Functions of Peroxisome Proliferator-Activated Receptor Gamma (PPARγ) in Gynecologic Disorders

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ABSTRACT: Peroxisome proliferator-activated receptor gamma (PPARγ) is a member of a class of nuclear hormone receptors intimately involved in the regulation of expression of myriad genes that regulate energy metabolism, cell differentiation, apoptosis, and inflammation. Although originally discovered as a pivotal regulator of adipocyte differentiation, the roles that PPARγ plays in gynecological disorders are still unknown. There are a number of studies on the functions of PPARγ and its agonists in gynecological disorders. In this mini-review, we provide a brief summary of the advances in recent years.

KEYWORDS: PPARγ, PPARγ agonists, gynecologic disorders

Introduction

Peroxisome proliferator-activated receptor gamma (PPARγ) is a highly conserved nuclear receptor expressed throughout the body. It has been detected in many tissues in rats,[1] mice,[2] pigs,[3] sheep,[4] and humans.[5] PPARγ controls adipocyte differentiation, glucose metabolism, and lipid homeostasis. The synthetic PPARγ agonists are rosiglitazone and pioglitazone.[6] For more than 20 years, many research reports on PPARγ have been published because of its important roles in the regulation of cellular metabolism, especially in the regulation of lipid homeostasis and energy metabolism. However, apart from established metabolic actions, PPARγ also functions as an inhibitor in several malignant cell lineages.[7] Peter et al demonstrated that PPARγ agonists can induce terminal differentiation, inhibit cell proliferation, promote apoptosis, and inhibit innate inflammation in many cancer models.[8] Although a great deal has been learned about PPARγ related to its function on the therapies of malignant tumors since its discovery, very little is known regarding how this factor affects the female reproductive system. This mini-review describes the way in which PPARγ regulates in the functions of the ovary and uterus and highlights the roles that it plays in the progression of gynecologic disorders and malignant tumors.

PPARγ and Gynecologic Disorders

PPARγ plays an important role in normal ovarian functions. Results from the studies in rats and sheep have shown that the expression of PPARγ protein is unstable. It is downregulated in response to the luteinizing hormone (LH) surge.[4,9] When the expression of PPARγ was disrupted, the females became sub-fertile and took longer to conceive and had smaller litters.[10] But the roles of PPARγ in ovarian steroidogenesis and somatic cell/oocyte interactions, which is the cause of fertility problems in females with reduced ovarian PPARγ expression, are still unknown[11] Rosiglitazone, a PPARγ agonist, could directly affect ovarian functions and enhance the activities of the oocyte. Troglitazone, rosiglitazone, and pioglitazone can induce ovulation, increase the ovulation rate, and promote pregnancy.

The immunoreactivity of PPARγ was not observed in normal ovary tissues, whereas positive staining was seen in ovarian epithelial tumors.[12] Knapp et al found, by immunohistochemical staining, that PPARγ expression was reduced in endometrial cancer (EC). The immunoreactivity of PPARγ protein was significantly lower in endometrial carcinoma than in secretory-phase endometrium ($P < 0.0001$) and endometrial hyperplasia ($P = 0.0015$). Lower immunoreactivity of PPARγ was also detected in proliferative endometrium than in secretory-phase endometrium ($P = 0.0163$) and endometrial hyperplasia ($P = 0.0008$). The results of the immunoreactivity of PPARγ are correlated with those of ERα (estrogen receptor α), ERβ (estrogen receptor β), PR (progesterone receptor), and Ki−67. Relatively low PPARγ expression was found in cervical tumor cells. The extent and intensity of immunoreactive PPARγ in normal cervix tissues were statistically much greater than those in carcinoma tissues. PPARγ mRNA expression

was approximately 2–6-fold higher in normal human cervical tissues than in carcinoma tissues. Therefore, in recent years, more and more studies have suggested that PPARγ is a potentially important player in the treatment of cancers, with some studies suggesting that PPARγ agonists may inhibit cell proliferation in neoplastic cell lines.[13–15] It has been demonstrated that PPARγ agonists play an important role in ovarian carcinoma. The data collected by Vignati et al have suggested that selective PPARγ agonists could be very effective agents against ovarian cancer and should be tested alone and in combination with other molecular-targeted agents or cytotoxic drugs. Tuller et al demonstrated that PPARγ signaling was also involved in the synergistic anticancer activity of clioquinol (5-chloro-7-iodo-8-hydroxyquinoline) and docosahexaenoic acid (DHA) in human ovarian cancer cells.[16] The PPARγ agonists thiazolidinediones (TZDs), such as rosiglitazone (Rosi), ciglitazone (CGZ), troglitazone (TGZ), and pioglitazone (Pio), can induce growth suppression of ovarian cancer cells and induce p63γ- and p73β-dependent apoptosis or growth arrest, leading to enhanced growth inhibition and apoptosis. Several *in vitro* studies have revealed that ciglitizone induces cell differentiation and apoptosis in choriocarcinoma cells.[17] Jung et al further found that ciglitizone-induced growth suppression in cervical carcinoma cells might be associated with the induction of the cyclin-dependent kinases (CDKs) such as p21/Cip1/Waf1 and p27Kip1.[18] STAT3 is known to be involved in the development and progression of many different tumor types, including cervical adenocarcinoma[19] and ovarian cancer.[20] In addition, the activation of STAT3 has a functional role in HPV16-mediated cervical carcinogenesis.[21] Interestingly, a recent paper demonstrated that the activation of PPARγ has a suppressive activity on STAT3.[22] In fact, PPARγ agonists negatively modulate STAT3 through direct and/or indirect mechanisms in cancer cells[23] (Fig. 1).

PPARγ and Endometrial Cancer Correlates with Polycystic Ovary Syndrome

Polycystic ovary syndrome (PCOS) is one of the most common diseases among women. Patients with PCOS always suffer from hyperandrogenism and hyperinsulinemia; the former then disrupts folliculogenesis,[24] and the latter will cause premature follicular atresia and antral follicle arrest.[25] The resulting anovulation also leads to unopposed estrogen production and endometrial proliferation, which leads to an increased risk of endometrial hyperplasia.[26] It is well known that endometrial hyperplasia is a precancerous lesion of EC. There are two major histological types of EC: endometrioid cancer (EEC) and non-EEC.[27] EECs are estrogen–dependent tumors with associated disturbances in lipid and carbohydrate metabolism and infertility. Sex hormones regulate the proliferation, differentiation, and apoptosis in the endometrium.[28] Increased estrogen exposure has long been known to be an important risk factor for EC.[29–32] It is understood that excessive or unopposed estrogen stimulates growth within endometrial tissues, and this has been proven in clinical trials to lead to hyperplasia and significantly increased EC, which spiked during the era of unrestricted estrogen therapy for hormonal replacement.

PPARγ can inhibit the conversion of androgens to estrogens through aromatase.[33] Aromatase is a rate-limiting enzyme in the conversion of testosterone into estrogen and plays a pivotal role in estrogen synthesis.[34] PPARγ can restrain the synthesis of estrogen by inhibiting the transcription process of aromatase. Furthermore, rosiglitazone can decrease the function of estrogen by decreasing the expression of ER to protect the endometrium.[35] Minge et al reported that PPARγ is a key factor regulating follicle quality and also has some role in promoting the development of follicles.[36] The results of in situ hybridization have shown that PPARγ cDNA is highly expressed in immature follicles and gradually reduces during the growth of terminal follicles. Inactivation of the PPARγ gene will affect follicle differentiation.

Tests on mice have confirmed that rosiglitazone can directly affect ovarian function and enhance the activity of the oocyte. Troglitazone, rosiglitazone, and pioglitazone can induce ovulation, increase the ovulation rate, and promote pregnancy. Thus, further reduced estrogen levels through the above ways may prevent the occurrence of EC.

Many *in vitro* experiments have demonstrated that TZDs could reduce insulin resistance by acting directly on pancreatic β-cells. They can also change the gene transcription of regulation on glucose and fatty acid metabolism, thus increasing insulin sensitivity, decreasing insulin concentration, and reducing androgen activity *in vivo* in women with PCOS.[37] Thus, treatments with PPARγ agonists for follicular dysplasia and excessive secretion of estrogen caused by PCOS may prevent EC to some extent (Fig. 2A).

Inhibition of Cell Proliferation

Yang et al reported that the effects of TZDs, such as CGZ and TGZ, cause a decrease in ovarian cancer cell proliferation through a PPARγ-independent mechanism.[38] The effects mainly occurred in the G0/G1 phase of the cell cycle, and also caused an increase of apoptosis by increasing caspase-3 activity and the levels of p53 and Bax protein expression.[39] This observation was partially supported by Linah et al. To investigate whether the effects of antiproliferation and cell-cycle arrest induced by select TZDs were through direct PPARγ transactivation, a dominant negative (DN) form of PPARγ or an overexpression (OE) of a wild-type PPARγ construct was transfected into an Ovcar3 cell line, respectively. The authors found that the PPARγ DN form was insufficient to change Ovcar3 cell proliferation, except when the cells were treated with CGZ and TGZ. These results indicated that the effects of CGZ and TGZ are not PPARγ-dependent.[40] Another PPARγ agonist, rosiglitazone, could inhibit ovarian cancer cell proliferation with G1 phase arrest and promote apoptosis.
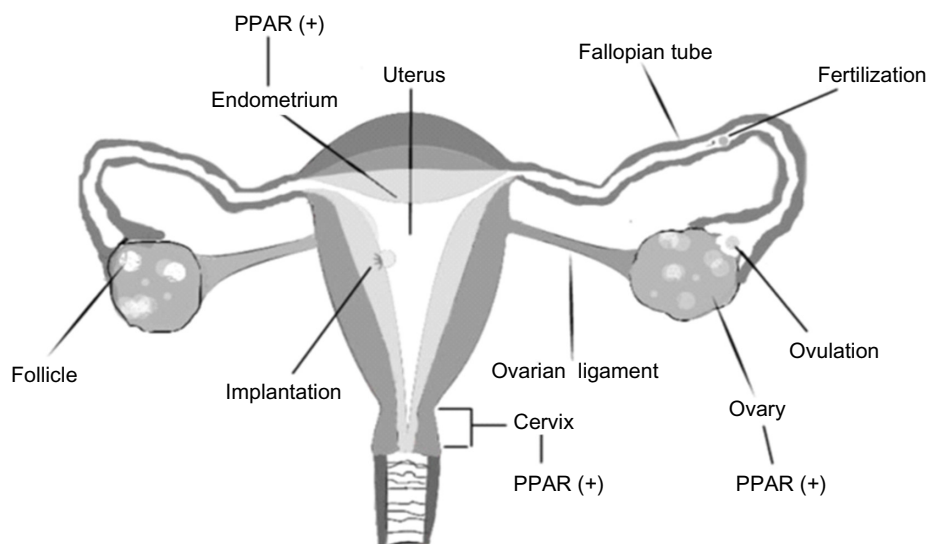
Figure 1. The expression of PPARγ protein in female reproductive system. The immunoreactivity of PPARγ protein detected by immunohistochemical staining was observed in ovary, cervical, and endometrial cells.

The effects of the cell growth inhibition are associated with the downregulation of *c–myc* mRNA and protein expression via the activation of PPARγ.[41]

Benson et al reported that telmisartan functioned as selective PPARγ partial agonist, activating the receptor to 25%–30% of the maximum level achieved by the full agonists such as pioglitazone and rosiglitazone.[23] Telmisartan has been characterized as a PPARγ ligand. It has been reported that telmisartan inhibits estradiol-induced proliferation of ELT-3 cells (a uterine leiomyoma cell line) by acting as a PPARγ ligand. It also inhibits angiotensin II-induced ELT-3 cell proliferation.[42] Koyamas found that telmisartan could
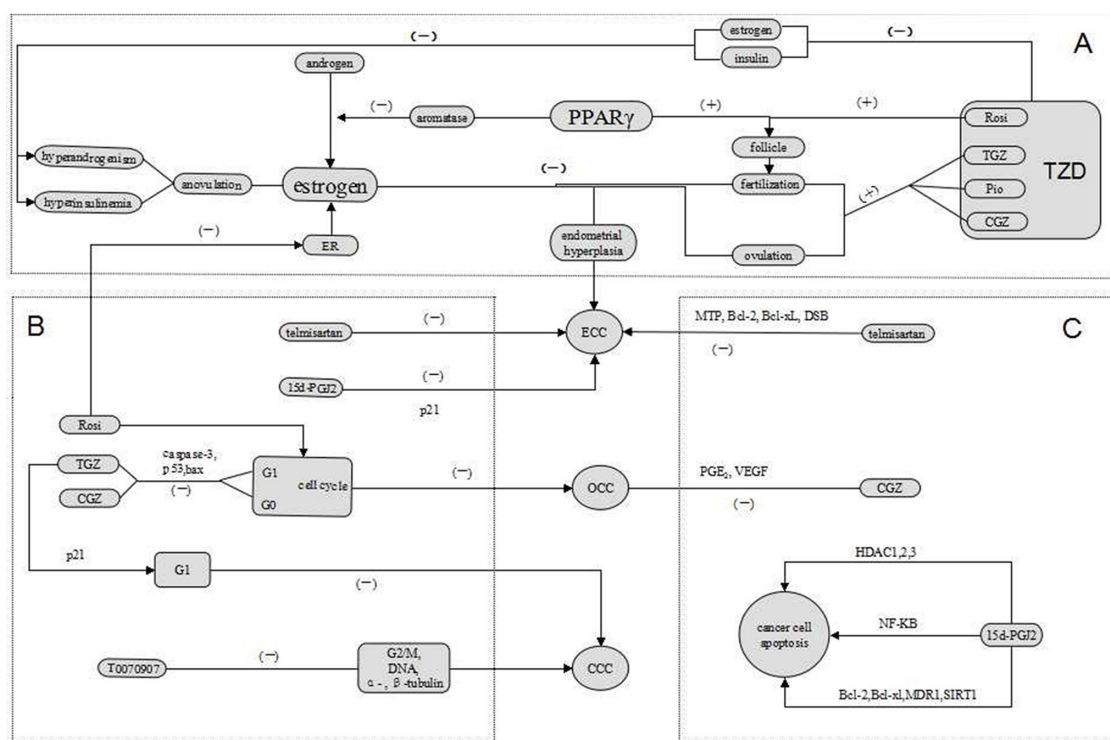
Figure 2. PPARγ functions in female reproductive system. (**A**) PPARγ prevents endometrial hyperplasia via the regulation of estrogen. (**B**) PPARγ inhibits the proliferation of ovary cancer cells (OCCs), endometrial cancer cells (ECCs), and cervical cancer cells (CCCs) via caspase-3, p53, Bax, p21, and α- and β-tublin. (**C**) PPARγ promotes the apoptosis of OCCs, ECCs, and CCCs via MTP, Bcl-2, Bcl-xL, DSB, PGE$_2$, VEGF, HDA1, 2, 3, NF-kB, MDRI, and SIRTI signaling pathways. PPARγ ligands include Rosi, TGZ, CGZ, Pio, 15d-PGJ$_2$, telmisartan, T0070907, and others.

also inhibit the proliferation of EC cells by affecting cellular viability.[43] Ota et al reported that a PPARγ ligand, 15-deoxy-delta-12,14-prostaglandin-J$_2$ (15d-PGJ$_2$), has antiproliferative activity in EC cells (Ishikawa, Sawano, RL95–2 cells).[44] 15d-PGJ$_2$ markedly suppressed cell proliferation in Ishikawa, Sawano, and RL95–2 cells in both dose- and time-dependent manners. The p21 protein is a universal cell-cycle inhibitor binding with cyclin–CDK complexes and proliferating cell nuclear antigen (PCNA), thereby serving as a potent growth inhibitor and an effector of cell-cycle checkpoint.[45] Qta et al suggested that PPARγ also regulates the expression of p21 in endometrial carcinoma tissues. On treatment with 15d-PGJ$_2$, p21 mRNA expression is increased in both dose- and time-dependent manners.[44] Expression of cyclooxygenase-2 (COX-2) plays a key role in tumorigenesis and development. Tumor necrosis factor-α (TNF-α) could increase COX-2 expression via a nuclear factor NF-kB pathway. Sakamoto et al demonstrated that 15d-PGJ$_2$ suppresses the TNF-α-induced COX-2 expression in ovarian carcinoma cells.[46] Jung et al also showed that a large portion of the human cervical carcinoma cell line C-4II displays growth arrest at the G1 phase with the induction of p21 following ciglitazone treatment. They also reported that PPARγ ligands suppress cervical cancer cell proliferation by inhibiting cell growth without triggering apoptosis at least in the cell line examined.[45]

DNA-damaging agents in the form of ionizing radiation and chemotherapeutic drugs are the main components of most current cancer treatment regimens. T0070907 is a kind of PPARγ antagonist. The suppression of PPARγ activity caused by T0070907 has been demonstrated by cell-based reporter gene and functional assays.[47–49] The treatment of T0070907 in some types of cervical cell lines could induce a significant G2/M phase arrest, decrease the synthesis of DNA, and then promote apoptosis and induce cell-cycle arrest. The treatment with T0070907 of cervical cells resulted in a significant reduction of the number of colonies. It also showed a significant time-dependent reduction in the expression levels of α- and β-tubulin proteins. But the relationship between suppression of PPARγ activity caused by T0070907 and the expression level of α- and β-tubulin protein has not been confirmed (Fig. 2B).[47]

Promotion of Apoptosis

The PPARγ agonist 15d-PGJ$_2$ is a nuclear transcription factor that regulates the expression of a large number of genes that are critical for the regulation of apoptosis, tumorigenesis, inflammation, and various autoimmune diseases. 15d-PGJ$_2$ is also known to induce tumor cell apoptosis. Edwin et al found that the effects of 15d-PGJ$_2$ on the induction of cell death are PPARγ-independent. It induces cellular apoptosis with the activation of the NF-kB caspase pathway. It is interesting that another PPARγ agonist, ciglitazone, has been demonstrated to inhibit the basal NF-kB activity with a relatively high concentration. 15d-PGJ$_2$ reduces the mRNA

expression of Bcl-2, Bcl-xL, MDR1, and SIRT1, which inhibit cell apoptosis. Thus, in turn, it promotes apoptosis. Treatment with 15d-PGJ$_2$ inhibits the expression of HDAC1, 2, and 3 mRNAs, which are early molecular changes of the tumor cells. Further investigation showed that the inhibition is enhanced when the dosage is increased.[50] PPARγ agonists also function as transcriptional trans-repressors and trans-activators. They induce apoptosis by upregulating the expression of pro-apoptotic proteins, such as Bax, Bad, and caspases.

Cisplatin is a kind of common cytotoxic anticancer drug. Yokoyama et al have investigated the effects of the combination of ciglitazone and cisplatin on the growth of ovarian cancer. Their results demonstrated that ciglitazone alone, cisplatin alone, or their combination, significantly suppressed the growth of ovarian tumor cells *in vitro* and prolonged the survival of mice with malignant ascites derived from ovarian cancer cells. Furthermore, the combination produced a significantly greater antitumor effect than cisplatin or ciglitazone alone, resulting in a decrease of PGE$_2$ concentration in serum as well as in ascites, and a reduction of vascular endothelial growth factor and micro-vessel density. The combination can induce apoptosis in solid ovarian tumors and significantly prolong the survival time of mice, as compared with cisplatin or ciglitazone alone. The combinative treatment remarkably decreased the expression levels of COX-2, microsomal PGE synthase (mPGES), and PG receptor 3 (EP3) proteins in tumors. An *in vitro* experiment showed that ciglitazone enhanced the cytotoxicity of cisplatin in ovarian cancer cells.[51] However, rosiglitazone may also enhance the release of PGE$_2$ in normal tissues. The treatment of endometrial tissues with rosiglitazone enhanced the release of PGE$_2$ during both stages of the estrous cycle and pregnancy. In studies of mRNA expression patterns at days 10–12 of the estrous cycle and days 14–16 of pregnancy, rosiglitazone acted in a more comprehensive way on both the release of PGE$_2$ and its own synthesis, which needs further investigation for PGE2 functions.[52]

Cell proliferation experiments have shown that the TNF-related apoptosis-inducing ligand (TRAIL)-dependent inhibition is further enhanced by the combined treatment with PPARγ ligands. Simultaneous exposure of TRAIL and PPARγ ligands in the treatment of ovarian cell lines resulted in an induction of apoptosis. Furthermore, additional treatment with PPARγ ligands led to increased protein expression of DR5 and a further decline of XIAP expression, resulting in the promotion of apoptosis.[53]

Telmisartan could induce apoptosis in EC cell lines. After the treatment of EC cells with telmisartan, a simultaneous increase in both annexin V+/PI2 fraction (early apoptotic) and annexin V+/PI+ (late apoptotic) subpopulations was detected. Mitochondrial transmembrane potential (MTP) is linked to cytochrome C release in many apoptotic cells.[54] Treatment of EC cells with telmisartan resulted in a decrease of MTP.

Telmisartan could decrease the expression levels of Bcl-2 and Bcl-xL proteins by splitting caspase-3 protein. Double-strand break (DSB) is the most critical marker of DNA damage.[55,56] Asselin et al found that DSBs could be induced before apoptosis when cells were treated with telmisartan (Fig. 2C).[43]

Autophagy

Autophagy is a kind of biological phenomenon similar to apoptosis. The dysfunction of autophagy was observed in cancer cells. Lysosome alterations are common in cancers. Disordered lysosomes lead to defective autolysosome formation, which may promote tumorigenesis. Autophagy is a lysosomal degradation pathway. It plays a role in the breakdown of disordered intracellular organelles, such as peroxisomes (pexophagy), mitochondria (mitophagy), endoplasmic reticula (reticulophagy), and ribosomes (ribophagy), which provides for the controlled recycling of macromolecules during cellular adaption and pathogenesis.[57,58] The lysosomal compartment is responsible for the controlled recycling of cellular organelles and macromolecules. Both heterophagic and autophagic cargos find their final destiny in lysosomes, where they are broken down by numerous hydrolyses.[59] Although it is still controversial whether autophagy is advantageous or disadvantageous in cancer therapy, recent findings suggest that autophagy induction for preventing cellular damage and mutation may be an important strategy for the inhibition of cancer initiation. As such, autophagy inhibition may be an appropriate approach to treating aggressive cancers and may augment the efficacy of cancer therapy. PPARγ plays an important role on the interface between cellular lipid metabolism, redox status, and organelle differentiation.[60] It has been demonstrated that lysosomes and autophagic vacuoles are defective in both nuclear receptor PPARγ1- and PPARγ2-deficient prostate epithelial cells,[61] suggesting PPARγ functions in lysosomes. However, the biological functions of PPARγ and its agonists in the therapy of gynecology disorders are still unknown.

Carcinogenesis

However, in certain aspects, some studies have reported that the treatment of PPARγ agonists also results in carcinogenesis. Both MT19c and cisplatin are anti-carcinogens. Both have significantly higher IC_{50} values when PPARγ is stimulated with rosiglitazone, suggesting that PPARγ may promote survival in at least some types of ovarian cancer cells.[61] For the uterus, the PTEN (phosphatase and tens in homolog) gene is a tumor suppressor in human EC.[62] In mice in which PTEN in the uterine was deleted, severe complex hyperplasia of the uterine epithelium occurred by 3 weeks of age and carcinoma occurred by 1 month. More importantly, this kind of mouse model resembles many aspects of type I human EC.[63] Furthermore, Daikoku's study suggested that Pten deletion in the uterine stroma and myometrium activates the pAKT–SREBP1–PPARγ pathway to trigger myometrial adipogenesis.[64] Increased levels of SREBP1 and PPARγ were also observed in mice with hepatocyte-specific Pten deletion, resulting in steatohepatitis.[65] El-Hage et al demonstrated that, in animal tests, Actos can cause cervix tumors in mice, and the combination of PPARα and PPARγ can cause uterine tumors in rats. There was a statistically significant trend of increasing risk of the corpus uteri cancer with increasing time since the initiation of pioglitazone in humans.[66] But the studies assessing the effects of PPAR ligands on tumorigenesis were controversial.[67]

Conclusion

PPARγ functions as an important mediator in the pathogenesis of gynecological disorders. The PPARγ agonists not only regulate the secretion of steroid hormone but also play key roles in both inhibiting the proliferation and promoting the apoptosis of cancer cells. In a summary, PPARγ agonists could be effective agents in the treatment of gynecologic disorders. Their combinations with other molecular targeted agents or cytotoxic drugs will improve the therapeutic effects.

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Author Contributions

Conceived and designed the experiments: PR. Analyzed the data: MJ. Wrote the first draft of the manuscript: PR. Contributed to the writing of the manuscript: YH, YLY. Agree with manuscript results and conclusions: MJ. Jointly developed the structure and arguments for the paper: YQZ. Made critical revisions and approved final version: MJ. All authors reviewed and approved of the final manuscript.

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