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1 **Non-genomic signaling of steroid receptors in cancer**

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21 **Abstract**

22

23 Steroid receptors (SRs) are members of the nuclear receptor family, which are ligand-activated
24 transcription factors. SRs regulate many physiological functions including development and
25 reproduction, though they can also be involved in several pathologies, especially cancer. Highly
26 controlled cellular responses to steroids involve transcriptional regulation (genomic activity)
27 combined with direct activation of signaling cascades (non-genomic activity). Non-genomic
28 signaling has been extensively studied in cancer, mainly in breast cancer for ER and PR, and
29 prostate cancer for AR. Even though most of the studies have been conducted in cells, some of
30 them have been confirmed *in vivo*, highlighting the relevance of this pathway in cancer.

31 This review provides an overview of the current and emerging knowledge on non-genomic
32 signaling with a focus on breast and prostate cancers and its clinical relevance. A thorough
33 understanding of ER, PR, AR and GR non-genomic pathways may open new perspectives for
34 the development of therapeutic strategies.

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

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43 **1. Introduction**

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

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

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

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

72

73 **2. ER non-genomic signaling**

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

79 *2.1. ER α*

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

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

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

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

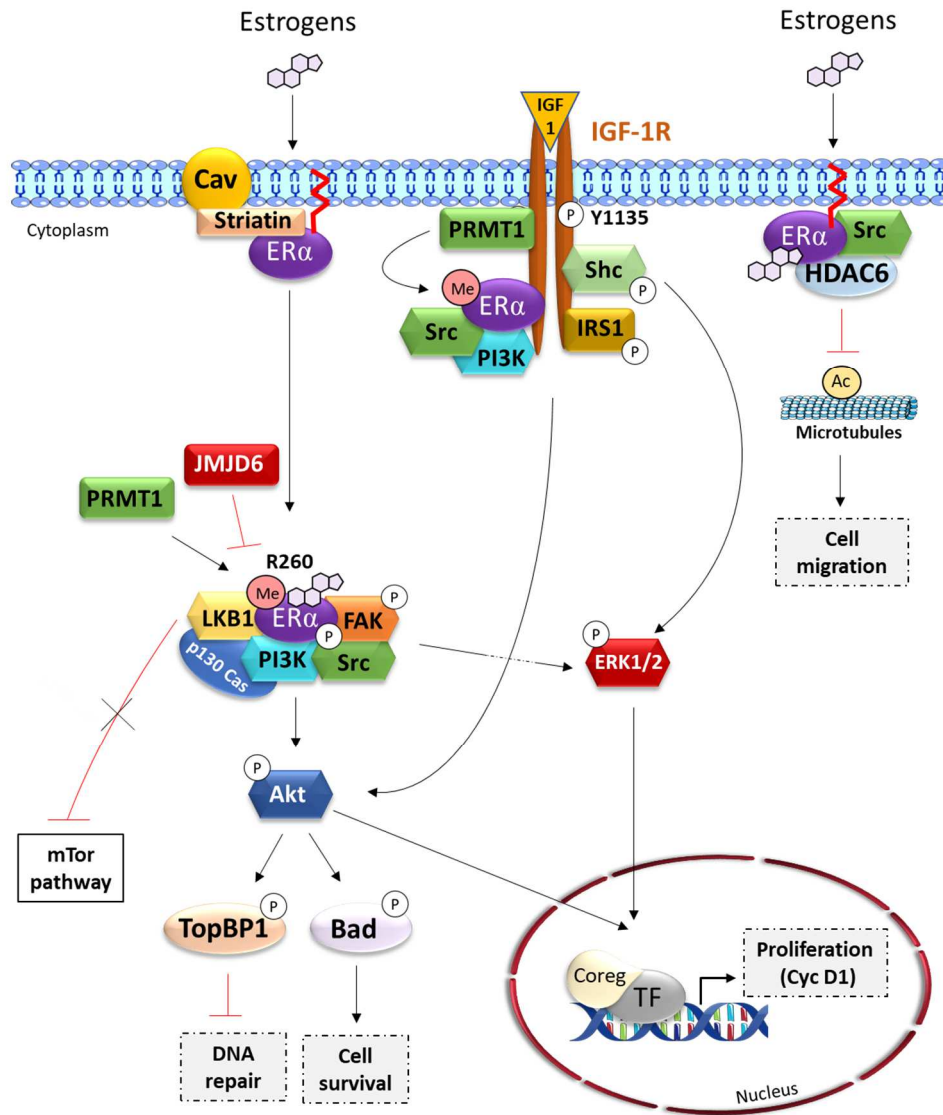
118 PRMT1 dimethylates ER α on R260, located at the end of its DNA-binding domain. This event
119 is required for the interaction of ER α with Src and the regulatory subunit p85 of PI3K. It should
120 be noted that enzymatic activities of Src and PI3K are also important to maintain ER α
121 methylation 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-Bouzaghrou 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.

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



163

164

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

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

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

180

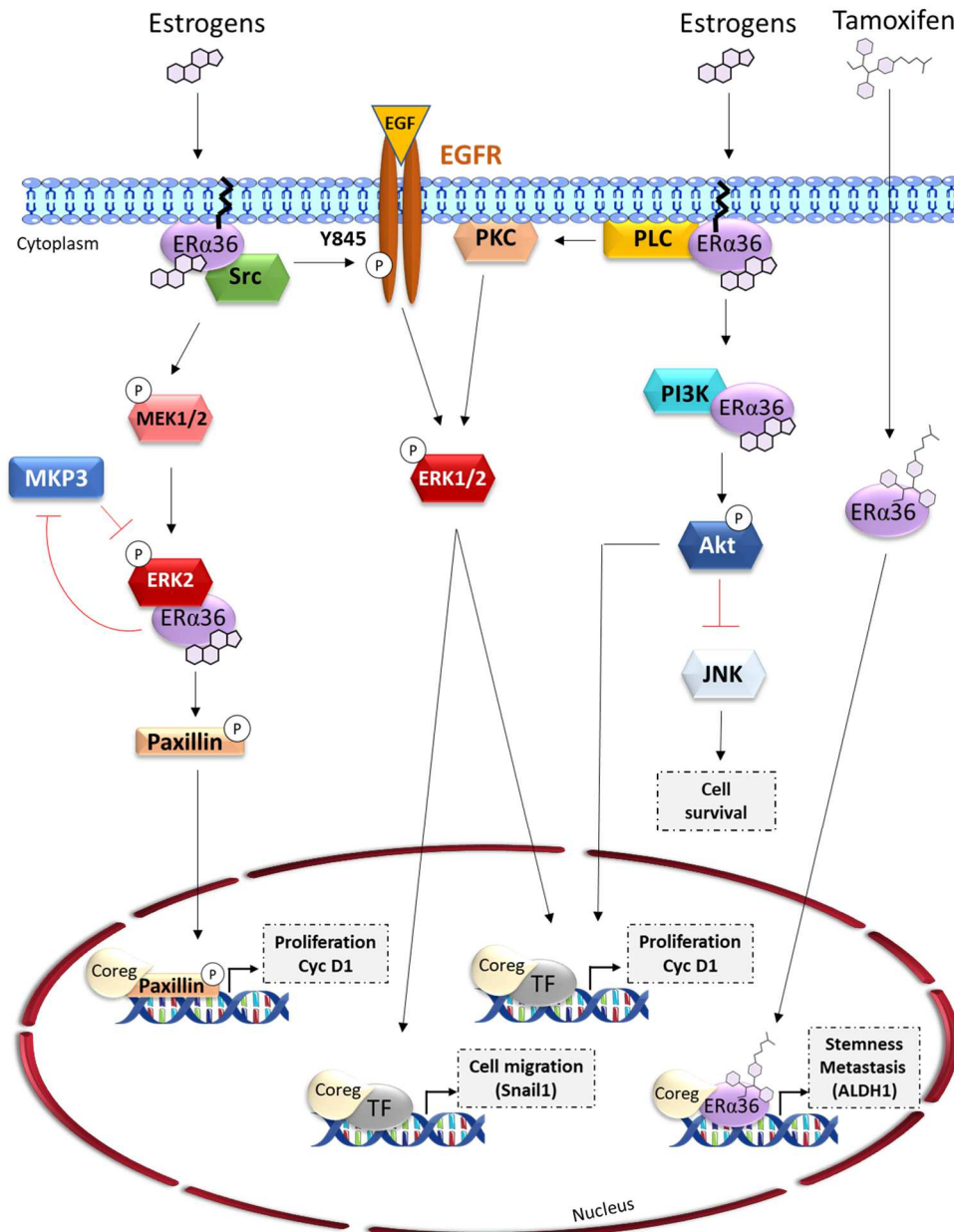
181 2.2. ER α 36

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

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

198 More recently, a poor prognosis associated with membranous ER α 36 expression was unveiled
199 exclusively in PR-positive BCs (Konan et al., 2020). The link between ER α 36 expression and
200 resistance to tamoxifen is probably due to an agonistic effect leading to a mitogenic signaling
201 that involves ERK1/2 (Zheng et al., 2007). In addition, tamoxifen induces ER α 36 localization
202 in the nucleus where it increases aldehyde dehydrogenase 1A1 expression, a cancer stem cell
203 marker, resulting in an increase in BC metastasis (Wang et al., 2018) (**Figure 2**). Interestingly,
204 it was also demonstrated that the pure anti-estrogen fulvestrant fails to degrade ER α 36 and
205 exerts an agonistic effect as opposed to its action on the canonical form of ER α (Zhang et al.,
206 2012).

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



222

223

224 **Fig. 2. Non-genomic signaling pathways mediated by ER α 36**

225 ER α 36 is mainly located at the plasma membrane, owing to post-translational modifications

226 such as myristoylation, and is the main mediator of non-genomic estrogen signaling. Firstly,

227 the estrogen-induced interaction between ER α 36 and Src activates ERK2 and triggers the

228 paxillin-dependent transcription of cyclin D1. ER α 36 can also interact directly with phospho-

229 ERK2 and stabilize it by preventing its dephosphorylation by the phosphatase MKP3. In

230 parallel, Src phosphorylates EGFR on Y845 and consequently induces the phosphorylation of

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

236

237 2.3. ER β

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

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

256 expression is rather associated with a better outcome (Zhou and Liu, 2020). A crosstalk between
257 ER β and the EGFR, IGF-1R and JAK/STAT signaling pathways was described in MDA-MB-
258 231 cells, however there is no clear evidence that it depends of a direct non-genomic effect of
259 ER β (Piperigkou et al., 2016).

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

269

270 **3. PR non-genomic signaling**

271 For several decades numerous studies have reported that progestins stimulate non-genomic
272 signaling pathways involved in the physiological function of the female reproductive tract but
273 also in the progression of certain cancers, such as BC (Daniel et al., 2011; Gellersen et al.,
274 2009). These non-nuclear actions of progestins are partly mediated by membrane progesterone
275 receptors (mPRs) belonging to a family of 7-transmembrane proteins called ‘progesterin and
276 adiponectin Q receptor family’ (PAQR) (Moussatche and Lyons, 2012; Smith et al., 2008). The
277 3 isoforms of mPRs (mPR α , mPR β , mPR γ) act predominantly as non-canonical G-protein
278 coupled receptors (GPCRs) by activating inhibitory G-proteins and underlying signaling
279 pathways (Dressing et al., 2011; Sleiter et al., 2009; Thomas et al., 2007). It was notably
280 described that, this mPR-dependent signaling is associated with an increased survival of BC

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

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

303 This ability of PR to activate MAPK pathways enables the regulation of cell cycle in BC cells.
304 More precisely, the expression of different cell cycle actors involved in S-phase entry, notably
305 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).

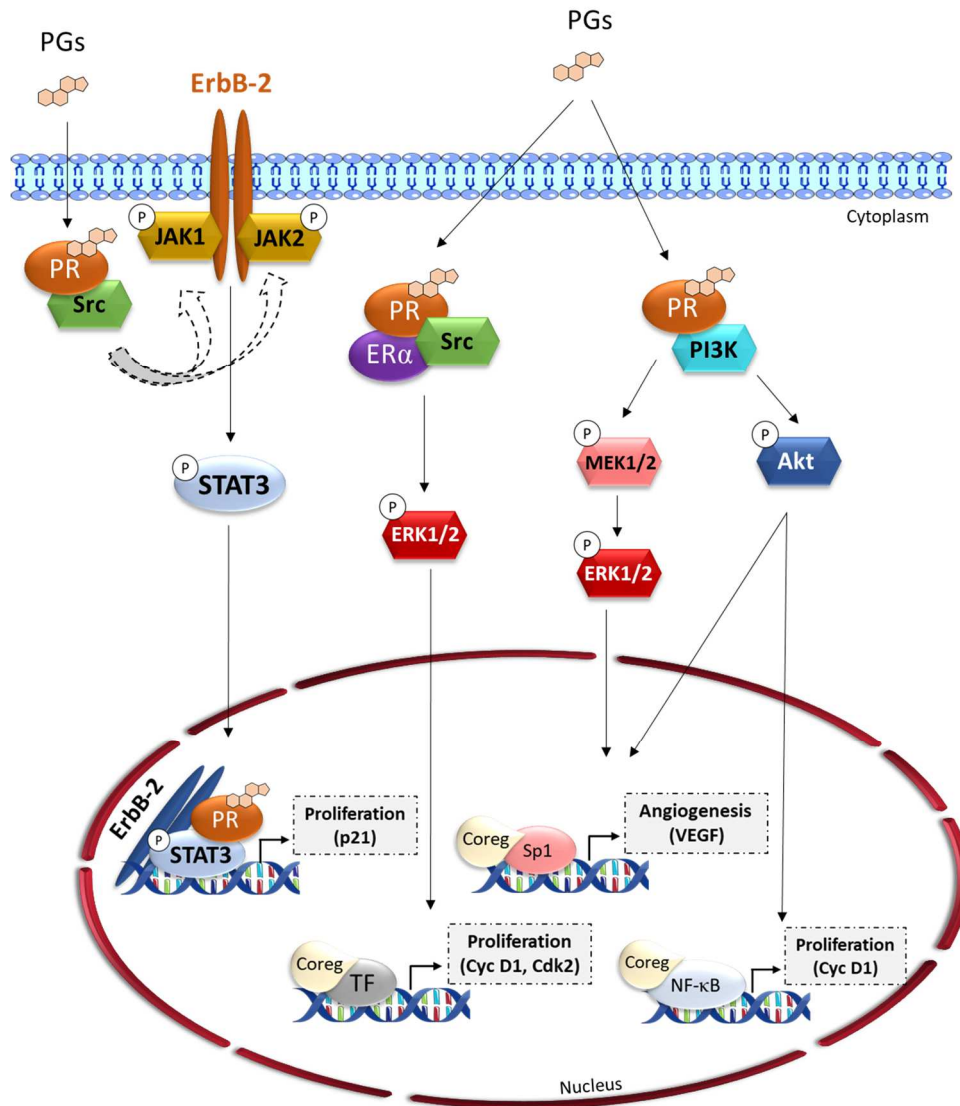
322 The lack of involvement of the PR-A isoform in the activation of this pathway in response to
323 progestin was demonstrated by Boonyaratanakornkit *et al.* This lack of effect was attributed to
324 its predominant nuclear localization and to the absence of the NTD domain necessary for its
325 interaction 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).

330 In addition, other studies highlighted the involvement of the PI3K/Akt pathway in non-genomic
331 effects of PR. For instance, the synthetic progestin medroxyprogesterone acetate, MPA, induces
332 a rapid phosphorylation of Akt in various BC cell lines, notably in T47D cells (Carnevale et al.,
333 2007; Saitoh et al., 2005; J. Wu et al., 2005). Interestingly, this effect has also been
334 demonstrated in the LM3 murine metastatic mammary tumor cell line, which lacks ER α
335 expression (Carnevale et al., 2007). This suggests that the initiation of the PI3K/Akt pathway
336 by progestins is not dependent on the ER α /PR cross-talk but relies on a direct interaction
337 between PR and the SH3 domain of the subunit p85 of PI3K (Boonyaratanakornkit et al., 2001).
338 At the functional level, the activation of this pathway induces cell proliferation through an NF-
339 κ B-dependent cyclin D1 expression (Saitoh et al., 2005) (**Figure 3**). Additionally, Wu *et al.*
340 demonstrated that natural progesterone induces VEGF (Vascular Endothelial Growth Factor)
341 secretion by T47D and BT-474 BC cells, through PI3K/Akt and MAPK pathways. A crosstalk
342 was identified with the PI3K/Akt pathway that seems to act upstream of the MAPK pathway.
343 It should be noted that MPA also has an impact on VEGF secretion but preferentially in a
344 PI3K/Akt dependent manner. This effect, which also involves the transcription factor Sp1 may
345 contribute to the initiation of the angiogenic switch and thus promote BC progression (J. Wu et
346 al., 2005) (**Figure 3**).

347 Furthermore, the study of Carnevale *et al.* also highlighted a potential role for non-genomic PR
348 signaling in metastasis formation. They demonstrated the ability of LM3 cells transfected with
349 PR or with a DNA-binding mutant, C587A-PR-B, to form lung metastases in Balb/c mice after
350 treatment with MPA. This effect was significantly reversed with LM3 cells transfected with the
351 mutant PR-B_{mPro} that is unable to activate non-genomic signaling. Therefore, this action could
352 be dependent on the activation of the p42/p44 MAPK or PI3K/Akt pathways (Carnevale et al.,
353 2007).

354 Finally, it was also shown in mouse and human BC models that after MPA treatment, non-
355 genomic PR signaling can induce STAT3 transcriptional activity and thus regulate genes
356 containing a STAT3 binding site (GAS Response Element) in their promoter, but lacking the
357 canonical progesterone response element (PRE). Among these genes we can notably retrieve
358 p21 (Proietti et al., 2005). This effect involves the PR-dependent activation of ErbB-2 and Src
359 that leads to the phosphorylation of the JAK1 and JAK2 kinases, required for the activation of
360 STAT3. The phosphorylation of the latter allows its interaction with PR-B and nuclear ErbB-
361 2, which act as coactivators of the STAT3 transcriptional activity (Diaz Flaqué et al., 2013;
362 Proietti et al., 2005) (**Figure 3**). Interestingly STAT3 can also promote the transcriptional
363 activity of PR itself to regulate the expression of genes, like the Bcl-X gene, that possess a
364 canonical PRE in their promoter (Proietti et al., 2011).

365 It is important to note that oncogenic effects of the non-genomic PR signaling have been mainly
366 described *in vitro* in BC cell models and in response to synthetic progestins such as MPA. The
367 latter which is classically used in combination with estrogen for hormone replacement therapy
368 is associated with an increased BC risk. However, MPA is also used in clinic to treat
369 endometrial cancer and metastatic BC. These ambivalent effects *in vivo* could potentially be
370 explained by a balance between the progestational and the androgenic properties of MPA,
371 which is also able to bind and activate AR at physiological concentrations (Ghatge et al., 2005).
372 Moreover, there is a controversy regarding the effect of the anti-progestin RU486. Carnevale *et*
373 *al.* showed that RU486 is unable to induce p42/p44 MAPK and PI3K/Akt pathways in T47D-
374 Y and LM3 cells transiently transfected with human PR, whereas Skildum *et al.* reported that
375 RU486 stimulates the p42/p44 MAPK pathway in T47D-Y stably transfected with PR. These
376 differences may be explained by the level and stability of PR expression in these models or
377 maybe by the ability of RU486 to act as a GR antagonist (Bardon et al., 1985; Carnevale et al.,
378 2007; Skildum et al., 2005).



379

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

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

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

393 **4. AR non-genomic signaling**

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

410 The first well-known cytosolic interaction involving AR is mediated by an androgen-directed
411 binding of AR to the SH2 domain of the p85 regulatory unit of PI3K (Baron et al., 2004).
412 Phosphorylated Y267 and Y363 residues of the N-terminal domain of AR are required for this
413 interaction, resulting in the activation of the PI3K p110 catalytic subunit, production of
414 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

440 the 371-381 region of the AR ligand-binding domain (LBD) was reported as a strong candidate
441 for the association with Src (Migliaccio, 2000; c) (**Figure 4**). Deletion mutant experiments
442 further showed that ER α interacts with the Src SH2 domain, whereas AR binds to the Src SH3
443 domain (Migliaccio, 2000). Simultaneous interaction of both receptors with the two Src
444 functional domains is thought to relax a constrained Src conformation, leading to Src activation
445 by autophosphorylation. Activation of the Src pathway itself is thought to be responsible for
446 proliferation (S-phase entry) (Guo et al., 2006; Migliaccio, 2000), resistance to apoptosis
447 (Kousteni et al., 2001) and cell invasion (Zarif et al., 2015) notably by activating Raf-
448 1/MEK1/ERK2 pathway, and several transcription factors (Migliaccio, 2000) (**Figure 4**).
449 Because of the multiple cell functions of Src, this non-genomic effect of AR is likely to be
450 partly responsible for key steps of prostate carcinogenesis. This was first demonstrated for
451 cancer initiation using an in vivo prostate regeneration system in which prostate tissue is
452 regenerated by combining the embryonic urogenital sinus mesenchyme and the postnatal
453 prostate epithelium. When overexpressed in this system in conjunction with AR, Src produced
454 sheets of undifferentiated cells with no glandular organization, a characteristic reminiscent of
455 poorly- or un-differentiated PCa (Cai et al., 2011; Zhou et al., 2005). Other fundamental steps
456 of prostate carcinogenesis are also influenced by AR-Src interaction such as local and
457 metastatic spread, resistance to ADT and ADT-induced neuroendocrine differentiation
458 (Vlaeminck-Guillem et al., 2014). Of note, AR itself can be phosphorylated on serine and
459 threonine residues, and Y534 at least is one of the final Src targets (Guo et al., 2006). Such
460 phosphorylation regulates the nuclear translocation of AR and favors its cell proliferative
461 effects. Moreover, cytoplasmic interactions between Src and AR, which can be observed with
462 low androgen levels, could sensitize AR to low ligand levels and therefore contribute to
463 persistent AR activation during ADT (Guo et al., 2006).

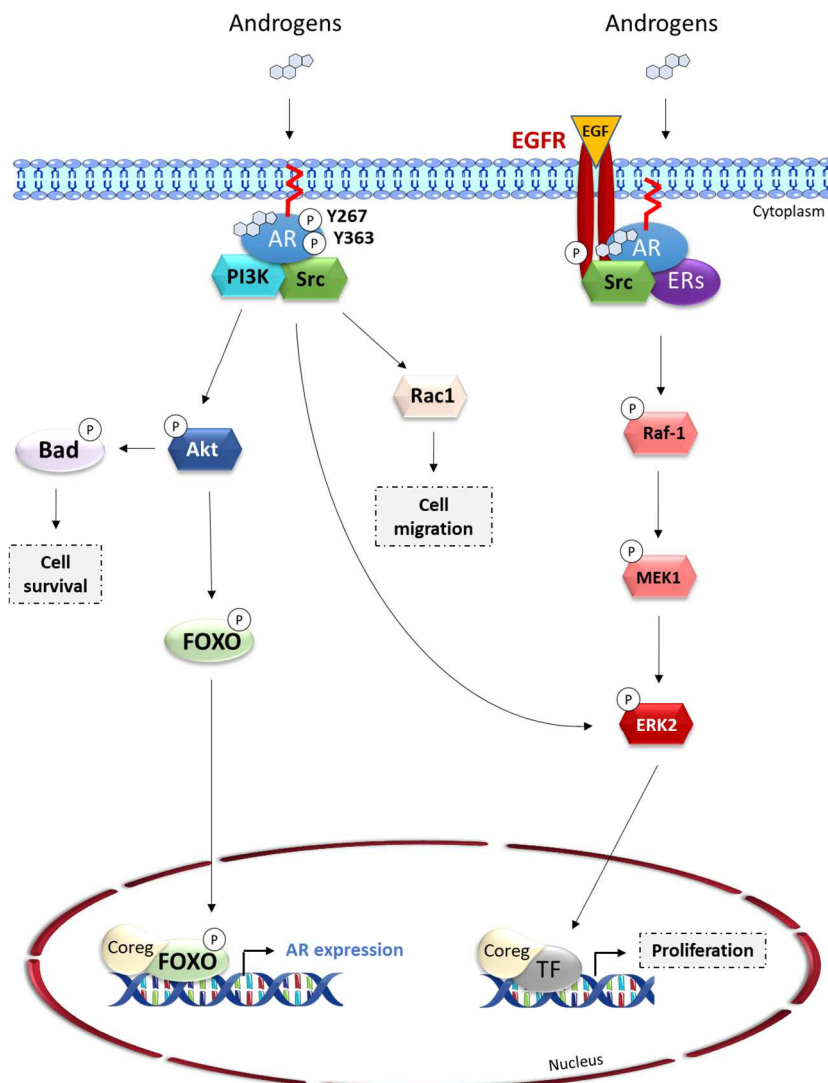
464 Since Src and AR are both proteins able to engage in multiple protein-protein interactions, it is
465 not surprising to count many proteins as interacting partners regulating their association.
466 Among these interacting proteins, RACK1 (receptor for activated C-kinase 1) and members of
467 EGF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

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

485 Whether other AR splicing variants could engage in non-genomic effects has seldom been
486 explored. While constitutively activated LBD-lacking variants, such as AR-V7 and AR^{V567es},
487 are nuclear and are unlikely to mediate non-genomic actions (Sun et al., 2010), the N-terminal

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

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



498

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

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

510

511 **5. GR non-genomic signaling**

512 Glucocorticoids (GCs) are essential steroid hormones for human life, regulating genes involved
513 in many different physiological pathways including inflammation and metabolism of glucose,
514 lipids, bone, and muscle (Nicolaidis et al., 2010). Synthetic GCs are widely prescribed to treat
515 autoimmune diseases and many types of cancers and also play important roles in diabetes and
516 metabolic diseases, including regulation of white adipocyte differentiation (Nicolaidis et al.,
517 2010). GCs activate GR, a steroid hormone-regulated transcription factor which activates and
518 represses specific genes. Aside from its well-described genomic pathway, GR is also associated
519 with rapid, non-genomic pathways, and most of these associations have been reported in the
520 context of inflammatory diseases (Panettieri et al., 2019). However, few studies have also
521 characterized non-genomic effects of GCs in cancers.

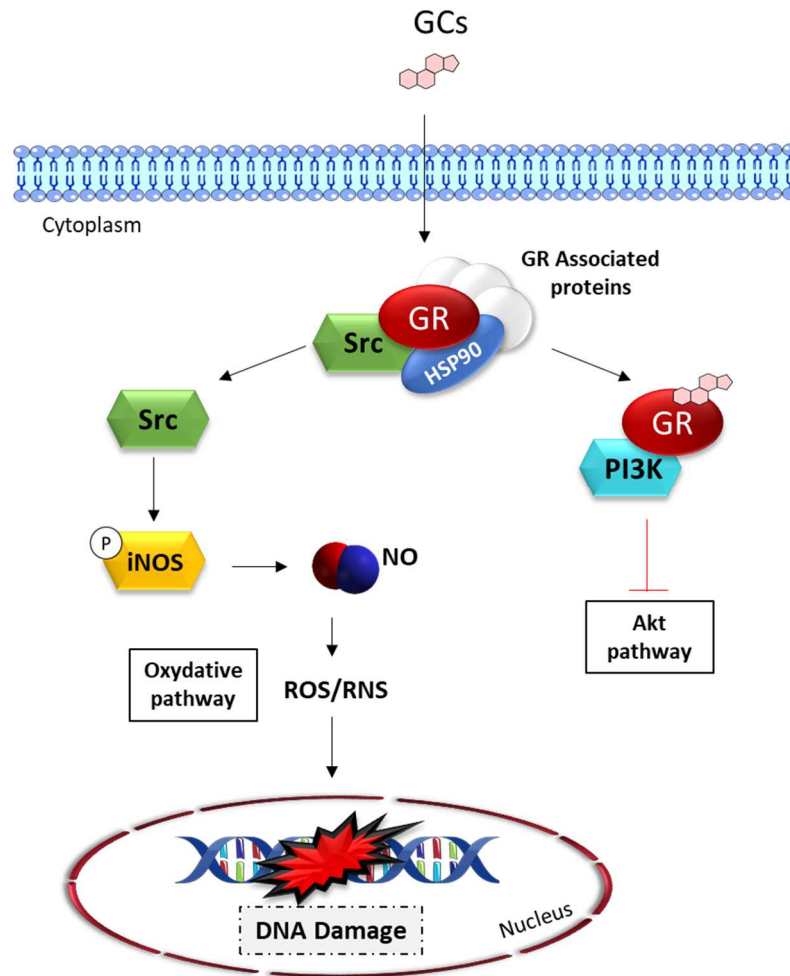
522 Two decades ago, Stournaras' lab demonstrated the non-genomic action of GCs in human
523 endometrial adenocarcinoma Ishikawa cells. Synthetic GC, called dexamethasone (dex), was

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

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

545 Unlike the findings presented for estrogen, androgen or progestin treatment, GC treatment leads
546 to the dissociation of GR and Src. Without any hormone stimulation, GR is retained in the
547 cytoplasm as a complex including heat shock proteins (*i.e.* HSP90) and several kinases of the
548 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.



569

570

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

572 Without glucocorticoids (GCs), GR is retained in the cytoplasm in a complex containing at least

573 HSP90. Unlike mechanisms displayed by other steroid receptors, in response to GCs, GR

574 dissociates from Src. In lung adenocarcinoma and breast cancer cells, the release of Src leads

575 to the phosphorylation of iNOS and to the subsequent activation of the oxidative pathway which

576 induces DNA damage. It was also demonstrated in skin cancer that GR can bind to the p85

577 subunit of PI3K to down-regulate the Akt pathway and consequently decreased tumor growth.

578 iNOS: inducible Nitric Oxide Synthase, NO: Nitric Oxide, P: Phosphorylation, ROS: Reactive

579 Oxygen Species, RNS: Reactive Nitrogen Species.

580

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

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

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

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

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

610 **7. Conclusions**

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

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

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636

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