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Gene Section
Review

PGR (progesterone receptor)

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Abstract

The progesterone receptor gene PGR is located on 11q22.1. The functional gene has 8 exons and 7 introns; the transcript is translated into 933 residues. The protein occurs as three isoforms viz. PR-A; PR-B; PR-C and 11 splice variants. PR-A and PR-B are structurally similar. The function of the splice variants is unclear, although some variants might be translated and others differentially expressed. The nuclear receptor PR isoforms are ubiquitously and uniformly expressed in target tissues. They may show differential expression in neoplasia with progressive changes. In the conventional pathway, PR undergoes conformational changes upon ligand interaction, translocates into the nucleus and binds PREs of responsive genes. PR can also function by non-genomic mode. It can activate the extra nuclear receptors, mPRs and PGRMC1 to influence cell proliferation and invasion via non-canonically routes. Both genomic and non-genomic modes of signaling may determine the relevance and the validity of PR in the progression, prognosis and management of breast cancer. The PR engages several systems, among them are PI3K/Akt/ MAPK and Wnt to influence cell adhesion, proliferation and apoptosis. The ER/PR axis is crucial in breast cancer, where the physiological outcome would be affected by the differential signaling initiated by the canonical and the non-canonical receptors. The crosstalk between the ER/PR axis and the growth factor/PI3K/Akt/mTOR system is also highly relevant. PGR mutations and polymorphism are infrequent in cancers. The polymorphic PROGINS has been linked, not indisputably, with cancer risk. Many SNPs have been identified, mostly inconsequential ones. Some may be related to breast, endometrial and colorectal cancer risk. PR produces good clinical outcome in breast cancer independently of ER. It displays greater correlation than ER with disease progression and prognosis. It may be differentially expressed in benign prostatic hyperplasia and progressive cancer. The expression may reflect androgen-insensitivity. PROGINS is said to increase ovarian cancer risk, but, paradoxically, reduce breast cancer risk. The use of progesterone antagonists or agonists has been advocated. PRs can act as activators or repressors of transcription, necessitating the identification of the functional PR/ER isoforms. Some new progestins, employed in HRT, have been claimed to prevent certain forms of cancer.

Keywords

Apoptosis; Breast cancer , Cancer prevention; Cancer progression and prognosis; Canonical signalling; Cell adhesion; Cell proliferation; Extranuclear receptors; Growth factor/PI3K/Akt/ MAPK; Isoforms; mPRs; Non-genomic signalling; Ovarian cancer; Polymorphism; Progesterone antagonists/agonists; Progesterone receptor gene; PROGINS; Splice variants; Wnt signalling

Identity

Other names: PR**,** NR3C3

HGNC (Hugo): PGR

Location : 11q22.1

Location (base pair)

Start: 101,029,624 bp end:101,130,524 bp reverse strand.

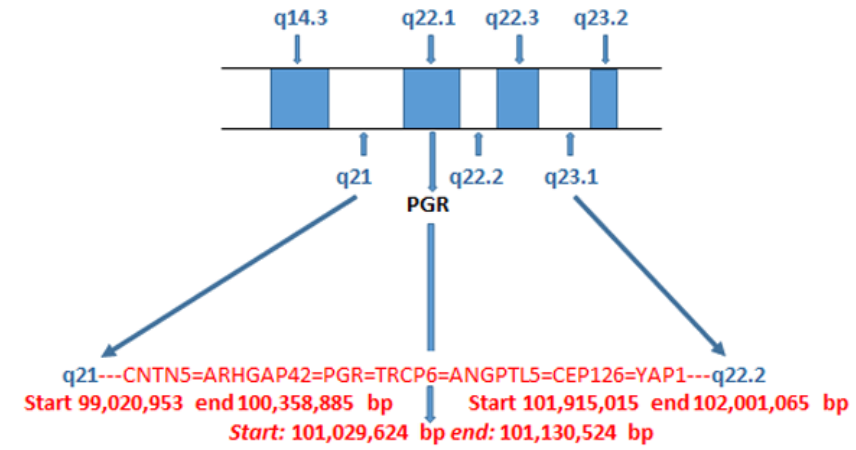

Figure 1: Diagrammatic representation of 11q22.1 with PGR together with local gene sequence. CNTN5: Contactin 5; ARHGAP42: RhoGTPase Activating Protein; PGR: Progesterone Receptor; TRCP: Transient Receptor Potential Cation Channel Subfamily C Member 6; ANGPTL5: Angiopoietin-like Protein 5; CEP126: Centrosomal Protein 12; YAP1: Yes-associated protein 1 of the Hippo signalling system

Exon/Intron	Start	End	Length
Exon 1	101,130,524	101,127,434	3,091
Intron 1-2	101,127,433	101,126,159	1,275
Exon 2	101,126,158	101,126,007	152
Intron 2-3	101,126,006	101,091,877	34,130
Exon 3	101,091,876	101,091,760	117
Intron 3-4	101,091,759	101,062,753	29,007
Exon 4	101,062,752	101,062,447	306
Intron 4-5	101,062,446	101,051,569	10,878
Exon 5	101,051,568	101,051,424	145
Intron 5-6	101,051,423	101,050,060	1,364
Exon 6	101,050,059	101,049,929	131
Intron 6-7	101,049,928	101,042,103	7,826
Exon 7	101,042,102	101,041,945	158
Intron 7-8	101,041,944	101,039,272	2,673
Exon 8	101,039,271	101,029,624	9,648

Figure 2: The figures shows PGR-001 transcript ENST00000325455.9 (not drawn to scale).

DNA/RNA

Description

The functional PGR gene has 8 exons and 7 introns. The 13,748 bps transcript is translated into 933 residues The gene has 11 splice variants. It uses separate promoters and translational start sites in Exon 1 to produce two principal isoforms, PR-A and PR-B (http://grch37.ensembl.org/Homo_sapiens/Gene/Summary?g=ENSG00000082175;r=11:100900355-101001255).

Protein

Description

The isoforms PR-A and PR-B are the products of a single gene. The top Figure 3 shows the use of separate promoters and translational start sites to produce the two principle PR isoforms PR-A (94 kDa) and PR-B (118 kDa). The isoforms contain a DNA binding domain and a ligand binding domain. N-terminal to the DBD is an AF-1 (activation function -1) and in the C-terminal direction a nuclear localisation signal and the LBD containing AF-2. The PR-B isoform has a 164 aminoacid stretch at the N-terminus with an AF-3 (Figure 3c). It is believed that AF-1 is thought to mediate ligand-independent activity, whilst AF-2 is attributed wih ligand-dependent PR activation. The N-terminal inhibitory subdomain of ?155 amino acids is not shown; The inhibitory domain does not function in the PR-B isoform.

AF-1 is about 456-546.

The third isoform is the splice variant PR-C. PR-C can bind the ligand, but in the absence of the DBD would not be able to bind to PREs of target genes.

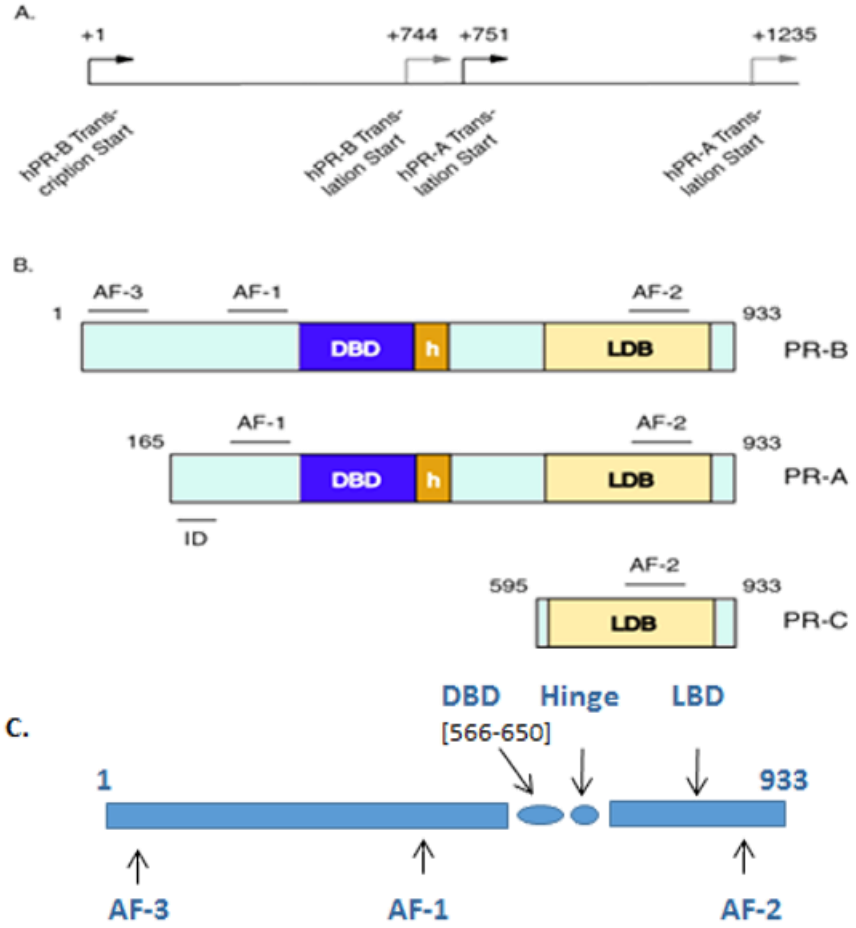

Figure 3: A and B reproduced from Li X, O'Malley B. (2003) by permission from Dr B. O'Malley. berto@bcm.edu. Figure C is based on Wardell et al. (2005). The dimensions of the domain are not drawn to scale.
The domain structure of PR isoforms. DBD: DNA binding domain; LBD: Ligand binding domain; AF-3, AF-1, AF-2: Activation domains

Alternatively spliced variants

Many truncated splice variants of PR are generated and these are not easily detected by standard anti-PR antibodies (Cork et al. 2012) and often specimens may be designated as PR-negative. However, in the absence of firm evidence that these are functionally relevant in the cancer process, the inability to detect them may not be of much consequence.

Besides the three major isoforms, several splice variants of the gene have been identified. These are a result of the deletion of some of the eight exons of PR or by the retention of intronic sequences (see Cork et al. 2008). Two variants were translated into protein and were found to be differentially expressed in the endometrium (Springwald et al. 2010). However, the functional status of the variants is unclear. Variants with the deletion of exons 4, 6 and 4/6 (delta exons), and another one with partly deleted exon 6 have been identified. Their expression was higher in early/mid proliferative endometrium than in the secretory phase (Marshburn et al. 2005).

This suggests that they might be functionally not relevant. For, in the proliferative phase oestrogen induces high mitotic activity in the epithelium and the stroma.

The secretory phase is characterised by the action of progesterone towards the differentiation of the endometrium.

It ought to be pointed out here that the PR delta 4/6 showed a slight difference in expression between 1/45 normal and 5/45 breast cancer tissues of the patients (Nagao et al. 2003). Whilst reports of deletion variants are many, some earlier work has claimed the detection of insertion variants. One such is a variant with a 232 bp nucleotide insertion sequence between exons 4 and 5 in normal endometrium (Yamanaka et al. 2002). However, in the absence of information whether the variant transcript is translated, the inference of a potential relevance in normal or pathological condition of the endometrium is not warranted.

Splice variants: PR-delta4, PR-delta6, PR-delta6/7, PR-T, PR-S, PR-M, PR-i45 (insertion variant) i45a and i45b.

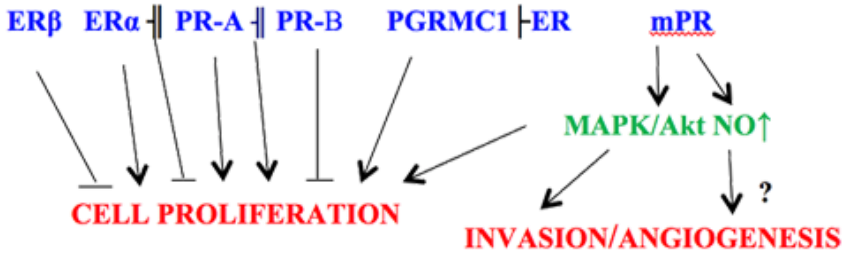

Figure 4: Figure 4 shows the effects of the canonical and non-canonical oestrogen receptor signalling. The isoforms can act as activators or repressors of transcription. PR-A is a ligand dependent repressor of PR-B. The PR-A and PR-B isoforms regulate different sets of target genes. The PR-B isoform is associated with increase in cell migration but not on cell proliferation or survival. PR-B activates many progesterone response genes by activating Src/MAPK signalling pathways, which can promote or inhibit cell proliferation (see also legend below). Progesterone induces endometrial proliferation and angiogenesis via the VEGF route. Both mPR and PGRMC1 can directly interact with progesterone and function independently of PR. PGRMC1 is also able to induce physiological effects by interaction with EGFR. Some of these pathways are not shown here. PGRMC1 : Progesterone receptor membrane component 1.

Expression

PR is expressed ubiquitously in human tissues as homo- or heterodimers. The isoforms are expressed in relatively equal abundance in most target tissues. In the event of neoplastic transformation, the isoforms might be differentially expressed and display progressive changes (see Scarpin et al. 2009).

Function

Function and Signalling

Progesterone signalling generates its physiological effects by the conventional canonical nuclear receptor (PR) pathway and also by the seven-pass membrane receptor (mPR).

The nuclear receptor PR is a transcription regulator. Upon ligand binding the principal isoforms PR-A and PR-B homo- or hetero-dimerize and function as transcription factors. The binding of ligands, agonist or antagonist, initiates a conformational change in PR leading to its translocation to the nucleus and binding to PRE of the responsive genes. The possibility that PR might function via a non-genomic mode cannot be excluded.

The rapidity of some responses to progesterone has suggested the presence of extranuclear receptor, such as the membrane associated mPRs and PGRMC1 (progesterone receptor membrane component 1). The mPRs are GPCRs belonging to the PAQR (progestin and adipoQ receptor) gene family (Tang et al, 2005.

The mPRs and the PGRMC proteins belonging to a different family are encoded by different genes. It has been noted that target cells may respond to progesterone and produce biological effects via the mPRs and the PGRMC1. This would involve the engagement and activation of allied signalling systems that culminate in the phenotypic outcome. The mPRs function like GPCRs and also directly interacts with progestrone. The physiological outcome can occur independently of PR. PGRMC1 can directly interact with progesterone even in the absence of PR. The present indications are that both increase cell proliferation and migration. In fact, PGRMC1 may also facilitate cell proliferation and tumour growth. A small molecule inhibitor of PGRMC1 counteracts these effects. This inhibitor also destabilises EGFR expression, which would suggest that the PGRMC1 effects are to mediated by interaction with EGFR (Ahmed et al. 2010a, b). Although cell proliferative signalling does seem to be modulated by mPRs and the PGRMC1, there is a need to resolve whether mPRs and PGRMC1 work in the same phenotypic direction or exert opposing effects. Recent developments make it imperative that the non-canonical mode of progesterone signalling is borne in mind while assessing the validity of PR in breast cancer management. The PR-mediated response to progesterone involves Wnt signalling, PI3K/Akt/ MAPK signalling; the phenotypic outcome is on cell adhesion, proliferation and apoptosis. The ER/PR signalling axis has assumed much significance in the management of breast cancer patients. However, interpretation of their expression and physiological effects are complicated by several factors. The cell proliferation/survival results depend upon the ER/PR signalling axis subject to the provision of which isoform of ER or PR is functional and the recognition that ER does influence PR function. ERα and ERβ are two ER isoforms. ERα is pro-proliferation whilst ERβ is inhibitory of cell proliferation. ERα binds to and downregulates PR. The PR-A promoter does contain an ERE half site/Sp1 binding site and ER does bind directly to this site (Petz and Nardulli. 2000). Three functionally different PR isoforms of PR, viz. PR-A, PR-B and PR-C have been identified (reviewed by Kariagina et al. 2008). High PR-A expression has correlated with tumour relapse and with associated mutations in the breast cancer susceptibility genes BRCA1 andBRCA2 (Hopp eet al. 2004; Mote et al.2004). The differential expression of the isoforms may be due to methylation (Pathiraja et al. 2011).

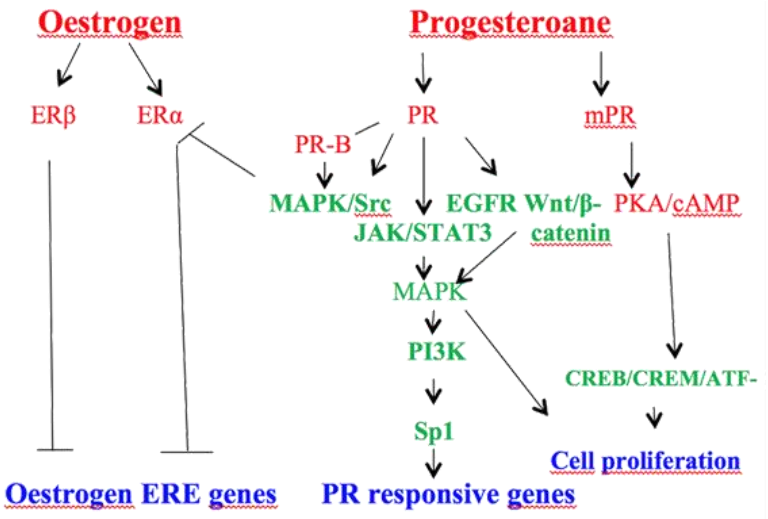

Figure 5: Figure 5 shows the routes of PGR signalling and the crosstalk with the ER signalling pathways and transactivation of EGFR, Wnt/?-catenin (CTNNB1) possibly influencing cell proliferation. This figures shows an additional mPR route to cell proliferation via PKA/cAMP activating the transcription factors CREB / CREM / ATF-1. The earlier figure has not shown this, but has indicated mPR working through the MAPK/Akt and NO route to cell proliferation and invasion. It ought to be noted here that the activation of the MAPK/ ERK1 (MAPK3)/ERK2 (MAPK1) route leads to cell survival and proliferation. The ASK1 (MAP3K5)/JNK/p38 (signalling is a pro-apoptosis route. There is considerable evidence of crosstalk between the ER/PR axis and the growth factor/PI3K/Akt/mTOR system as shown here. This can effectively explain the downregulation of PR. One has to be mindful also of the possibility that PR may be expressed as splice variants that may not be detected by the antibodies that are currently employed for PR assessment. The PR signalling system may engage in crosstalk with neighbouring genes. The YAP/TAZ of the Hippo system is known to target ER/PR. YAP and WBP2 (WW domain binding protein-2) have been shown to transactivate ER/PR (Dhananjayan et al. 2006). The YAP and ER/PR may be co-ordinately regulated in breast cancer. However, it would be necessary to know whether the changes expression of ER and PR occur of their isoforms uniformly or in a differential fashion before any firm conclusions can be drawn concerning how this co-ordination takes place and what the outcome might be.

The PR-A and PR-B isoforms seem to regulate different sets of target genes. PR-B isoform is associated with increase in cell migration but not on cell proliferation or survival. Suppression of PR-B inhibits cell migration. Many publications have reported contradictory phenotypic effects of PR agonists and antagonists. These are most likely the outcome of the differential signalling by the canonical and the non-canonical receptors, which is not often taken into cognisance. The differential signalling is highlighted in Figure 5

The ER/PR signalling axis displays a complex circuitry of interaction and inter-regulation. When ER is non-functional the hormonal response is attenuated. When functional, ER can induce the expression of PR. Equally, PR can regulate ER function. In breast cancer cells, both oestrogen and progesterone can activate the Src/Erk pathway. PR possesses two domains that can interact with the ligand-binding domain of ERα and in this way mediate the activation of Src signalling (Ballaré et al. 2003). In fact, PR may regulate ER function in breast cancer and possibly also negatively regulate other oestrogen-activated signalling to suppress cell proliferation (Mohammed et al. 2015). Besides operating the canonical path of genetic transcription by binding to EREs in responsive genes, the ER can also function in a non-genomic fashion which does not involve direct genetic regulation. ER can influence cell proliferation by the activation of PI3K/MAPK signalling. Also, the G-protein coupled receptor GPCR30 has been recognised as a membrane receptor of oestrogen and the activation of GPCR30 leads to signalling by the non-genomic mode. The oestrogens produce many physiological effects by activating of GPCRs and driving PI3K/Akt and MAPK/ERK signalling. Oestrogens can also upregulate the expression of MMPs and promote invasion. Therefore, the overall outcome would be a result of the balance of activation of the ESR1/PR axis, including the balance of the PR isoforms. This probably applies also to the promotion or inhibition of inflammatory responses. Presumably, this is one of the reasons why so much controversy has surrounded the clinical value of PR in breast cancer, which is nonetheless shown to be a significant factor in patient management (reviewed by Sherbet, 2011, 2017). Another caveat to be considered is that the ER/PR signalling axis may be influenced by neighbouring genes such as the YAP1/ TAZ of the Hippo system.

Mutations

Somatic

PGR mutations are infrequent in cancers; the frequency is around 1% for all cancers. Mis-sense mutations were the most frequent type. The mutation frequency for endometrial cancer, adenocarcinoma of the stomach, cutaneous melanoma, small cell lung

cancer (SCLC), and oesophageal carcinoma was between 2.6% to 4.4% of samples with PAMs (point accepted mutations). The frequency of all PGR mutation for breast cancer was 0.52% and for ovarian cancer 0.32 (IntOGen; www.intogen.org/search?gene=PGR).

Among the many polymorphic forms of the PGR gene is the polymorphism called PROGINS. This has a PV/HS-1 Alu insertion in intron 7 and two point mutations, V660L in exon 4 and H770H in exon 5. The Alu element has a half ERE/Spl binding site, which enhances the transcription function of PROGINS in response to oestradiol (Agoulnik et al. 2004). PROGINS may be associated with enhanced risk of ovarian, breast and prostate cancer (Leite et al. 2008; Govindan et al. 2007; Engehausen 2005). Equally, some studies have denied the link of PROGINS with cancer risk.

Over the past decade several SNPs in the PGR gene have been identified; many are inconsequential ones, but some have been related to possible links to the risk of development of breast, endometrial and colorectal cancers and endometriosis. The SNPs occur in the exons and some in the promoter region of the gene which is thought to have altered the expression of the receptor. These findings have not enabled substantive conclusions regarding their significance to the disease process. The presence of SNPs in the ER genes should also be sought whilst looking any PGR abnormalities. The perceived changes in the expression of PGR transcripts or the proteins cannot be assumed to be a direct consequence of the SNPs in PGR genes. The latter could well be a secondary outcome of alterations in ER.

Implicated in

Breast cancer

Prognosis

ER and PR are invaluable aids in assessing the growth and progression of breast cancer. These receptors are important prognostic markers. The correct functioning of PR seems to be essential for proper growth signalling by ER. In historical perspective, the significance of PR is highlighted by the finding that ER+/PR+ patients have good prognosis and may respond better to hormone treatment than ER+/PR- patients. Combining ER/PR expression with cell proliferation markers is predictive of nodal involvement and 5-year disease free survival (Osborne, 2005; Andronas et al. 2003). Furthermore, ER-/PR+ tumours respond to endocrine therapy better than ER-/PR- tumours. Possibly, PR may produce good clinical outcome independently of ER. Patients with PR+ disease show longer survival (Osborne, 1998; Osborne et al. 2005; Lapidus et al. 1998). A recent report states that post-menopausal women are at greater risk of developing PR-negative ovarian cancer than a corresponding group of pre-menopausal women. The use of oral contraceptives or HRT did not have any influence (Shafrir et al. 2016). However, this study has not differentiated between PR-B and PR-A expression. This is an important provision. They subscribe to the view that the deregulation of ER signalling could have led to the loss of PR. ERα can totally suppress PR signalling and in the absence of ERα, PR-A can inhibit the suppressor effects of PR-B. It is needless to say that the established view is that pre-menopausal women run a higher risk of ovarian cancer than post-menopausal women. But for this generalisation the corresponding information on PR status is not currently available. Also, paradoxically, the situation obtaining in breast cancer is quite the opposite. The use of aromatase inhibitors has no plainly perceived advantage in ER+/PR- breast cancer. Whether the findings have any beraring on the use of these inhibitors in ovarian cancer is debatable.

Purdie et al. (2014) reported that the breast cancer molecular subtype luminal A reflects the best prognosis. Indeed, luminal A consistently shows high PR expression than luminal B (Prat et al. 2014). Caronongan et al. (2016) have analysed ER/PR data derived from both immunohistochemical and ligand binding assays, The IHC-determined PR correlated more significantly than ER with both nodal status and 5-year disease-free survival. Also in ligand binding assays, PR correlated better than ER with survival. A clear differentiation between PR and ER has emerged from this study, with PR displaying greater correlation than ER with disease progression and prognosis.

Cytogenetics

There is very little cytogenetic assessment of the association of PR and ER with chromosomal abnormalities and the prevalence of homogeneusly staining regions. Efforts were made in this regard some years ago. Some reports have claimed correlations of reduced ER and or PR with cytogenetic abnormalities. But no valuable information has accrued so far.

A translocation involving Xq24 of the PGRMC1 locus has been reported to be associated with reduced expression of PGRMC1 (Mansouri et al. 2006).

The deletion of 11q21 is not infrequent in lymphoproliferative disorders and non-Hodgkin's lymphomas. The known translocations involving 11q21 do occur at the identified breakpoints (Fletcher et al. 1993). Whether these affect 11q22.1 is not known. The 11q22-q23.1 region itself does harbour breakpoints at which translocations and deletions occur in hematologicval malignancies including AML and non-Hodgkins lymphoma

(Tanaka et al.2001). Interestingly, a breakpoint has been established which includes the PGR sequence in 11q22.2-q25 (Ben-Abdallah-Bouhjar et al. 2013). Ovarian non-Hodgkin's lymphoma can be ER- and PR-negative (Johansson et al. (2003), but one should hasten to add that there is no suggestion that this is due to the loss of or translocation involving the PR locus.

Genetic recombination, whether in the form of translocations or sister chromatid recombination, tend to occur at fragile sites and these recombinations can include growth factor genes and genes linked with tumorigenesis. Sister chromatid recombination occurs more frequently at the fragile sites. Five fragile sites can be identified in the region 11q13 to q23.3, viz. three common fragile sites FRA11F 11q14.2, FRA11G 11q23.3 and FRA11H 11q13, and two rare folate sensitive fragile site r-FRA11A 11q13.3 and r-FRA11B 11q23.3 (Debacker and Kooy, 2007).

Prostate cancer

Prognosis

High levels of PR have been claimed to correlate with prostate cancer progression. Differential expression has also been reported in benign prostatic hyperplasia and cancer. However, given that ligand activated PR-A can inhibit PR-B effects, it is essential to note this differentiation and appropriately check the status of both isoforms to make a valid conclusion.

A link seems to have been established between PR expression levels and androgen-insensitivity of prostate cancer. The findings appear to suggest that PR could be taking control in the loss of androgen mediated regulation (Detchokul et al. 2015). It has been suggested this could be due to the similarities between the androgen receptor and PR in respect of their DNA binding domain sequences.

Ovarian cancer

Note

The expression of genetic variant PR isoforms and PROGINS has been attributed with alteration of risk of developing ovarian cancer. But, equally, this has been strongly disputed. There is no overwhelming evidence that the isoforms or the PROGINS haplotype expression is associated with gynaecological malignancies. Quite paradoxically, the PROGINS allele has been attributed with enhancing ovarian cancer risk while decreasing breast cancer risk. A similar differentiation has also been claimed in respect of the risk of developing PR-negative ovarian cancer in post-menopausal women. The status of the BRCA genes could be relevant in this context. An illuminating fact that has emerged recently is the association of PR polymorphism in the presence of PROGINS with ovarian cancer risk in a group of patients carrying mutations in the BRCA1 cancer susceptibility gene. Three of the variants which were associated unfavorably with enhanced risk also adversely affected disease-free survival (Tecza et al. 2015). It would be interesting to see such a link exists in breast cancer which has a familial link with ovarian cancer.

At present there is no evidence of an association in cervical neoplasia or uterine fibroids. Mutation at a low frequency and some SNPs have been related to some gynaecological malignancies and breast cancer as stated above.

To be noted

Note

The use of progesterone antagonists or agonists to control cell proliferation is not a new thought. The effects of agonists such as mifepristone, ORG 31710 and onapristone as single agents or in combination with inhibitors of the interacting ER system were investigated some while ago (Klijn et al. 2000). However, a most important obstacle to the proper assessment the outcomes of many subsequent studies is that one has to have accurate information on the functional PR and ER isoforms. PRs can act as activators or repressors of transcription. PR-A is a ligand dependent repressor of PR-B, mPR and ERβ. The prevailing molecular environment is a critical factor.

Mifepristone can inhibit cell proliferation, and downregulate VEGFA expression and suppress angiogenesis (Elmaci et al. 20016). Combination with angiogenesis inhibitors would be an open option.

There has been enhanced interest in mifepristone and its metabolite metapristone as therapeutic agents, given that they can suppress ER and glucocorticoid receptor induced cell proliferation. Mifepristone is also said to influence E-cadherin expression which would suggest possible suppression of invasion. This is claimed to be associated with the suppression of EMT (Yu et al. 2016). Other adhesion dependent modes of action have also been implicated.

These findings vastly strengthen the case for the therapeutic use of the drug.

In a placebo controlled double blind trial disease free progression was noted over a two year period in a third of eligible patients with unresectable meningioma treated with mifepristone (Ji et al. 2015). Onaprinstone also inhibits cell proliferation. However, its hepatotoxicity might have muted the interest in it.

Many clinical trials assessing the effects of mifepristone are underway; the outcome is awaited. The results of trial with ovarian cancer are not encouraging.

Shapiro et al. (2011) have developed small molecular inhibitors that reduce the interaction of ER and AR with DNA. One inhibitor that they have

studied in some detail is 8-((benzylthio)methyl)theophylline (TPBM; 8-benzylsulfanylmethyl-1,3-dimethyl-3,7-dihydropurine-2,6-dione) which decreases ER binding to ERE responsive genes. The structurally related ER inhibitor, p-fluoro-4-(1,2,3,6-tetrahydro-1,3-dimethyl-2-oxo-6- thionpurin-8-ylthio)butyrophenone (TPSF) was markedly more effective It was around 15-fold more potent than the parent compound. It would be interesting to see the phenotypic outcome of combination of these inhibitors with PR inhibitors. This research group has studied the PR inhibitor 6-Thio-8-(2-ethylbutyl)thiotheophylline. This is novel in the sense that it binds outside the PR ligand-binding pocket (Aninye et al. 2012). Largely. such studies have not strayed beyond in vitro tests.

Over the past few years several new progestins have surfaced, mainly for use in HRT. They may have protective effect by opposing cell proliferation induced by oestrogens. Indeed, it has been claimed that some progestins may prevent certain forms of cancer.

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