Non-Genomic Actions of Estrogens on the DNA Repair Pathways Are Associated With Chemotherapy Resistance in Breast Cancer

Javier E. Jiménez-Salazar1,2, Rebeca Damian-Ferrara3, Marcela Arteaga1, Nikola Batina4 and Pablo Damián-Matsumura1*

1 Department of Biology of Reproduction, Division of Biological Sciences and Health (DCBS), Autonomous Metropolitan University (UAM), Mexico City, Mexico, 2 School of Medicine, National Autonomous University of Mexico (UNAM), Mexico City, Mexico, 3 Monterrey Institute of Technology and Higher Education (ITESM), School of Engineering and Sciences, Monterrey, Mexico, 4 Nanotechnology and Molecular Engineering Laboratory, Department of Chemistry, Division of Basic Science and Engineering (DCBI), Autonomous Metropolitan University (UAM), Mexico City, Mexico

Estrogens have been implicated in the etiology of breast cancer for a long time. It has been stated that long-term exposure to estrogens is associated with a higher incidence of breast cancer, since estradiol (E2) stimulates breast cell growth; however, its effect on DNA damage/repair is only starting to be investigated. Recent studies have documented that estrogens are able to modify the DNA damage response (DDR) and DNA repair mechanisms. On the other hand, it has been proposed that DDR machinery can be altered by estrogen signaling pathways, that can be related to cancer progression and chemoresistance. We have demonstrated that E2 promotes c-Src activation and breast cancer cell motility, through a non-genomic pathway. This review discusses scientific evidence supporting this non-genomic mechanism where estrogen modifies the DNA repair pathways, and its relationship to potential causes of chemoresistance.

Keywords: chemoresistance, estrogen receptor, DNA repair mechanisms, DNA damage response (DDR), c-Src activation, breast cancer

INTRODUCTION

The role of estrogens in the onset of breast cancer, its progression in early stages of the disease, and during invasion, has long been demonstrated (1, 2). Up to now there are few published studies on the role of these steroid hormones regarding the mechanisms of resistance to chemotherapy (3). The lack of information may be due, in part, to the fact that not all the genomic and non-genomic mechanisms of action of estrogens are yet known, as new signaling pathways continue to be reported (4–6).

Surgery and chemotherapy are the main options in the treatment of breast cancer and, when the tumors are detected in early stages, most of the cases are successful; however, when there is resistance to these treatments, the chances of adverse results increase considerably (7). Currently, resistance to chemotherapy against breast cancer is considered a multifactorial phenomenon, since it involves various mechanisms that can be activated from or through treatment (3). A wide variety
of pathways have been described that induce resistance to cancer therapy, of which some stand out because of their association with estrogenic effects, in this review we will focus on three of them: A) resistance induced by altered DNA repair mechanisms ([8]; B) inhibition of apoptosis through activation of PI3K/AKT (phosphatidylinositol 3-kinase/protein kinase B) pathway, which promotes cell survival (9, 10); C) the abnormal expression of proteins that regulate cell cycle progression, including p53 (tumor protein 53 KDa), MDM2 (Mouse double minute 2 proteins that regulate cell cycle progression, including p53 to be regulated (14).

Estrogen receptor binding affinity to E2 (14, 17). Mass spectroscopy studies have shown that the difference between mERα and ERα is the presence of a molecule of fatty acid, primarily palmitate (palmitoylation) or myristate (myristoylation) that facilitates its anchorage to the plasma membrane (22, 23), the authors conclude that both, intracellular ERα and mERα are the same protein (15, 17, 24).

The non-genomic mechanisms of ER are characterized by the fact that should not enter the nucleus, and their effects are observed in short periods of time, ranging from a few seconds to minutes (16). Particularly, it has been shown that mERα can be found in the form of a monomer and that it can homodimerize, in the presence of estradiol, to activate Gtα and Gβγ proteins, thus increasing the intracellular concentration of the second messengers AMP and calcium (15). In addition, mERα homodimer can physically interact to the p85 subunit of the PI3K kinase, to the SH2 (Src Homology 2) domain of the c-Src kinase, or even activate membrane receptors with tyrosine kinase activity, such as Epidermal Growth Factor Receptor (EGFR) which stimulates the ERK (extracellular-signal-regulated kinase) or PI3K signaling pathways, increasing cell proliferation, survival, and migration of breast cancer cells (25, 26).

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There is evidence that mERα-induced activation of c-Src can not only induce proliferation, it also favors the ubiquitination of ERα and subsequent degradation via proteosome (28). The loss of ERα favors EMT and tumor cell migration because ERα forms a complex with the MTA3 (Metastasis-associated protein 3) protein, in order to directly suppress the SNAIP gene. The absence of ERα or MTA3 results in aberrant expression of SNAIP and loss of E-cadherin expression, which facilitates the migration of breast cancer cells (29, 30). In addition, there is evidence that even the simple activation of the transcription factor SNAIP1 can induce transcriptional repression of ERα, demonstrating the importance of its loss in breast cancer, which correlates with poor prognosis, increased recurrence after treatment and increased incidence of metastasis (31, 32)

ESTROGENS INDUCE CHEMORESISTANCE BY ALTERING DNA REPAIR MECHANISMS

Various signaling pathways in cancer cells induce DNA repair and stimulate chemoresistance, avoiding the lesions generated by
chemotherapy (33). DNA double-strand breaks (DSB) are highly deleterious, being sufficient to trigger cell death, or induce genomic instability by changing chromosome structure (34). Direct DSB are induced by ionizing radiation, UV light (photodynamic therapy), and free radicals (35) or certain anti-cancer drugs (36). Indirect DSB, associated with replication, occur after initial DNA damage. The most common example occurs when the replication fork meets a single-stranded break (SSB) on the leader strand of the DNA template, which can collapse, turning SSB into a DSB. Direct DSBs are repaired mainly by non-homologous end joining (NHEJ) mechanisms, while indirect DSBs are repaired predominantly by homologous recombination (HR) pathways. DNA adducts are a different form of DNA damage, which are caused by alkylating agents and are repaired by the base excision repair (BER) pathway, which removes a base or short sequence of nucleotides where the damaged base is found. The nucleotide excision repair (NER) pathway removes a single strand of damaged DNA with a length of 24–30 base pairs. Another important DNA repair pathway is the direct repair (DR) pathway, which can repair damaged DNA without removing the damaged base (37). Recent studies have documented interactions between DNA damage repair pathways and genomic and non-genomic mechanisms of ER (38, 39). Diverse studies in patients with ER-positive breast cancer, showed that the DNA repair capacity was reduced by 50% compared to free-disease women, effect that was associated to the decrease in the NER pathway (40–42) (Figure 1).

DNA damage response activates diverse repair mechanisms by inducing signals through three major effector kinases, ATM, ATR (ataxia telangiectasia and Rad3-related), and DNA-PK (DNA-dependent protein kinase). On one hand, ATM and DNA-PK recognize DSB, while ATR responds to SSB in the replication forks. The downstream signaling of ATM, ATR, and DNA-PK, involves a large amount of proteins; however, there are key effector proteins including CHK1 (Checkpoint kinase 1), BRCA1 (Breast Cancer gene 1), p53, and MDM2 that signal other targets, such as BRCA, cyclin D, pRb (retinoblastoma protein), and p21 (21 kDa protein), in addition to the control points of the cell cycle and the machinery that regulates the apoptosis process (43, 44).

**FIGURE 1** | Chemoresistance pathways induced by estrogen receptor, through the direct activation of c-Src kinase. Conventional radiotherapy and chemotherapy kill most cancer cells, but there are some that can evade the cytotoxic effects of treatment and restart accelerated tumor proliferation. This promotes cancer recurrence and subsequent metastasis. Chemoresistance can be ascribed to 1) Resistance induced by altering DNA repair pathways (NER, nucleotide excision repair; BER, base excision repair; HR, homologous recombination; NHEJ, non-homologous end-joining). 2) Inhibition of apoptosis and activation of pathways involved in cell survival. 3) Abnormal expression of proteins that regulate cell cycle progression. 4) High plasticity of tumor cells with which they activate the process of EMT, epithelium-mesenchymal transition that facilitates migration and invasion to distant sites.
There are different molecular mechanisms through which estrogens and ER\(\alpha\) contribute to the radioresistance and chemoresistance. Several reports have shown that ER\(\alpha\) could regulate the expression of ATM, a phosphotransferase of serine residues whose main function is to activate different signals in response to DNA damage. The proposal indicates that ER\(\alpha\) does not exert directly to the promoter of the ATM gene, but ER\(\alpha\) targets the miRNAs (miR-18a and 106a) in order to inhibit ATM expression. It has also been demonstrated that the expression of miR-18a and 106a is significantly reduced in tissues of patients diagnosed with ER\(\alpha\)-positive breast cancer (45).

Like other steroid hormone receptors, ER\(\alpha\) is a substrate of DNA-PK, a key component of the NHEJ, that phosphorylates serine and threonine residues. Estrogens promote the formation of the DNA-PK/ER complex, the phosphorylation of \(^{118}\)Ser in ER\(\alpha\), that is required for its transcriptional activation and maintains its stability. This report has been corroborated by the fact that inhibition of DNA-PK promotes ER\(\alpha\) degradation via proteasome (46, 47) (Figure 2).

ATR protein, a Serine/Threonine (Ser/Thr) kinase, is activated by alterations in the replication process, and requires its binding to ATRIP (ATR Interacting Protein) and TopBP1.

**FIGURE 2** | Molecular mechanisms by which estrogens mediate chemoresistance. DNA alterations induce responses to DNA damage (DDR), activating different DNA repair mechanisms: NER, nucleotide excision repair; BER, base excision repair. DNA double-stranded breaks activate ATM and PK DNA effector kinases. ATM is repressed by ER through mir-18a and miR106a, and PK DNA phosphorylates ER\(\alpha\) in the 118Ser residue, improving its transcriptional activation and preventing its degradation via proteasome. BRCA-1 represses ER\(\alpha\) activity and ER regulates BRCA1 transcriptionally. Single-stranded DNA breaks activate the ATR kinase, which is blocked by non-genomic mER\(\alpha\x2c\) signaling that activates the PI3K/AKT pathway through c-Src kinase and EGFR. On the other hand, CHK1 and CLASPIN are repressed, inducing the activation of the PI3K/AKT pathway.
(DNA topoisomerase II binding protein 1) proteins. The latter is a phosphoprotein that is specially regulated by Akt. Several studies indicate that E₂ induces phosphorylation of TopBP1 at the site of interaction with AKT. When TopBP1 is phosphorylated in 1189Ser, its association to ATR is avoided and their functions are avoided (48). It has been proposed that E₂ can block the activation of ATR, after DNA damage, through a mechanism mediated by the ERα-Src, as it can activate the PI3K/AKT pathway (Figure 2). It is also probable that the mERα-Src complex induce the activation of EGFR and PI3K/AKT pathway to restrict ATR signaling in the tumor process (48, 49).

Another proposed mechanism is that mER-E₂ complex inhibits the activation of Chk1, a Ser/Thr kinase that is required for cell cycle arrest, since it is activated at checkpoints in response to DNA damage. Alternatively, Claspin (Chk1-interacting protein) binds directly to the kinase domain of Chk1, inducing cell cycle arrest (50). Therefore, E₂ can induce the ER/c-Src or ER/c-Src/EGFR pathways in order to activate the PI3K/AKT pathway, where AKT inhibits the phosphorylation of the 345Ser in Chk1 and precludes the formation of the Chk1/Claspin complex, preventing the cell cycle arrest (43).

BRCA1 is a human tumor suppressor protein related to estrogens actions, responsible for inducing DNA repair mechanisms and it is an effector downstream of the signaling cascade, recruited at sites of DNA damage. It works directly on homologous repair mechanisms, influences cell cycle arrest and other repair pathways. There is evidence that BRCA1 modifies estrogen-mediated tumor progression, as increased E₂-ER signal accelerates preneoplasia and cancer development in the absences of BRCA1, favoring breast de-differentiation and tumorigenesis (51, 52). Some reports suggest that BRCA1 represses the transcriptional activity of ERα, the mechanism suggests the physical interaction is between the amino-terminal of BRCA1 and the AF-1 domain of ERα, the binding has not been fully demonstrated; however, the carboxyl-terminal (where the repression domain is present) is required to achieve the repression of ERα activity, since mutant BRCA1 proteins that lack this domain do not inhibit ERα (53, 54). While BRCA1 suppresses the function of ERα, estrogens promote BRCA1 transcription (55–57).

**ESTROGENS INDUCE RESISTANCE THROUGH IMPROPER EXPRESSION AND ACTIVATION OF THE PROTEINS THAT CONTROL THE CELL CYCLE**

Radiation therapy and chemotherapy result in delayed progression of cell cycle stages. This occurs through activation of the DDR, that activates different control points (Chks) at different stages of the cell cycle. These checkpoints are found in G1/S, S, early G2, and late G2 phases (11, 58). In tumor cells, one or more of these checkpoints are disabled due to genetic changes and other alterations that occur during tumorigenesis. Cells in G2/mitosis phase are more sensitive to radiation and those that are in late S-phase are more radiologically resilient (59). It has been demonstrated that Chk 1 kinase activation is essential for stopping the cell cycle in G1/S or G2/M checkpoints, in response to DNA damage (60). The G1/S checkpoint pathway is primarily regulated by two key effectors, the transcription factor p53 and the cell division cycle phosphatase 25A (Cdc25A), p53 is a tumor suppressor and DNA damage sensor that can activate different cellular processes, such as cell cycle arrest, DNA repair, and even apoptosis. The main function of Cdc25A is the inhibition of the CDK2 (cycrin-dependent kinase)-cyclin A/E and CDK1-cyclin B complexes (61). On the other hand, p53 has a bidirectional relationship with the ER that affects both, its expression and function. The TP53 gene is transcriptionally repressed by ERα due to the recruitment of the nuclear coregulators NCoR (nuclear coregulators), including SMRT (silencing mediator for retinoid and thyroid hormone receptor) and histone deacetylases HDAC (histone deacetylases) (62). It is known that ERα interacts physically with p53 inducing functional repression of the p53 transcriptional activity. In addition, estrogens induce the formation of the ERα/p53 complex, associate directly at the p21 promoter to block its transcription, avoiding the arrest of the cell cycle and promoting radioresistance (63). It has also been demonstrated that the ERα/p53 complex can bind to the MDM2 protein, a ubiquitin E3 ligase, which ubiquitinates the carboxyl-terminal domain of p53, inhibiting its function. The ERα/p53/MDM2 complex negatively regulates the activity of ERα through ubiquitination, induced by the ubiquitin ligase of MDM2 (64).

Non-genomic mechanisms of estrogens have been described in the regulation of the cell cycle. This mechanism begins when E₂, due to its lipophilic properties, diffuses through the plasma membrane, and binds to the mERα (44). The activation of the receptor facilitates the interaction of mERα with the SH2 domain of c-Src kinase, and with the p85 alpha subunit of PI3K, the formation of the mER-Src/PI3K complex triggers the activation of mERα via Akt and PKCζ (Protein kinase C, zeta). Activation of Akt increases the transcription of cyclin D1, and PKCζ controls the association of Ras GTPase to the mERα/Src/PI3-K complex, inducing the Raf/MEK/ERK pathway, favoring the translocation of ERK to the nucleus and the consequent release of p27 outside the nucleus, stimulating the G1 to S transition of the cancer cells (65) (Figure 3A).

A different non-genomic mechanism reported for E₂, in cells where the presence of ER or mER is undetectable, is through the G Protein-coupled Estrogen Receptor (GPER) that belongs to the superfamily of seven transmembrane domain receptors. GPER plays a critical role in the signaling of steroids in triple-negative tumors. GPER mechanism starts it binds to E₂, inducing conformational changes that activates the trimeric G-protein that is coupled to the receptor, which induces the activation of c-Src kinase and the formation of the c-Src/PI3-K complex that favors the activation of Akt and PKCζ pathways, where Akt increases the transcription of cyclin D1, and PKCζ activates the Ras/Raf/MEK/ERK pathway, promoting the G1/S transition in cancer cells (66).
Programmed cell death, a process known as apoptosis, is highly regulated as it plays a critical role in development and homeostasis by eliminating unnecessary cells. The process of apoptosis is carried out by the activation of two major signaling pathways: the intrinsic pathway, which proceeds in the mitochondrion, sensing irreparable DNA damage, and inducing the formation of a homodimer of the members of the pro-apoptotic protein superfamily (Bax, Bak, Bad, Bid, Puma, Blim). Homodimers of pro-apoptotic proteins induces the presence of protein-permeable pores in the outer mitochondrial membrane that release cytochrome c, and the activation of the initiating caspases (caspase 9) and the effector caspases (caspase 3). The extrinsic pathway occurs at the cellular membrane level, its signaling starts with the activation of the death receptors Fas and the ligand inducer of TRAIL (TNF [tumor necrosis factor]-related apoptosis protein); the ligand-receptor interaction induces the activation of caspase 8 and trigger effector caspases 3, 6, and 7, being caspase 3 the most frequently activated (67). The onset of apoptosis is the last mechanism that protects cells from irreparable DNA damage. To prevent the uncontrolled proliferation of cells, p53 induces the expression of pro-apoptotic genes such as FAS-R, BAX, PUMA, and NOXA (68, 69).

FIGURE 3 | Mechanisms of estrogen-induced resistance and signaling of its receptors. (A) Control of the cell cycle. ER functions as a transcription factor to regulate p53 expression, in addition ER can physically interact with p53 to inhibit p53 function. Moreover, it signals through the c-Src kinase and switches on the PI3K and Ras/MAPK pathways to promote activation of Cyclin D and release the p27 repressor from the nucleus to promote cell cycle progression. (B) Inhibition of apoptosis ER functions as a transcription factor to induce the expression of the anti-apoptotic protein Bcl2 and functions as a transcriptional co-repressor of Bad to inhibit its synthesis. Furthermore, mERα associates with c-Src, to activate the PI3k/Akt pathway; Akt phosphorylates Bad to preclude the formation of Bad/Bad homodimer and block the release of cytochrome C and thus the process of apoptosis. (C) Cellular plasticity promotes TEM. E2 diffuses through the plasma membrane binds to mER, induces phosphorylation of c-Src, its associated with ZO1, and forms the p-Src/ZO-1 complex, that favors the dissociation of the Tight Junctions and promotes that ZO1 and ZONAB are translocated to the nucleus, inducing the transcription of HER-2, which triggers EMT and migration of tumor cells.

One of the most important functions of DDR is to stop proliferation by activating cell cycle control points before inducing death by apoptosis. In the cell cycle arrest, E2 play a relevant role in resistance induction since some reports indicate that the ERα stimulates cell cycle progression through positive transcriptional regulation of cyclin D, since ERα interacts to an AMPc-response element (CRE) present in the cyclin D gene promoter, and induces the synthesis of the c-myc oncogene which controls the expression of cyclin D1 (70). The induction of c-Myc by E2 is also generated by the binding of ERα to an CRE, present in the promoter region of the c-myc gene (60, 71). The E2-ER rapidly activates the cyclin E/CDK2 complex accelerating the transition from G1 to S; furthermore, ER negatively regulates the expression of the p21 inhibitor to induce the progression of the cell cycle (72). At the same time that the cell cycle is stopped, E2 must also block the apoptosis process, inducing the expression of some anti-apoptotic proteins such as Bcl-2 and BclXL (73, 74). It has been reported that ER can positively regulate the transcription of Bcl2 and BclXL by direct binding to ERE sites present in their promoters or, as in the case of McI1, through Sp1 sites. ER can additionally function as a transcriptional repressor of proapoptotic genes such as Bad, Bak, Bid, or Puma to inhibit the intrinsic pathway of apoptosis (75–77).

In addition to the genomic mechanisms, estrogens can induce effects through non-genomic mechanisms (mERα) and are
independent of ER-mediated transcription. As mentioned before, ERα can interact with several proteins in this process, including c-Src, the p85 alpha subunit of PI3K, caveolin 1, EGFR (epidermal growth factor receptor), IGFR1 (insulin-like growth factor receptor 1 IGFR1), and HER2 (human epidermal growth factor receptor 2) (78). The formation of this complex rapidly increases the activity of PLCζ and signal crosstalk by activating the MAPK and the PI3K/Akt pathways. Akt mediates the phosphorylation of Bad pro-apoptotic protein. Bad phosphorylation inhibits dimers formation in the mitochondria and increases the activity of PLCζ, phospholipase Cζ, and PLCζ, regulating membrane fusion and cell death. Finally, another study shows that deregulation in the expression of mesenchymal phenotype markers (80–82), that are associated to cell adhesion and invasion.

These changes contribute to the acquisition of a frontal polarity (front to rear) that generates a migration front, characteristic of mesenchymal cells (83). Due to the heterogeneity of the cell populations that occur in cancer, it should be noted that not all stages of EMT can be carried out on all cancer cells, nor are all the markers expressed, making it more difficult to detect them.

Development of resistance to cancer treatments remains as a major impediment in medical oncology. Resistance may not only precede but may also arise because of therapy. The use of doxorubicin, a cytotoxic drug commonly used in clinical practice, may promote resistance in HCT colon cancer cells through the activation of TGFβ signaling and phosphorylation of Smad2 and Smad3. This enhances the expression of Snail, Slug, vimentin, and N-cadherin, mesenchymal phenotype marker proteins, and decrease epithelial markers such as E-cadherin and occludin (84). One of the main inducers of these changes are estrogens through c-Src signaling. Our research has demonstrated the role of E2 in EMT by triggering c-Src, the formation of the p-Src/ZO-1 (Zonula occludens protein) complex that promotes the dissociation of ZO-1 and ZONAB (ZO-1-associated nucleic acid-binding protein) proteins from tight junctions, and higher expression of mRNA encoding for HER2. These changes were correlated with decreased expression of the epithelial markers occludin and protein crumbs homolog 3 (CRB3) and increased synthesis of N-cadherin and the transcription factor SNAIL, that induced E2-dependent migration of MCF-7 and T47D breast cancer cells. Incubation with the ER antagonist Fulvestrant precluded the effects of E2 on c-Src phosphorylation, p-Src/ZO-1 complex formation, ZO1/ZONAB nuclear translocation and MCF-7 cell migration. Our findings suggested that E2 promotes tight junction dissociation during tumor progression and increases MCF-7 cell migration (27) (Figure 3C).

There is in vivo and in vitro evidence that supports the fact that estrogens contribute to tumor chemoresistance, through the activation of c-Src. It has been shown that c-Src activation can be considered a marker of tumor progression. Ye and collaborators identified high concentrations of phosphorylated c-Src in tyrosine 419 (419Y-cSrc) in serum samples from patients with nasopharyngeal carcinomas (NPC), which were associated with an unfavorable prognosis in parameters such as survival, disease-free period, and survival free of distant metastases. In the same study, blocking or inactivating c-Src in PCN cell lines decreased cell viability, colony formation, cell migration, in vitro invasion, and in vivo metastasis (85). Studies on 50 primary ERα+ and 200 ERα-breast cancer tumor samples demonstrated that E2 induces activation of c-Src kinase and rapidly stimulates the ubiquitination of ERα and its subsequent degradation, via proteosome. In the same report, but in cell lines, blocking proteosome activity was shown to increase ERt levels (28).

Finally, another study shows that deregulation in the activation of c-Src kinase in solid tumors favors the epithelium-mesenchyme transition and chemoresistance in breast cancer cells, favoring their migration and invasion (86).

**CONCLUSIONS**

Several studies have examined the role of estrogens, and their receptors, in chemoresistance; however, their molecular mechanisms of action remain elusive. Its association with DNA damage and repair mechanisms are just beginning to be studied, especially those related to kinase activation such as c-Src, EGFR, HER2, ERK, or PI3K/AKT.

One mechanism by which estrogens favor the proliferation of breast cancer is through the induction of DNA damage, although...
they can also contribute to chemoresistance by altering the mechanisms of DNA repair, preventing apoptosis, or deregulating the control mechanisms of the cell cycle, most of them induced by the activation of c-Src.

Considering that ERα is expressed in more than 60% of the breast tumors, estrogen-mediated chemoresistance has become a challenge to find better treatments. For this reason, knowing and understanding the pathways through which estrogens activate drug resistance will allow the design of better therapeutic strategies.

Overall, the above-mentioned research suggests that estrogens and their genomic and non-genomic signaling contribute to tumor chemoresistance and a better understanding of the molecular mechanisms of DNA repair, cell cycle regulation, apoptosis inhibition, and cell plasticity that induces EMT could improve the development of novel combination therapies or tumor markers.

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AUTHOR CONTRIBUTIONS

JJ-S and PD-M conceived of the presented idea. PD-M wrote the manuscript with support from JJ-S, NB, MA, and RD-F. All authors contributed to the article and approved the submitted version.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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