Carnevale et al., 2007). This suggests that the initiation of the PI3K/Akt pathway by progestins is not dependent on the ER α /PR cross-talk but relies on a direct interaction between PR and the SH3 domain of the subunit p85 of PI3K (Boonyaratanakornkit et al., 2001). At the functional level, the activation of this pathway induces cell proliferation through an NF- κ B-dependent cyclin D1 expression (Saitoh et al., 2005) (**Figure 3**). Additionally, Wu *et al.* demonstrated that natural progesterone induces VEGF (Vascular Endothelial Growth Factor) secretion by T47D and BT-474 BC cells, through PI3K/Akt and MAPK pathways. A crosstalk was identified with the PI3K/Akt pathway that seems to act upstream of the MAPK pathway. It should be noted that MPA also has an impact on VEGF secretion but preferentially in a PI3K/Akt dependent manner. This effect, which also involves the transcription factor Sp1 may contribute to the initiation of the angiogenic switch and thus promote BC progression (J. Wu et al., 2005) (**Figure 3**).

Furthermore, the study of Carnevale *et al.* also highlighted a potential role for non-genomic PR signaling in metastasis formation. They demonstrated the ability of LM3 cells transfected with PR or with a DNA-binding mutant, C587A-PR-B, to form lung metastases in Balb/c mice after treatment with MPA. This effect was significantly reversed with LM3 cells transfected with the mutant PR-B_{mPro} that is unable to activate non-genomic signaling. Therefore, this action could be dependent on the activation of the p42/p44 MAPK or PI3K/Akt pathways (Carnevale et al., 2007).

Finally, it was also shown in mouse and human BC models that after MPA treatment, non-genomic PR signaling can induce STAT3 transcriptional activity and thus regulate genes containing a STAT3 binding site (GAS Response Element) in their promoter, but lacking the canonical progesterone response element (PRE). Among these genes we can notably retrieve p21 (Proietti et al., 2005). This effect involves the PR-dependent activation of ErbB-2 and Src that leads to the phosphorylation of the JAK1 and JAK2 kinases, required for the activation of STAT3. The phosphorylation of the latter allows its interaction with PR-B and nuclear ErbB-2, which act as coactivators of the STAT3 transcriptional activity (Diaz Flaqué et al., 2013; Proietti et al., 2005) (**Figure 3**). Interestingly STAT3 can also promote the transcriptional activity of PR itself to regulate the expression of genes, like the Bcl-X gene, that possess a canonical PRE in their promoter (Proietti et al., 2011).

It is important to note that oncogenic effects of the non-genomic PR signaling have been mainly described *in vitro* in BC cell models and in response to synthetic progestins such as MPA. The latter which is classically used in combination with estrogen for hormone replacement therapy is associated with an increased BC risk. However, MPA is also used in clinic to treat endometrial cancer and metastatic BC. These ambivalent effects *in vivo* could potentially be explained by a balance between the progestational and the androgenic properties of MPA, which is also able to bind and activate AR at physiological concentrations (Ghatge et al., 2005). Moreover, there is a controversy regarding the effect of the anti-progestin RU486. Carnevale *et al.* showed that RU486 is unable to induce p42/p44 MAPK and PI3K/Akt pathways in T47D-Y and LM3 cells transiently transfected with human PR, whereas Skildum *et al.* reported that RU486 stimulates the p42/p44 MAPK pathway in T47D-Y stably transfected with PR. These differences may be explained by the level and stability of PR expression in these models or maybe by the ability of RU486 to act as a GR antagonist (Bardon et al., 1985; Carnevale et al., 2007; Skildum et al., 2005).

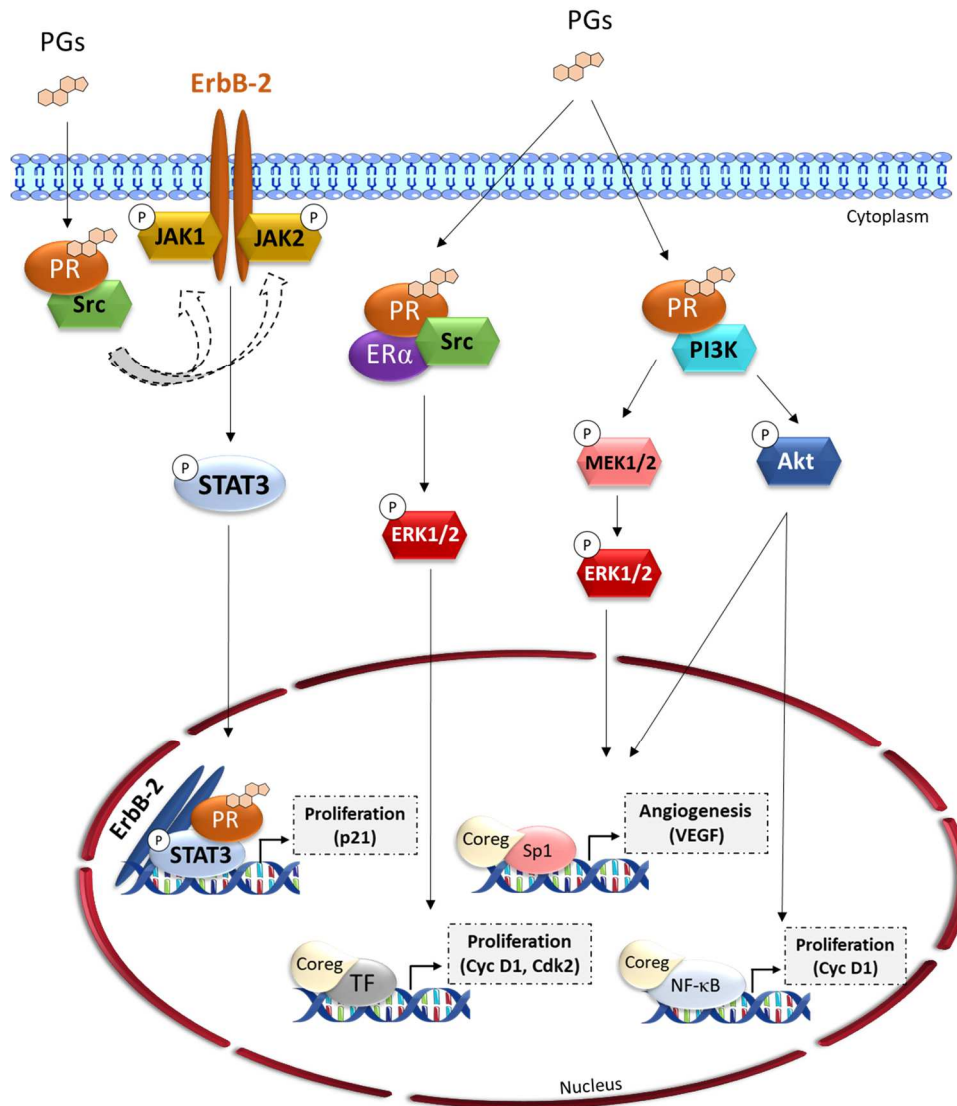


Fig. 3. Non-genomic signaling pathways mediated by PR

In response to progestins (PGs), a crosstalk between PR and ERα allows the recruitment of Src and the subsequent activation of the MAPK pathway which stimulates the expression of different cell cycle activators (Cyclin D1, Cdk2...). PR-dependent activation of the PI3K/Akt pathway may also enhance the proliferation through an NF-κB-dependent increase in cyclin D1 expression and initiate an angiogenic switch by inducing VEGF expression. This expression, which relies on the Sp1 transcription factor, can also be induced by the MAPK pathway. Moreover, STAT3 which is phosphorylated and consequently activated by a PR-initiated signaling cascade involving ErbB-2, Src, JAK1 and JAK2 can form a nuclear complex with PR and ERbB-2 to regulate expression of proliferation genes possessing a STAT3 binding site in

their promoter but lacking the canonical progesterone response element, such as p21. Cdk2: Cyclin-dependent kinase 2, Coreg: Coregulators, Cyc D1: Cyclin D1, P: Phosphorylation, TF: Transcription Factors.

4. AR non-genomic signaling

Similarly to other sex steroids, many of the cellular responses to androgens do not require the genomic activity of the canonical nuclear AR. AR, mostly in a ligand-activated form, associates with various molecular substrates in the cytoplasm and the cytoplasmic layer of the plasma membrane (Leung and Sadar, 2017). These non-genomic AR signals mostly result in the activation of intracellular kinase cascades, essentially PI3K/Akt and MAPK pathways, and the enhancement of cell proliferation and survival (**Figure 4**). They have essentially been described in prostate tissues but could be observed in others, such as in triple-negative BC cells, where assembly of a AR/Src/PI3K complex favors cell invasiveness (Giovannelli et al., 2019). In NIH3T3 fibroblast cells and fibrosarcoma cells, AR was also described to induce migration through non-genomic activation of the Rho-like GTPase Rac1 (Castoria et al., 2003, 2014) (**Figure 4**). These findings have been recently reported in prostate cancer-associated fibroblasts from patients (Di Donato et al., 2021), thus expanding to human cancer specimens the results previously observed in cultured cells. The non-genomic effects of androgens may also include direct actions of hydrophobic testosterone on membrane phospholipids, with the consequent modification in membrane fluidity, as well as interactions with membrane receptors non related to the AR-encoding gene (Heinlein and Chang, 2002; Thomas, 2019).

The first well-known cytosolic interaction involving AR is mediated by an androgen-directed binding of AR to the SH2 domain of the p85 regulatory unit of PI3K (Baron et al., 2004). Phosphorylated Y267 and Y363 residues of the N-terminal domain of AR are required for this interaction, resulting in the activation of the PI3K p110 catalytic subunit, production of phosphatidylinositol-3,4,5-triphosphate (PIP₃), and activation of Akt. This latter will in turn,

415 phosphorylate substrates including the pro-apoptotic BAD protein and forkhead box proteins,
416 such as FOXO that is able to regulate AR expression (**Figure 4**). Of note, the phosphatase and
417 tensin homolog (PTEN), frequently lost during prostate carcinogenesis, transforms PIP₃ into
418 PIP₂ (inactive form), reinforcing the potential clinical significance of this non-genomic AR
419 activity in PCa. It is interesting to note that Akt can phosphorylate AR at S213 and S791
420 residues, thereby increasing AR-mediated nuclear control of target-gene expression (Wen et al.,
421 2000). Such a crosstalk between non-genomic and genomic AR signaling is remarkable because
422 (i) it underlines how fine the AR pathway can be regulated and (ii) it may be one of the
423 mechanisms that help PCa cells to escape androgen deprivation therapy (ADT) in castration-
424 resistant PCa (Leung and Sadar, 2017). Non-genomic AR effects have also been observed in a
425 context of low androgen levels (0.1-10 nM), *i.e.* those obtained under ADT (Unni et al., 2004).
426 Androgens are also well-known to induce cell proliferation by increasing the kinase activity of
427 Src, stimulating the Src/p21ras/ERK pathway in PCa cells (Kousteni et al., 2001; Migliaccio,
428 2000). Direct physical interaction between cytoplasmic AR and membrane Src was first
429 evidenced through coimmunoprecipitation assays (Migliaccio, 2000) and further confirmed
430 using bioluminescent assays (Kim et al., 2007). The involvement of Src in the previously
431 described AR/PI3K complex was also demonstrated in NIH3T3 cells (Castoria et al., 2003).
432 Palmitoylation of AR is likely to play a role in favoring AR plasma membrane anchorage, as
433 observed with other sex steroid receptors (Pedram et al., 2012). Of interest, in the LNCaP
434 prostate cancer cell line, the AR-Src interaction is strengthened when ER β also physically
435 interacts with Src (Migliaccio, 2000). The formation of the AR/Src/ER β tripartite complex,
436 which also associates with EGFR can be induced by EGF (Migliaccio et al., 2005) (**Figure 4**).
437 Moreover, an EGF-dependent interaction between AR, Src and ER α has also been described in
438 MCF-7 and T47D BC cells. In the C-terminal domain of ER α , the phosphorylation of Y537
439 seems to be involved in the Src/AR/ER α complex interaction, while a proline-rich sequence in

the 371-381 region of the AR ligand-binding domain (LBD) was reported as a strong candidate for the association with Src (Migliaccio, 2000; c) (**Figure 4**). Deletion mutant experiments further showed that ER α interacts with the Src SH2 domain, whereas AR binds to the Src SH3 domain (Migliaccio, 2000). Simultaneous interaction of both receptors with the two Src functional domains is thought to relax a constrained Src conformation, leading to Src activation by autophosphorylation. Activation of the Src pathway itself is thought to be responsible for proliferation (S-phase entry) (Guo et al., 2006; Migliaccio, 2000), resistance to apoptosis (Kousteni et al., 2001) and cell invasion (Zarif et al., 2015) notably by activating Raf-1/MEK1/ERK2 pathway, and several transcription factors (Migliaccio, 2000) (**Figure 4**). Because of the multiple cell functions of Src, this non-genomic effect of AR is likely to be partly responsible for key steps of prostate carcinogenesis. This was first demonstrated for cancer initiation using an in vivo prostate regeneration system in which prostate tissue is regenerated by combining the embryonic urogenital sinus mesenchyme and the postnatal prostate epithelium. When overexpressed in this system in conjunction with AR, Src produced sheets of undifferentiated cells with no glandular organization, a characteristic reminiscent of poorly- or un-differentiated PCa (Cai et al., 2011; Zhoul et al., 2005). Other fundamental steps of prostate carcinogenesis are also influenced by AR-Src interaction such as local and metastatic spread, resistance to ADT and ADT-induced neuroendocrine differentiation (Vlaeminck-Guillem et al., 2014). Of note, AR itself can be phosphorylated on serine and threonine residues, and Y534 at least is one of the final Src targets (Guo et al., 2006). Such phosphorylation regulates the nuclear translocation of AR and favors its cell proliferative effects. Moreover, cytoplasmic interactions between Src and AR, which can be observed with low androgen levels, could sensitize AR to low ligand levels and therefore contribute to persistent AR activation during ADT (Guo et al., 2006).

Since Src and AR are both proteins able to engage in multiple protein-protein interactions, it is not surprising to count many proteins as interacting partners regulating their association. Among these interacting proteins, RACK1 (receptor for activated C-kinase 1) and members of EGF signaling (EGFR and erb-B2), which coordinate the AR/Src interaction, illustrate how this complex acts as a means of integrating several membrane-initiated signals (Kraus et al., 2006; Migliaccio et al., 2005).

One particular AR splice variant is included in this list of AR-Src complex-interacting proteins (Yang et al., 2011). Indeed, several independent studies have shown that some AR splice variants, lacking either N-terminal or more frequently C-terminal domains, are expressed in both normal and cancer conditions, sometimes playing an indispensable role in resistance to ADT (Messner et al., 2020). The membrane-bound AR splice variant, named AR8, was identified in castration-resistant PCa cell lines (Yang et al., 2011). Owing to the insertion of a unique 33-aa sequence after the N-terminal domain encoding the first exon, exon 2, responsible for the translation of the first zinc finger, is deleted. Moreover, an alternative exon encodes a specific C-terminal end. Therefore, AR8 lacks a functional DNA-binding domain and cannot behave as a transcription factor similarly to the full-length AR (AR-FL) (Ji et al., 2020). This splice variant was proven to be primarily localized at the level of the plasma membrane, probably through palmitoylation of two cysteine residues in its unique C-terminal sequence. Owing to its intact N-terminal domain, AR8 is able to dimerize with AR-FL and contribute to the EGFR/AR-FL/Src complex formation to promote the Src-mediated AR-FL phosphorylation and subsequent activation (Yang et al., 2011).

Whether other AR splicing variants could engage in non-genomic effects has seldom been explored. While constitutively activated LBD-lacking variants, such as AR-V7 and AR^{v567es}, are nuclear and are unlikely to mediate non-genomic actions (Sun et al., 2010), the N-terminal

lacking AR45 variant, equivalent to ER α 36, could interact with AR-FL and modulate its non-genomic actions (Ahrens-Fath et al., 2005).

Overall, the findings presented above highlight how non-genomic AR-mediated pathways have a potentially major clinical significance. In this context, preventing the formation of AR/Src and/or AR/PI3K complexes and consequently inhibiting their activities could provide new approaches to counteract the deleterious effects of these pathways. Interestingly, whether Src kinase inhibition could be of interest in treating prostate and breast cancers has been and is still under investigation in several trials (Martellucci et al., 2020). As it could be expected, solely inhibiting non-genomic activities does not seem to be sufficiently effective, but promising results are emerging in PCa for combination therapies containing classical ADTs.

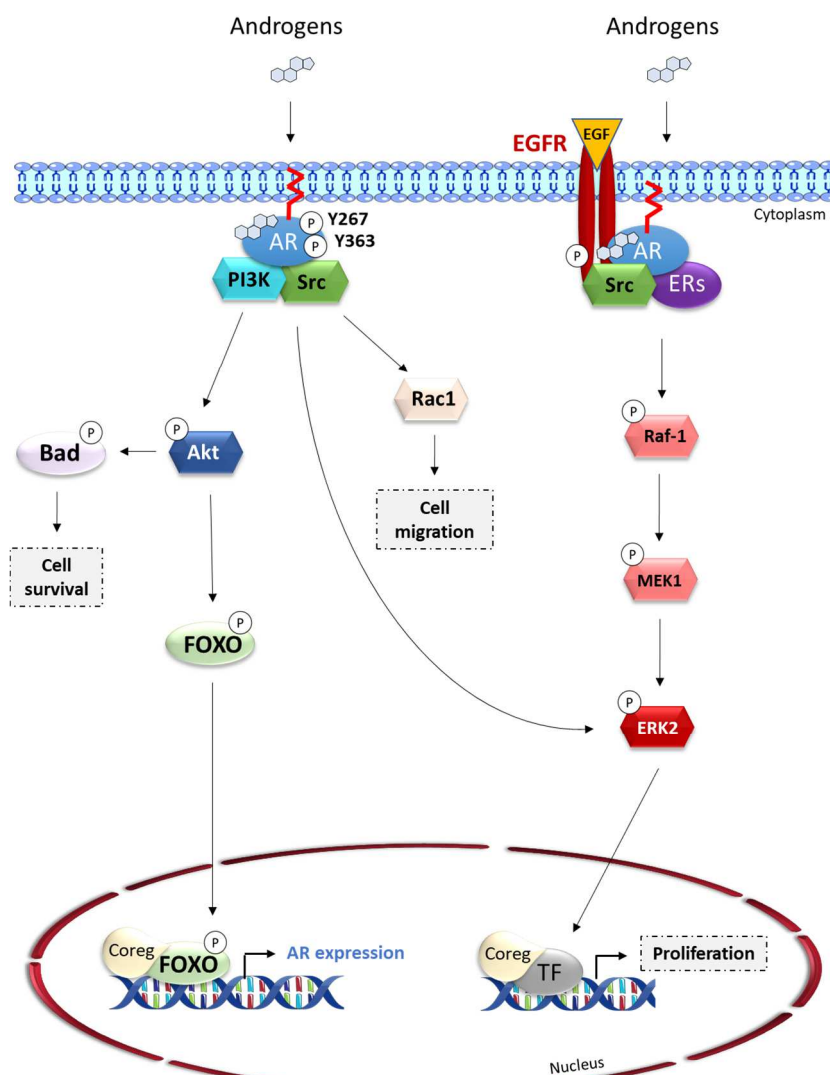


Fig. 4. Non-genomic signaling pathways mediated by AR

Cytoplasmic AR, located close to or even anchored to the plasma membrane (through palmitoylation) can interact, even at low androgen levels, with several proteins such as Src and PI3K. In association with these proteins, AR induces several cytoplasmic pathways including the ubiquitous MAPK and Akt pathways to enhance cell proliferation and/or survival through phosphorylation cascades. Among downstream targets are several transcription factors including FOXO (which notably acts as a regulator of AR expression) or AR itself. In parallel, EGF through its receptor EGFR can induce the formation of a complex involving AR/Src and ERs (ER α in BC cells or ER β in PCa cells). The subsequent activation of the Raf1/MEK1/ERK2 signaling notably controls cell proliferation. Coreg: Coregulators, P: Phosphorylation, TF: Transcription Factors.

5. GR non-genomic signaling

Glucocorticoids (GCs) are essential steroid hormones for human life, regulating genes involved in many different physiological pathways including inflammation and metabolism of glucose, lipids, bone, and muscle (Nicolaidis et al., 2010). Synthetic GCs are widely prescribed to treat autoimmune diseases and many types of cancers and also play important roles in diabetes and metabolic diseases, including regulation of white adipocyte differentiation (Nicolaidis et al., 2010). GCs activate GR, a steroid hormone-regulated transcription factor which activates and represses specific genes. Aside from its well-described genomic pathway, GR is also associated with rapid, non-genomic pathways, and most of these associations have been reported in the context of inflammatory diseases (Panettieri et al., 2019). However, few studies have also characterized non-genomic effects of GCs in cancers.

Two decades ago, Stournaras' lab demonstrated the non-genomic action of GCs in human endometrial adenocarcinoma Ishikawa cells. Synthetic GC, called dexamethasone (dex), was

shown to drive polymerization of actin and stabilization of microfilaments, without any changes in total cellular actin level or actin transcript concentrations (Koukouritaki et al., 1997, 1996). Authors observed that dex-dependent changes in actin cytoskeletal dynamics were associated with rapid changes in cellular cAMP levels, suggesting the involvement of regulatory molecules with kinase activity. They further demonstrated that tyrosine kinase inhibitors, genistein and erbstatin analogue (EA), inhibit dex-induced actin polymerization. In addition, dex rapidly and transiently increased the levels of FAK and paxillin phosphorylation without affecting their levels of expression. In summary, GCs induce changes in the cytoskeleton correlated with rapid tyrosine phosphorylation of the cytoskeleton-associated proteins FAK and paxillin (Koukouritaki et al., 1999).

Different reports demonstrated a functional link between GR and Src or PI3K, by modulating their oncogenic activities. For example, in skin carcinogenesis, GR counteracts the proliferative effects induced by the PI3K/Akt pathway (Leis et al., 2004). As (i) GR was shown to play a tumor suppressive role during mouse skin tumorigenesis (Budunova et al., 2003) and (ii) PI3K and its downstream effector Akt are activated during mouse skin tumor progression (Segrelles et al., 2002), Leis et al. investigated the crosstalk between GR and PI3K/Akt in skin tumorigenesis (Leis et al., 2004). Interestingly, they demonstrated that co-expression of GR and Akt in keratinocytes highly decreased the Akt-driven tumor growth. They found a physical association between GR and the p85 subunit of PI3K, resulting in a decrease in Akt activity. Using a transcriptionally defective GR mutant, authors attributed the down-regulation of the PI3K/Akt activity to non-genomic actions of GR (Leis et al., 2004) (**Figure 5**).

Unlike the findings presented for estrogen, androgen or progestin treatment, GC treatment leads to the dissociation of GR and Src. Without any hormone stimulation, GR is retained in the cytoplasm as a complex including heat shock proteins (*i.e.* HSP90) and several kinases of the MAPK signaling pathway, such as Src (Croxtall et al., 2000; Flaherty et al., 2017; Löwenberg

549 et al., 2006; Marchetti et al., 2003; Pratt and Dittmar, 1998) (**Figure 5**). This was observed in
550 thymocytes, T lymphocytes, A549 lung adenocarcinoma and BC cell lines (MCF-7 and MDA-
551 MB-231). However, GR and Src are rapidly dissociated from HSP90 after dex treatment in
552 A549 cells (Croxtall et al., 2000) and BC cells (Flaherty et al., 2017) (**Figure 5**). In A549 cells,
553 inhibition of GR translocation inside the nucleus prevents the rapid release of GR from the
554 HSP90 complex, but has no effect on the dissociation of GR and Src, and the subsequent
555 activation of lipocortin-1 and release of arachidonic acid in order to regulate inflammation
556 (Croxtall et al., 2000). In BC, authors showed that stress hormones, such as GCs, increase the
557 levels of reactive oxygen species (ROS) and reactive nitrogen species (RNS) that induce DNA
558 damage and reduce DNA repair (Flaherty et al., 2017). It is well documented that Src
559 phosphorylates inducible nitric oxide synthase (iNOS) in BC cells in order to promote nitric
560 oxide (NO) generation (Tyryshkin et al., 2010). Flaherty *et al.* demonstrated that inhibition of
561 Src decreased the GC-dependent induction of RNS production. Because GCs binding to GR
562 lead to the dissociation of GR and Src, these data unveil an indirect mechanism in which GR-
563 mediated signaling regulates iNOS pathways in BC (Flaherty et al., 2017) (**Figure 5**).
564 Finally, some studies demonstrated differences in the efficacy of various GCs to exert non-
565 genomic versus genomic activities (Buttgereit et al., 1999; Croxtall et al., 2002; Lipworth,
566 2000), mostly in the context of anti-inflammatory properties. Such observations could be of
567 utmost importance in the cancer field, if we consider that GCs are frequently used in the clinic
568 to counteract the effects of chemotherapy when treating solid cancers.

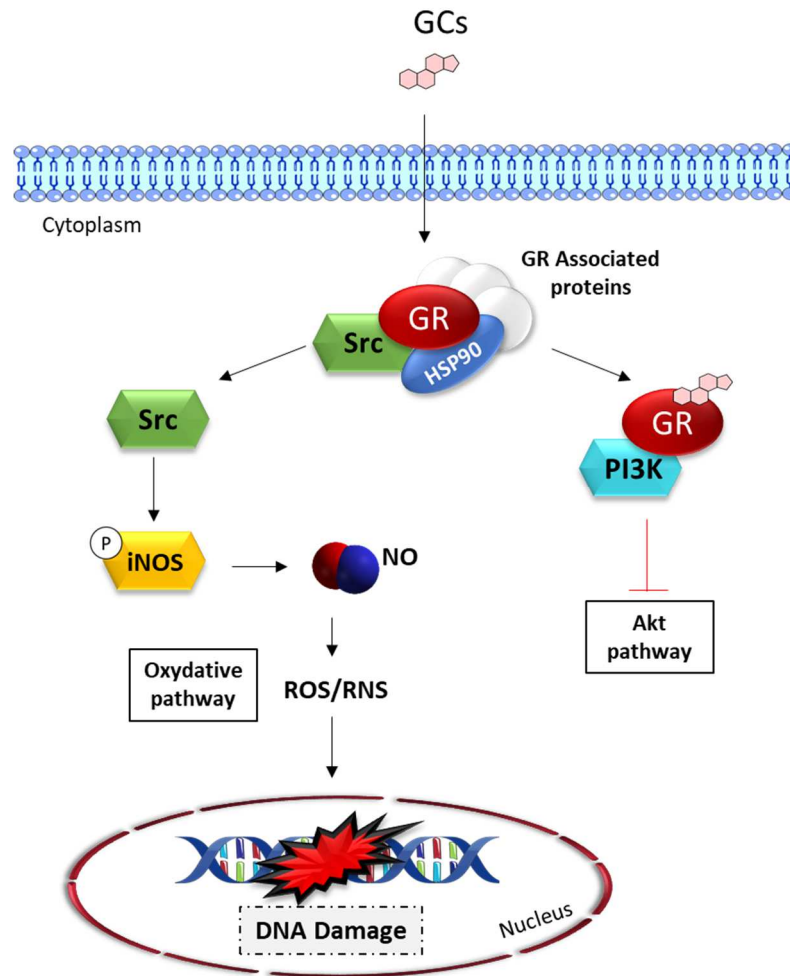


Fig. 5. Non-genomic signaling pathways mediated by GR

Without glucocorticoids (GCs), GR is retained in the cytoplasm in a complex containing at least HSP90. Unlike mechanisms displayed by other steroid receptors, in response to GCs, GR dissociates from Src. In lung adenocarcinoma and breast cancer cells, the release of Src leads to the phosphorylation of iNOS and to the subsequent activation of the oxidative pathway which induces DNA damage. It was also demonstrated in skin cancer that GR can bind to the p85 subunit of PI3K to down-regulate the Akt pathway and consequently decreased tumor growth. iNOS: inducible Nitric Oxide Synthase, NO: Nitric Oxide, P: Phosphorylation, ROS: Reactive Oxygen Species, RNS: Reactive Nitrogen Species.

6. Targeting of the non-genomic signaling of SRs in cancer

Currently, many molecules that modulate the activity of steroid receptors have been identified and some of them are usually used in clinic. We can notably cite the selective estrogen receptor modulator, tamoxifen, used for the treatment of ER α + BC and the anti-androgen, enzalutamide, used to treat PCa but which appears to be also effective on AR+ triple-negative BC in a phase II study (Traina et al., 2018). However, the development of resistance to ER α - or AR-directed therapies is a major clinical problem and the recent advances in the understanding of the rapid non-genomic action of steroid receptors represent a hope for the development of new therapeutic approaches.

Following the model of the peptide coactivator binding inhibitors that prevent the interaction of SRs with their transcriptional coactivators listed in the review by Skowron et al., two peptides designed to block the estradiol- or androgen-induced interaction of ER α and AR with Src and consequently inhibit the underlying signaling pathways were described in literature. The first one is a phosphorylated 6-amino acids peptide corresponding to the sequence surrounding the Y537 of ER α (Varricchio et al., 2007) and the second one is a proline-rich peptide whose sequence corresponds to amino acids 377-386 of AR (Migliaccio et al., 2007). Interestingly, those peptides that do not affect the transcriptional activity of ER α and AR, inhibit the growth of MCF-7 or LNCaP cells xenografts in nude mice, respectively. Another strategy consists in inducing ER α nuclear sequestration by using a Tat-conjugated peptide mimicking the ER α nuclear export sequence that competes with the full length receptor to interact with the nuclear export protein CRM1. This peptide does not affect the transcriptional activity of ER α but it inhibits estradiol-induced S phase entry in MCF-7 BC cells (Lombardi et al., 2008).

Another promising therapeutic agent is the resveratrol, a naturally occurring polyphenolic compounds found in grapes. It has been shown to exert an antiproliferative effect in breast and ovarian cancer notably by targeting the non-genomic signaling of ER α . More precisely,

resveratrol modulates in a dose-dependent manner the ER α -associated PI3K signaling pathway in MCF-7 cells (Pozo-Guisado et al., 2004) and it can also inhibit the crosstalk between ER α and IGF-1R in BG-1 ovarian adenocarcinoma cells (Kang et al., 2013). All together, these data offer many opportunities for further research.

7. Conclusions

The non-genomic signaling of steroid hormones, mediated by specialized membrane receptors or by non-canonical extranuclear functions of SRs, plays a crucial role in the regulation of many cellular functions. Most of the molecular mechanisms of non-genomic effects of SRs notably involve the PI3K/Akt and MAPK pathways, largely described for their participation in the development and progression of various types of cancers (Wilkenfeld et al., 2018). More specifically, extranuclear activities of ER α and PR are mainly described for their involvement in breast tumorigenesis, whereas AR is best known for its association with PCa. Concerning GR, it seems to be an exception, with a repressive effect on the PI3K/Akt signaling pathway in skin cancer and a glucocorticoid-induced dissociation of the GR/Src complex in breast and lung cancers.

A better understanding of these pathways remains an ongoing challenge as they are involved in the development of resistance to different therapeutic strategies like ADT or other endocrine therapies. Underlying mechanisms may include direct activation of the PI3K/Akt and MAPK pathways themselves but also a switch from steroid hormone-dependent to growth factor-dependent tumor growth. As we recently described that the ER α /PI3K complex is associated with poor prognosis and resistance to fulvestrant in BC (Jacquemetton et al., 2021), (i) determining the prognostic value of different signaling complexes involving SR and kinases (*i.e.* Src or ERK) but also (ii) studying their impact on the response to treatments of various cancers, could pave the way for future studies with the opportunity to develop alternative strategies and identify new therapeutic targets.

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