REVIEW

Peroxisome proliferator-activated receptor gamma and BRCA1

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Peroxisome proliferator-activated receptor gamma agonists have been proposed as breast cancer preventives. Individuals who carry a mutated copy of *BRCA1*, DNA repair-associated gene, are at increased risk for development of breast cancer. Published data in the field suggest there could be interactions between peroxisome proliferator-activated receptor gamma and BRCA1 that could influence the activity of peroxisome proliferator-activated receptor gamma agonists for prevention. This review explores these possible interactions between peroxisome proliferator-activated receptor gamma, peroxisome proliferator-activated receptor gamma agonists and BRCA1 and discusses feasible experimental directions to provide more definitive information on the potential connections.

Key Words

- ▶ BRCA1
- ▶ peroxisome proliferator-activated receptor gamma
- ▶ PPARG agonist
- ▶ breast cancer prevention

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BRCA1, DNA repair-associated gene (*BRCA1*), is one of the most highly associated cancer susceptibility genes, principally with breast and ovarian cancer (Turnbull *et al.* 2018). Currently recommended preventive strategies are primarily surgical (Ludwig *et al.* 2016, Andrews & Mutch 2017) with evaluation of the relative effectiveness of the lifestyle-driven (Lammert *et al.* 2018) and hormonal approaches used, more generally, for reduction of breast cancer risk (Pujol *et al.* 2012, Phillips *et al.* 2013, Dabydeen *et al.* 2015, Alothman *et al.* 2017) considered more investigational.

Molecular studies have identified dysregulation of TNF receptor superfamily member 11a (RANK)/TNF superfamily member 11 (RANKL) and nuclear factor NF-kappa-B p105 subunit (NFKB1) as possible intersecting pathways with *BRCA1* mutation-related breast cancer pathophysiology that may be approachable with pharmacologic chemoprevention (Sigl *et al.* 2016, Kotsopoulos *et al.* 2017, Nolan *et al.* 2017).

Questions arise as to other possible interacting signaling pathways in cancer prevention. Peroxisome proliferator-activated receptor gamma (PPARG), a member of the PPAR family of nuclear hormone transactivators, functions as a heterodimer with retinoid X receptor in normal physiology and development (Derosa *et al.* 2018). It has been characterized as a potential therapeutic target for cancer therapy and prevention (Yun *et al.* 2018).

PPARG ligands have been variously considered as potential chemopreventives as well as cancer therapeutics (Peters *et al.* 2012). This class of drugs is also considered for treatment of diabetes and cardiovascular disease. Considerations of relative efficacy vs potential side- and off-target effects have not only tempered enthusiasm for the drug class but also stimulated the synthesis and investigation of new generation PPARG therapeutic ligands and inhibitors (Ahmed *et al.* 2007, Rubenstrunk *et al.* 2007, Youssef & Badr 2013, Chandra *et al.* 2017). Phase 1 studies of efatutazone, a more recently developed

and highly selective peroxisome proliferator-activated receptor gamma (PPAR γ) agonist that can be delivered orally, demonstrated an acceptable safety profile for cancer therapy, alone and in combination with other drugs (Pishvaian *et al.* 2012, Esteva *et al.* 2013, Smallridge *et al.* 2013, Komatsu *et al.* 2014, Murakami *et al.* 2014). Rosiglitazone was investigated in a pilot study in breast cancer where safety and systemic biological activity were documented, but there was no significant evidence of efficacy (Yee *et al.* 2007).

Experimental animal *in vivo* studies have yielded mixed results on efficacy for cancer chemoprevention with a PPARG agonist. It is challenging to derive a clear answer from these investigations as studies have been performed in a diverse range of rodent cancer models, employed different PPARG agonists, utilized a variety of dosing schedules and were not always investigated as single agents. In addition, pharmacological intervention is initiated at different time points relative to cancer initiation and study durations are mixed. Positive impacts provide support for the principle of PPARG agonist chemoprevention (Kocdor *et al.* 2009, Li & Brown 2009, McCormick *et al.* 2015, Ory *et al.* 2018) but when significant effects are limited to hyperplasia and/or preneoplasia, alterations in cancer histology and/or mean tumor volume, there is less enthusiasm (Borbath *et al.* 2007, Wu *et al.* 2008, Skelhorne-Gross *et al.* 2012, Nakles *et al.* 2013, Bojková *et al.* 2016, Alothman *et al.* 2018). Occasional published studies report no effect at all (Yee *et al.* 2005).

In breast cancer prevention research one of the most highly targeted groups for development of new therapeutic approaches is women carrying a *BRCA1* mutation. *In vitro* and *in vivo* molecular and genetic research provide potential intersecting points for *BRCA1* and PPARG pathways, raising the possibility that *BRCA1* status could influence response to therapy. Some (Pignatelli *et al.* 2003, Subbaramaiah *et al.* 2012, Apostoli *et al.* 2015), but not all (Rogue *et al.* 2010), published data indicates that *BRCA1* expression can be increased by PPARG agonist therapy. Loss of PPARG in mammary adipocytes is reported to reduce *Brca1* expression (Skelhorne-Gross *et al.* 2012). It has been suggested that PPARG agonists could reduce mammary cancer development through inhibition of aromatase expression that would be, at least in part, mediated through PPARG agonist driven *Brca1* upregulation (Margalit *et al.* 2012).

From the other side, PPARG expression is reported upregulated specifically in *BRCA1* mutant breast cancers (Heublein *et al.* 2017). When qualitatively

assessed by immunohistochemistry at the protein level, PPARG remains detectable at the protein level in normal-appearing mammary epithelial cells with *Brca1* exon 11 deletion in combination with *Trp53* germ-line haploinsufficiency, with a relative increase and more uniform expression in adenocarcinomas (Nakles *et al.* 2013). One Phase 1 study showed that higher levels of PPARG correlate with an enhanced therapeutic response to the PPARG agonist efatutazone (Pishvaian *et al.* 2012) although this observation was not replicated in a second study (Komatsu *et al.* 2014). Interestingly, at the RNA level, loss of full-length *Brca1* exon 11 in non-cancer cells is correlated with significantly decreased *Pparg* expression in cardiac muscle and whole mammary gland (Singh *et al.* 2013, Dabydeen *et al.* 2015).

Conclusions

In summary, it is not yet clear whether or not interactions between PPARG and *BRCA1* modify the impact of a PPARG agonist used as a breast cancer chemopreventive. The PPARG agonist efatutazone is effective in significantly reducing mammary hyperplasia in mice with targeted deletion of *Brca1* exon 11 in mammary epithelial cells, but there is no profound effect on invasive cancer incidence (Nakles *et al.* 2013, Alothman *et al.* 2018). However, preservation of one intact *Brca1* allele is sufficient to significantly improve the preventive response. More uniformly positive effects from PPARG agonist exposure are reported in *in vivo* models of mammary cancer with two intact *Brca1* genes (Kocdor *et al.* 2009, Ory *et al.* 2018). This could be an indication that initial levels of endogenous *BRCA1* impact therapeutic response; however, this question still needs to be directly and specifically investigated in order to make a definitive statement (Fig. 1A). For example, therapeutic preventive response could be evaluated in a series of mouse models that develop mammary preneoplasia and cancer in the presence of two intact *Brca1* genes as well as with one and two *Brca1* alleles, perhaps in both the presence and absence of *p53* heterozygosity, to evaluate the impact of specific genetic gain/loss determinants on response to efatutazone. Mammary-targeted *Esr1* and *CYP19A1* overexpression models are possible human pathophysiologically paralleled experimental directions to build *Brca1* deletion models on to explore this question (Jones *et al.* 2008, Alamri *et al.* 2016). Polyoma middle T (PyMT), Wnt, HER2/Neu and simian virus 40 T antigen (TAG) overexpression models are opportunities to pursue

Question 1: Do BRCA1 levels influence the response to a PPARG agonist?

Question 2: Do BRCA1 levels increase following exposure to a PPARG agonist?

Question 3: Do reduced BRCA1 levels result in decreased PPARG expression levels?

Figure 1

Questions to address for a more comprehensive understanding of peroxisome proliferator-activated receptor gamma and BRCA1 interactions. (A) Schematic illustrating the possibility that reduced levels of BRCA1 indicated by the vertical gradient of white to blue might influence the response to a PPARG agonist as indicated by the corresponding vertical gradient of white to orange labeled. (B) Schematic illustrating how the impact of a possible increase in BRCA1 expression levels indicated by the horizontal white to blue gradient mediated by exposure to a PPARG agonist could be determined to be related or unrelated to downstream PPARG agonist activity by experimentally blocking the BRCA1 increase. (C) Schematic illustrating the possibility that reduced BRCA1 levels indicated by the horizontal blue to white gradient could correspond to reduced PPARG levels indicated by the horizontal green to white gradient resulted in a reduced response to a PPARG agonist indicated by the horizontal orange to white gradient.

studies of metastatic disease and interactions with other cancer-linked signaling pathways (Tilli *et al.* 2003, Fantozzi & Christofori 2006). The same ductal carcinoma *in situ* human xenograft model used to demonstrate efatutazone efficacy (Ory *et al.* 2018) could be re-tested with cells engineered to interrupt *Brca1* expression or introduce specific clinically relevant mutations.

A second question is whether or not upregulation of normal full-length *BRCA1* expression levels contribute to

PPARG agonist efficacy (Fig. 1B). Before this question can be clearly answered, researchers, however, need to establish whether or not *BRCA1* expression is, in fact, uniformly and reproducibly upregulated by PPARG agonists. A related issue is whether or not levels of normal *BRCA1* expression are sufficiently upregulated when a second allele contains a *BRCA1* mutation, as occurs in the clinical setting. At present *BRCA1* expression levels have not been uniformly reported in published studies of PPARG agonist

therapy; however, it is possible that potential publication bias against negative or less marked results could have influenced reporting (Diaz-Cruz *et al.* 2006, Mlinarić *et al.* 2017). Disparate results that may have been found could be due to differences between the pharmacology of specific PPARG agonists, dose and schedule, timing of measurement and even acquired differences between cell lines or incorrect cell line identification as authentication of cell lines has only more recently been recognized as an important component of experimental design (Almeida *et al.* 2016). Even after recognizing all these challenges, from an experimental point of view, it is still feasible to design a mechanistic experiment using a panel of relevant normal, premalignant and malignant mammary human epithelial cell lines and primary cells to compare reproducibility of *BRCA1* upregulation in different experimental reagents, establish if there are dose–response relationships, and evaluate both short- and longer-term exposures. Once optimal clinically relevant conditions are established, one could then test if blocking *BRCA1* upregulation would modify impact of PPARG agonist therapy. In cell lines and primary material theoretically this could be accomplished with either genetic deletion of *BRCA1* or siRNA or related approaches with read-out of PPARG agonist activity centering on downstream genes and signaling pathways as well as cellular morphology and behavior.

A third question is whether or not loss of normal *BRCA1* function and/or expression impact PPARG expression levels (Fig. 1C). Published data are insufficient to answer this question as seemingly conflicting initial studies reporting reduced expression in cardiomyocytes and mammary tissue (Singh *et al.* 2013, Dabydeen *et al.* 2015) with loss of full-length *Brc1* and increased levels in human breast cancers carrying a *BRCA1* mutation (Heublein *et al.* 2017) have not yet been rigorously reproduced. Theoretically both observations could be true as loss of full-length *Brc1* is not the same as *BRCA1* mutation, the former studies are in mouse tissues and the later in human tissue, and RNA was examined in the mice and protein in the humans but additional work examining both RNA and protein are needed to clarify the issues. *BRCA1* can play a role in transcriptional regulation (Mullan *et al.* 2006). Understanding the biology could be significant as there have been some suggestions that higher levels of PPARG expression could serve as a biomarker predictive of a positive response to a PPARG agonist (Pishvaian *et al.* 2012). An interesting speculation is whether or not a PPARG-mediated

increase in *BRCA1* expression levels could secondarily be associated with increased PPARG expression levels that would then contribute to an enhanced response to a PPARG agonist. The impact of *BRCA1* deletion on PPARG mRNA and protein expression could be approached utilizing a panel of mammary epithelial cell lines and primary cells representing human normal, premalignant and malignant cells to assess both if PPARG expression levels are altered by loss of mutation of *BRCA1*, and if this occurs reproducibly across different cell lines and stages of cancer development.

Appropriate experimentation in human tissues and *in vitro* and *in vivo* model systems is merited when the promise of current therapeutic PPARG agonists is sufficiently convincing (Ferrari *et al.* 2016, Wang *et al.* 2016, Vella *et al.* 2017). The impact of specific *BRCA1* variants on PPARG expression levels, signaling and downstream gene regulatory networks could be assessed with specific mutation and variant targeting (Findlay *et al.* 2018). Experiments focusing on the impact of functional *BRCA1* haploinsufficiency in the presence of different mutations could be performed (Sedic & Kuperwasser 2016). Biological effects of known PPARG functions related to cell growth and differentiation could be stringently examined in the presence and absence of *BRCA1*. Measurements of downstream gene regulatory networks that follow PPARG activation could be evaluated and compared to determine if there were significant differences correlated with *Brc1* gene dosage in murine cancer prevention models (Savic *et al.* 2016, Alothman *et al.* 2017, 2018).

There are additional questions that could also be approached. For example, the majority of published data to date has focused on RNA expression differences but newly designed studies could examine whether or not PPARG agonists reproducibly increase *BRCA1* protein expression, follow-up with assessment of the biological and/or pathogenic significance and explore protein-based and metabolic interactions. Studies in which *BRCA1* expression levels are deliberately varied should be correlated with assessment of PPARG levels and intentional manipulation of PPARG levels performed to assess how combinations of changes in expression of *BRCA1* and PPARG impact response to specific PPARG agonists. Dose–response experiments might elucidate whether or not response to a PPARG agonist is a threshold event at the cellular level, occurring at the same magnitude once that expression threshold has been reached, even with low versus high PPARG levels, or differentially regulated at different PPARG expression levels. Finally, targeted

mechanistically based molecular studies examining PPARG agonists might also reveal possible opportunities for rational combination therapy for breast cancer prevention (Johnson & Brown 2010).

Declaration of interest

The author declares that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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