Chapter

Interaction of Bisphenol A with G Protein: Coupled Receptors - New Paradigms in Breast Cancer

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Abstract

The massive use of bisphenols, actually bisphenol A, in consumer products and food packaging has been associated with certain hazardous conditions for human health, which include their interactions with a family of specific membrane receptors and their effects as endocrine disruptors related to breast cancer. For this reason, bisphenol A was removed from many products, but it has been replaced by structural analogs whose pathways of action and metabolic effects are so far partially unknown. This chapter emphasizes the discovery of bisphenols, their uses in human life, and their impact on health population by focusing on breast cancer. Regarding their mechanisms of action, we have focused on the signaling routes activated by bisphenols following their binding to G protein–coupled receptors.

Keywords: estrogen, bisphenols, GPCRs, breast cancer, endocrine disruptors, G protein-coupled estrogen receptor 1 (GPER-1), angiotensin receptors (AT), adrenergic receptors (AR), chemokine receptors

1. Introduction

Significant evidence suggests that endocrine disruption is attributable not only to pharmaceutical products or rare contaminants, but also to exogenous chemical compounds ubiquitously found in everyday life of the modern world. Endocrine-disrupting chemicals (EDCs) enter the human body where they act similarly to endogenous hormones, altering endocrine homeostasis and causing adverse effects on human health [1–7]. Interestingly, the US Food and Drug Administration identified more than 1800 chemical disruptors of endocrine pathways involving estrogen, androgen, and thyroid hormones [8]. EDCs have been related to the development of disorders such as adulthood diabetes, poor semen quality, polycystic ovary syndrome, neurodegenerative disorders, and cancer [1, 8]. Changes in the physiological levels of hormones circulating in the human body may be involved in the high incidence of tumors of the reproductive system in both men and women [8]. Indeed, breast cancer is the most common cancer diagnosed in women worldwide that has been associated in a small percentage with genetic predisposition (*BRCA1* and *BRCA2* mutations) whereas the majority of breast tumors have been categorized as sporadic breast cancer [9]. In fact, lifestyle factors such as smoking, alcohol consumption, sedentary lifestyle, and obesity have been related to the development of the disease. However, an increasing body of evidence suggests that etiology for

breast cancer may be related at least in part to exposure to chemicals of some kind. Indeed, recent studies show that environmental pollutants could also play a role in the pathogenesis and progression of breast cancer. Evidence from epidemiological studies and basic science using *in vitro* and *in vivo* models suggests that exposure to EDCs may be positively correlated with breast cancer development, particularly when the exposure occurred during critical stages of human life. The list of suspected environmental pollutants having a role in breast cancer is extensive and includes polychlorides, biphenyl ethers, phthalates, triclosan, octylphenol, dichlorodiphenyltrichloroethane, and bisphenols (BPs). Bisphenol A (BPA), or 4,40-dihydroxy-2,2-diphenylpropane, is one of the main compounds of this class; BPA is an organic synthetic plastic monomer that was first synthesized in the 1890s as a synthetic estrogen and a key element in the manufacture of cans, reusable water bottles, and medical equipment. BPA regulates several processes, such as cell proliferation, migration, and apoptosis, leading to neoplastic changes due to its ability to mimic the actions of estrogen at multiple levels by activating both α and β estrogen receptors (ERα and ERβ). The effects of BPA on the reproductive system of rats were reported in the 1930s. Now, 91 years later, several studies performed in mice have demonstrated DNA damage, induction of oxidative stress, and epigenetic changes in oocytes [8]. BPA can induce various types of modifications in the reproductive system of men and women, supporting multiple oncogenic signaling routes such as STAT3, PI3K/Akt, and MAPK pathways [8]. Benign lesions that can progress to breast or ovarian cancer due to BPA depend on several molecular and epigenetic mechanisms that will determine whether the endocrine or the reproductive system is affected and will be reviewed in this chapter. Moreover, the effects of BPs on GPCRs associated with breast cancer development or progression are addressed.

2. Xenoestrogens derived from anthropogenic activity

2.1 Some historical aspects of bisphenol A and related compounds

In 1891 Aleksandr Dianin, a Russian chemist from Saint Petersburg, combined phenol with acetone in the presence of an acid catalyst, synthesizing for the first time the chemical substance called 4,40-dihydroxy-2,2-diphenylpropane [10], a molecule that was later recognized by the name of bisphenol A [11]. In 1936, the English scientists Dodds and Lawson reported that BPA exhibited important estrogenic properties inducing complete cornification in vaginal smears of ovariectomized rats treated with this compound [12]. In the 1940s, BPA was basically considered a synthetic estrogen and its potential carcinogenic properties in humans started to be studied [13, 14]. Therefore, BPA is one of the first compounds of anthropogenic origin in which an endocrine-disrupting activity has been verified.

Later in the 1950s, it was found that the reaction of BPA with phosgene generated a polycarbonate, unalterable over time, easy to mold, versatile, and transparent. Due to these multiple qualities, together with its chemical stability, the industry began to use it rapidly and massively to manufacture all types of plastic containers [2]. Currently, BPA has been used to produce various electronic and construction products, automotive parts, medical and clinical articles, toys for children, hygiene and personal care items, and storage products. In addition, it is used for the inner lining of metal cans for preservation of food and beverages [2]. For this reason, BPA is today one of the most used chemical products worldwide. Several studies have suggested that the greatest human exposure to BPA (>90%) is likely to occur through food contamination and, to a lesser extent, by dust ingestion and absorption through the skin or dental surgeries [8].

The proestrogenic activity of BPA resurfaced in the early 1990s when a team led by David Feldman identified through mass spectrometry the presence of this molecule in a growth medium of yeast (*Saccharomyces cerevisiae*) and even in the pure water contained in the autoclaved polycarbonate flasks [15]. In turn, one of the first effects of BPA was evaluated in breast cancer cells. Indeed, in estrogen-sensitive MCF-7 human breast cancer cells (ERα-positive cells), BPA induced a great expression of progesterone receptors and increased their proliferation rate [3, 15]. From this period to date, numerous investigations have reported the potential risk that continuous exposure to BPA implies for human and animal health and ecosystems [3]. This evidence has contributed to consider BPA as one of the main xenoestrogens of ubiquitous environmental distribution. In response to these effects, the industry has sought alternatives to traditional BPA, generating a variety of new bisphenols, such as bisphenol S (BPS), bisphenol AF (BPAF), bisphenol E (BPE), bisphenol B (BPB), and bisphenol F (BPF) among other phenolic molecules, some of which have also been related to estrogenic activity and are considered physiological disruptors of varying degrees in humans [3, 16].

2.2 Routes of BPA exposure and metabolism

The continuous presence of BPA in our environment suggests that several routes of exposure may exist. Oral ingestion seems to be the main route, given the storage of food and liquids in plastic containers that include BPA among its major constituents, which also diffuses into the environment after exposure to high temperatures or frequent washing. The US EPA has established a safe daily intake of 50 g BPA/kg of body weight per day based on the assumption that the main source of exposure to BPA is through food ingestion [17]. Not only in humans but also in primates, ingested BPA is rapidly absorbed (5–15 min later) by the intestinal wall and is transformed into BPA glucuronide following its first passage through the intestine and liver; in addition, a small fraction of BPA is also transformed into a sulfate conjugate [4, 16, 18, 19]. Conjugated forms of BPA are estimated to have no endocrine activity [19, 20]. In murine models, and after oral administration of nanomolar doses of BPA, oxidation products of this compound have been found, suggesting the formation of secondary metabolites with greater estrogenic activity than the parent molecule [5]. BPA has a half-life between 4 and 5 h, and most of the conjugated forms are finally excreted through the urine [4, 5, 16]. Inhalation seems to be another route of entry, inducing cough, bronchospasm, and asthmatic attacks; similarly, eye exposure may cause conjunctivitis, itching, and periorbital edema whereas skin contact usually produces localized redness and inflammation [19].

BPA has been detected in all biological fluids, including serum, urine, cerebrospinal fluid, and milk, in most of today's human populations. In fetal tissues, BPA has been found in concentrations similar to those present in maternal blood, showing that it can cross the transplacental barrier [19]. Furthermore, toxicological data indicates that human embryos and neonates, unlike adults, cannot conjugate BPA increasing its possibility to exert toxic effects [5]. Epidemiological and experimental studies suggest that embryonic exposure to BPA is in the long term related to the occurrence of a series of disorders, such as precocious puberty, infertility, metabolic disorders, and a series of hormone-dependent tumors, like breast cancer [1, 5, 17, 20, 21].

2.3 Pathophysiological effects of bisphenols: endocrine, metabolic, and carcinogenic disruptors

To date, only a few studies have explored the effects produced by exposure to BPs, mainly BPA, during intrauterine or postnatal life together with their effects on

general human health. Multiple metabolic disorders, polycystic ovary syndrome, spontaneous abortion, infertility, endometrial hyperplasia, hormone-dependent tumors, immunity alterations, cardiovascular pathologies, neurodegenerative disorders and obesity have so far been reported among their deleterious effects on human health [1]. Dumitrascu et al. in 2019 [1] highlighted that women suffering from polycystic ovary syndrome exhibited higher circulating levels of BPA and testosterone than healthy women and that high androgen levels decreased BPA clearance. Furthermore, they pointed out that women with endometriosis showed high levels of BPA in serum, suggesting an association between this compound and the disease. It has also been suggested that patients with high urinary levels of BPA have a high probability of implantation failure during *in vitro* fertilization procedures. In young people, an early exposure to BPA has been associated with high percentage of body fat, elevated body mass index, and abdominal circumference and numerous neurological implications, such as anxious or depressive behavior, all conditions that have been suggested to increase the risk of developing cancer. Comparative studies between BPA and its analogs (BPB, BPF, and BPS) show that they have toxic effects on the testes and spermatogenesis that are mediated by an increase in the levels of oxidative stress and a decrease in the levels of enzymes with antioxidant activity [22]; some of them may also have a neuroendocrine disrupting activity [6] (see **Figure 1**). Examples of neurobehavioral disorders associated with BPA in different experimental models (rodents, zebrafish, and *Caenorhabditis elegans*) range from cognitive deficit, increased anxiety, socio-sexual deficiencies to hyperactivity or autism spectrum disorders. It is postulated that neurological effects may be due to the weak estrogenic effect of BPA or its analogs by binding to estrogen receptors in different areas of the brain [6, 23].

With regard to the risk of developing malignant neoplasms, the greatest association has been observed with breast, ovarian, and prostate cancer though the studies have not been conclusive [1]. To overcome the effects of BPA associated with an increased public concern about the risk of developing endocrine-related cancer due to exposure to BPA [24], the industry has replaced it with analogs such as BPS, BPB, BPF, or BPAF, which are now parts of products labeled as BPA-free [25]. Nevertheless, *in vitro* assays have demonstrated that BPAF has a stronger binding affinity for estrogen receptors when compared with BPA [26].

Likewise, recent studies have shown that both BPA and BPS can contribute to breast cancer malignancy by disrupting the organization of acinar structures and by affecting the normal development of the mammary gland [9]. To date, the effects of BPA in eukaryotic cells have been reported to be mediated primarily by steroid receptors, including ERα and ERβ, estrogen-related receptors (ERR), androgen receptors (AR), and peroxisome proliferator-activated

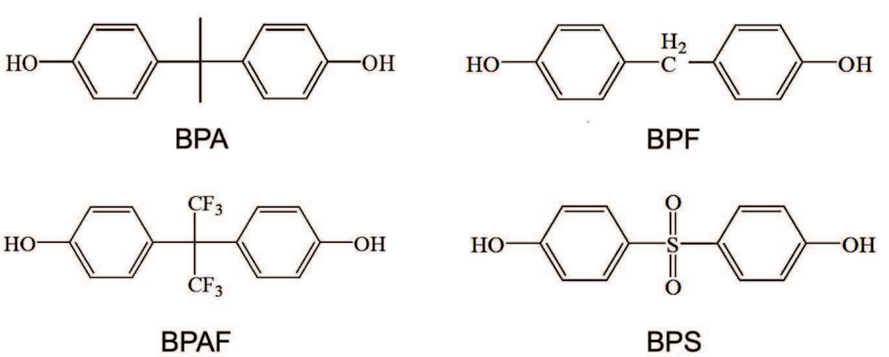

Figure 1.
Structure of main bisphenols produced by industrial activity. BPA, bisphenol A; BPF, bisphenol F; BPAF, bisphenol AF; BPS, bisphenol S.

receptors (PPAR) [24]. Other interactions include signaling by stimulation of angiotensin (AT), α-adrenergic (AR,) or chemokine (CXC) receptors.

3. Bisphenols and their role in breast cancer

Although BPA does not possess the potency of estrogen, it is ubiquitously distributed in nature and its resistance to enzymatic or chemical degradation makes it even more dangerous. Breast cancer has a high mortality in women in many countries, and approximately 10% of these tumors are due to genetic influence whereas 90% are related to lifestyle or associated with negative elements present in the surrounding environment [1]. The most harmful effects attributed to EDCs would occur during breast development when this tissue is more susceptible to developing atypical differentiation. *In vivo* studies show that prolonged exposure (60 days) of breast cells to 400 μg of BPA/kg of body weight induces an increase in the density of mammary buds [27], in cell proliferation, and in the levels of oxidative stress without significant differences in the expression of estrogen receptors [1, 27, 28]. Previous studies have demonstrated that women who exhibit mutations in the tumor suppressor genes *BRCA1* and *BRCA2* in mammary gland cells have a greater risk of developing breast cancer and also a high susceptibility to the negative effects of environmental BPA [1, 27, 29]. In normal or cancerous adult breast tissue, BPA has been associated with an increased proliferation rate and with the induction of chemoresistance in ERα-positive cells [1, 30, 31]. BPA can also modify DNA repair, inactivate p53, and induce changes in genes associated with apoptosis to stop cell death through DNA methylation. By activating vascular endothelial growth factor, BPA can increase angiogenesis in breast tumors [32] and at the same time activate the MAPK and STAT pathways to modulate the proliferation kinetics of human mammary epithelial cells [1, 33].

Breast cell cultures developed in a 3D fashion are one of the most widely used models to gain a better understanding of the role of bisphenols in breast cancer. Using this approach and MCF-12A cells, which exhibit a typical luminal epithelial morphology, it was observed that low doses of BPA and BPS generated a disruption in the normal organization of the mammary acinus and promoted cell invasion [9]. Interestingly, mammospheres of MCF-7 cells (ERα-positive cell line) treated with 10 nM BPA displayed high expression of aldehyde dehydrogenase 1, a marker of breast stem cells, and SOX-2, a key transcription factor for cell pluripotentiality and self-renewal. That effects were not observed when MDA-MB-231 (ERα-negative cell line) was used instead of MCF-7 cells, suggesting that the receptors through which BPA modulates its signaling exhibit a different expression pattern in this kind of cancer, highlighting the implications of the heterogenicity of tumor mammary tissue when evaluating the effects of EDCs [34].

Evidence suggests that BPA may play an important role in the lifecycle and carcinogenesis of mammary epithelial cells and challenge us to continue studying its role in the origin and progression of breast cancer. One approach is to determine the relationship between BPA and G protein–coupled receptors (GPCRs) signaling, considering the recent evidence of the role of GPER-1 in breast cancer progression. Interestingly, approximately 20% of human neoplasms are related to some alteration in GPCRs [35]. The first relationship of GPCRs with tumorigenesis dates back to the 1980s, when a novel proto-oncogene called *MAS1* was described together with its ability to encode a hydrophobic protein of 325 amino acids with seven transmembrane domains. Today, it is known that the *MAS1* proto-oncogene generates a GPCR that binds to angiotensin (1–7), a metabolite of angiotensin II [35]; therefore, MAS1 receptor is part of the signaling cascade that supports the endocrine activity

of the renin-angiotensin-aldosterone system (RAS), which regulates the proliferative or antiproliferative effects produced by hormones participating in the RAS pathway [36]. At present, it has been shown that components of RAS are expressed in various types of cancer, including breast cancer [37]. Additionally, several members of the large family of GPCRs have been identified as promoters of carcinogenesis, interacting directly or indirectly with BPA and other phenolic compounds to generate disruptive effects not only during adulthood but also during intrauterine and early postnatal life.

4. Implications of bisphenols on GPCRs signaling in breast cancer: GPER-1, angiotensin, CXC, and α-adrenergic receptors

4.1 General characteristics of GPCRs

The ability to receive and transmit a variety of external and internal signals is a fundamental feature to coordinate morphological and functional activities of multicellular organisms. The notion that receptive structures and substances mediate cellular responses was envisioned in 1897 by Paul Ehrlich with his "side chain" theory [38] and formulated more directly in 1905 by John Newport Langley [39]. However, at that time, the techniques to verify this hypothesis did not exist. It was not until the 1970s that Lefkowitz, using (−)[^{3}H] alprenolol, a potent β-adrenergic antagonist, achieved the specific binding of this ligand to β-adrenergic receptors in frog red blood cells [40] and purified the β-adrenergic receptor (AR) by using affinity chromatography [41]. Since then, it has been demonstrated that the binding of a β-adrenergic agonist to its receptor leads to the activation of the heterotrimeric G protein with the subsequent production of cAMP [42]. The structure of this receptor was later investigated in more detail by Kobilka employing X-ray crystallography who found a surprising homology of β-adrenergic receptor with the previously described rhodopsin receptor [43, 44]. Elucidation of the structural and functional features of the β-adrenergic receptor, including its crystallization, constitutes one of the most relevant scientific milestones in recent times on the knowledge of GPCRs.

Currently, technical advances in molecular biology have made it possible to determine the genetic code of numerous receptor proteins, identifying their amino acidic sequence and allowing interesting evolutionary relationships. GPCRs represent approximately 4% of all genes encoded by the human genome, generating between 650 and 800 different types of GPCRs, constituting the most numerous family of membrane receptors, regulating a large number of physiological and pathological processes [39]. It is estimated that 60% of all commercially available drugs target at least one particular GPCR [45].

The most accepted classification of GPCRs is supported by the International Union of Basic and Clinical Pharmacology (IUPHAR), which based on structural and phylogenetic criteria has grouped them into the families of rhodopsin (family A), secretin (family B), and glutamate (family C) and into the adhesion receptor or frizzled/taste2 families [46]. The structural characteristics and the degree of homology between the different families make it possible to determine that all GPCRs in humans derive from a single common ancestor [46, 47]. GPCRs are characterized by having seven transmembrane helices, with an amino-terminal end located extracellularly and a carboxy-terminal end located toward the interior of the cell, in the vicinity of which the interaction with the heterotrimeric G protein occurs, promoting intracellular signaling events once the receptor is activated by its corresponding agonist [46]. It is estimated that GPCRs arose about 1200 million

years ago, during the evolutionary separation of alveolates (organisms that do not have GPCRs in their genome) from fungi and plants (organisms that do present some types of GPCRs) [47, 48]. More than 80% of all GPCRs belong to the rhodopsin family, characterized by highly conserved motifs and significant structural and functional diversity [46, 47].

GPCRs are integral proteins of the plasma membrane that interact with a large number and variety of signals such as photons, ions, neurotransmitters, peptides, and hormones of different chemical nature [49]. Among the physiological responses triggered by GPCRs are the regulation of cell survival, motility, and cell proliferation [47]. It has been shown that in addition to classical nuclear ERα and ERβ receptors, endogenous estrogens can exert their biological activity by binding to cell membrane-sited receptors, particularly some of the large family of GPCRs [50, 51].

4.2 Bisphenols and their effects beyond nuclear estrogen receptors

As mentioned before, BPA is one of the most studied xenoestrogens, initially developed as estrogen and now produced in large quantities and added to many consumer products such as coatings for cans, dental fillings, plastic bottles, feeding bottles, and some medical devices, causing ubiquitous human exposure. Indeed, more than 1 mg/kg of BPA has been detected in some foods, such as vegetables, probably due to leaks from plastic irrigation devices [24].

It is estimated that approximately 70% of breast carcinomas depend on estrogen and consequently are clinically classified as "hormone-sensitive breast cancer" or ERα-positive tumors. Interestingly, numerous reports indicate that xenoestrogens (chemicals that induce estrogen or antiestrogen responses) can disrupt normal estrogen-dependent signaling. Among the main xenoestrogens, BPA and some of the newly derived bisphenols stand out for their industrial origin and frequent occurrence in our "modern" society and ecosystems, generating a series of alterations in human beings and the environment. With no doubt, BPA is so far one of the most studied xenoestrogens though 17β-estradiol is the most potent form of estrogen when compared with BPA or other bisphenols [1, 50]. In men, estrogens favor serum levels of HDL cholesterol (high-density lipoproteins) to improve the cardiovascular condition and maintain bone mass and sperm maturation. In women, estrogens have strong effects on the female reproductive organs, including the breast, uterus, and menstrual cycle regulation. Moreover, altered estrogen balance is implicated in the pathophysiology of breast, ovarian, colorectal, prostate, and endometrial cancer. Similarly, estrogen unbalance has been implicated in metabolic, autoimmune, cardiovascular, neurodegenerative, and mood disorders [51].

BPA has long-term disruptive effects, even when contact has occurred during prenatal development. Intrauterine BPA exposure in pregnant Wistar rats alters the histoarchitecture of the mammary gland by increasing angiogenesis in female offsprings at postnatal day 50 or 110 [52]. Other studies, also using a murine model, indicate that prenatal exposure to BPA or its analogs, BPS and BPAF, induces accelerated development of the mammary gland, generating in the long term an increased susceptibility to spontaneous preneoplastic lesions, characterized by lobuloalveolar hyperplasia and perivascular inflammation [53].

As expected, the effects of BPA or other bisphenols have already been validated by studying their genomic activities on the pathways of nuclear estrogen receptors and it is only in the last years that the impact on GPCRs such as GPER-1, angiotensin, chemokines, and adrenergic receptors, as alternative estrogen-binding molecules, has begun to be elucidated [54]. Here, we present some evidence about interactions between BPs, GPCRs, breast cancer, and cancer progression.

4.3 G protein: coupled estrogen receptor 1 (GPER-1)

Since the discovery of nuclear ERα by Jensen, the binding of estradiol to cell surface receptors was considered highly unlikely [50]. However, a series of investigations that demonstrated increased levels of cAMP shortly after estrogen stimulation, as well as increased cell proliferation of ERα-deficient cells following stimulation with 17β-estradiol, suggested the presence of a membrane-located receptor that was interacting functionally with estrogen [50, 55]. In 2002, the activity of a membrane estrogen receptor, provisionally called "ER-X," was revealed, though its structure was not investigated [56]. Additionally, a glutamate receptor of the groups I and II sensitive to estrogen, whose activity was independent of Erα, was reported [57]. Given this background, several groups investigated an orphan membrane receptor called GPR30 (G protein-coupled receptor 30), described in 1997 by Carmeci et al., [58] which was strongly expressed in estrogen-sensitive breast cancer cells. In 2005, Thomas et al. demonstrated the specific binding of estrogen to GPR30 in SKBR3 breast cancer cells, a cell type that expresses GPR30 but not nuclear estrogen receptors [59]. In addition, Revankar et al. reported the localization of GPR30 in the endoplasmic reticulum and that its binding to estrogen increased intracellular calcium levels [60]. Subsequently, several groups, including ours, have described that GPR30 is primarily sited in the plasma membrane of breast cancer cells [50, 61]. Due to the ability of GPR30 to bind to estrogen, it was renamed as GPER-1 (G protein-coupled estrogen receptor 1) [61], a protein of 375 amino acids encoded by a gene located in chromosome 7p22.3 [61, 62]. GPER-1 activation triggers a non-genomic or "fast" intracellular signaling cascade characterized by cAMP production and increased intracellular calcium levels [63, 64], Src activation through Gβγ, with subsequent release of HB-EGF (heparin-binding EGF-like growth factor) and transactivation of EGFR (epidermal growth factor receptor) [61]. In addition, the activation of phospholipase C and cFos and several kinases such as ERK1/2 MAPK, PI3K (phosphoinositol 3-kinase), and Akt has also been described [50, 61, 63, 64].

In female GPER-1 null mice, an alteration of glucose homeostasis has been observed associated with a low release of insulin, reduced bone growth, and increased blood pressure [65] whereas male knock-out mice suffer deterioration of the cardiac function [66]. Furthermore, GPER-1 also modulates the immune system, inducing apoptosis of T cells and inhibiting the inflammatory process [67]. In summary, GPER-1 promotes a series of key biological functions attributed exclusively to nuclear α and β receptors in reproductive tissues, the cardiovascular system, the immune system, and the nervous system, among others [61]. GPER-1 has been linked to regulation of growth, migration, and survival of cancer cells [68] since it is expressed in ERα-positive and -negative breast tumors and their corresponding human breast cancer cell lines [50]. Clinical investigations have shown that patients with GPER-1 positive breast tumors and four to six months of tamoxifen treatment developed resistance to therapy and suffered an increase in breast tumor mass and reduced survival [68–70]. GPER-1 activation also produces an increase in the number of breast cancer stem cells (CSCs) by activating the TAZ protein (transcriptional coactivator with PDZ-binding motif), one of the components of the Hippo signaling pathway [71]. The ability to reprogram CSCs is also attributed to elevated TAZ in breast cancer [72]. A recent investigation using tumor cells isolated from ERα/PR-positive breast tumors showed that silencing of GPER-1 generated, *in vitro* and *in vivo*, mammospheres with a reduced population of CSCs [73]. By comparison, the activation of GPER-1 by estrogen or tamoxifen induced the phosphorylation of PKA, stimulating the growth of malignant cells, and the activation of BAD-Ser118, an event related to an increase in the activation

of glucokinase with the consequent production of ATP in the mitochondria, which in turn may promote the maintenance and proliferation of CSCs [73]. Recently, we have reported that continuous exposure of MCF-7 cells (ERα/GPER-1-positive) to tamoxifen significantly increased intracellular calcium mobilization and cell proliferation through GPER-1 overexpression [64]. In addition, tamoxifen, estrogen, and the synthetic GPER-1 agonist, G1, have been shown to promote cell proliferation and cell cycle progression of cancer-associated fibroblasts (CAF) [74].

In general, xenoestrogens have been shown to have similar binding affinities for ERα, ERβ, and GPER-1. Interestingly, the phytoestrogen genistein and BPA have high affinity for GPER-1 [75]. It has been shown that nanomolar concentrations of BPA stimulate the proliferation of TM4 mouse Sertoli cells. Exposure of TM4 cells to ICI 182,780 or G15 (a GPER-1 antagonist) abolished the proliferative response promoted by BPA, pointing out a strong dependence from ERα/ERβ and GPER-1 [76]. In addition, it has been shown that BPA can produce a hypothalamic disrupting effect, particularly on the gonadotropin-releasing hormone (GnRH) release axis and, therefore, on the reproductive cycle in humans [77]. Moreover, nanomolar concentrations of BPA induce through GPER-1 and αvβ3 integrin, which acts as a vitronectin receptor, the proliferation of male germ cells [78].

A study using triple-negative breast cancer cells (TNBC) showed that BPS trigger cancer cells migration, through activation of the GPER/Hippo-YAP signaling pathway. The dephosphorylation of YAP (yes-associated protein) promotes its accumulation in the nucleus, upregulating *CTGF* and *ANKRD1* genes. GPER/Yap inhibition reduces triple-negative breast cancer cells' migration promoted by BPS [79]. In addition, nanomolar concentrations of BPAF and BPB have been shown to exert higher estrogenic effects than BPA on SKBR3 breast cancer cells (GPER-1-positive/ERα-negative), by activating GPER-1 signaling pathways [54]. Similarly, bisphenols can also exert estrogenic effects via GPER-1 in ERα-positive breast cancer cells. Thus, BPAF triggers intracellular calcium mobilization, production of reactive oxygen species (ROS), and activation of ERK1/2 MAPK and Akt pathways and increases cell proliferation in MCF-7 cells [80]. BPAF also upregulates GPER-1 and ERα protein expression whereas silencing of GPER-1 markedly reduced BPAF-stimulated cell proliferation [80]. Furthermore, 4,4′-thiodiphenol (TDP), another molecule derived from BPA, has similar effects to those produced by BPA [81]. By activating GPER-1 signaling, BPA has also been shown to increase migration and proliferation of bovine vascular endothelial cells and SKBR3 and MDA-MB-231 breast cancer cells *in vitro* and to promote tumor growth *in vivo* [82]. Furthermore, treatment of endothelial cells with BPA, but under hypoxic conditions, induced the expression of HIF-1α (hypoxia-inducible factor-1 alpha) and VEGF (vascular endothelial growth factor) [82]. These observations support the hypothesis that BPA, through the biological activity of vascular endothelial cells, promotes the development of breast tumor cells via GPER-1.

The inflammatory response is an important component of many diseases, including metabolic diseases and cancer. Notably, BPA and BPS promote persistent inflammatory states through increased expression of IL-19, EGFR, and TGF-β, among other regulatory molecules [82, 83]. Interestingly, biological fluids from cancer patients contain elevated levels of the bioactive peptide hormones known as kinins [84], and the kinin B1 receptor (B1R), another member of the GPCR family stimulated by kinin B1R agonists (Lys-des[Arg^9]bradykinin or des[Arg^9]bradykinin), is expressed in ductal breast carcinoma *in situ*, invasive ductal carcinoma, and benign fibroadenomas [84, 85]. In addition, we have previously determined that stimulation of kinin B1R promotes cell proliferation, chemotaxis, and release of metalloproteinases (MMP-2 and MMP-9) from breast cancer cells through the EGFR/ERK1/2 pathway [85, 86]. Although there is no research directly linking

bisphenol activity with the kinin B1R, we have recently reported that both GPER-1 and B1R are overexpressed in ERα-positive breast cancer cells continuously exposed to tamoxifen [64], suggesting a possible cross-talk between both GPCRs in estrogen-sensitive breast cancer cells, to increase cell proliferation and cancer progression under persistent exposure to bisphenols. If other GPCRs of the GPER-1 family such as the orphan GPCR, GPR161 (G protein-coupled receptor 161), is activated by bisphenols, it is an unexplored and interesting field since GPR161 is overexpressed in TNBCs and correlates with a bad prognosis. Overexpression of GPR161 in human mammary epithelial cells produces an increase in cell proliferation, migration, intracellular accumulation of E-cadherin, formation of multiacinar structures in 3D cell cultures, and invasion through a rapamycin signaling-dependent pathway [87].

4.4 Angiotensin receptors

Specific angiotensin-binding sites in tissues were discovered in the 1960s by Merlin Bumpus, following tracking of radioactive angiotensin infused into live rats [88]. The physiological relevance of this finding was related to the best-known responses triggered by angiotensins, such as vasoconstriction or aldosterone secretion [88, 89]. Subsequently, the specific and saturable binding of radiolabeled angiotensin was demonstrated in homogenates, subcellular fractions, and tissues of several species, including humans [90]. Additionally, pharmacological experiments showed different tissue responses to angiotensin and the presence of different types of angiotensin receptor (AT) proteins [91, 92]. The classification of angiotensin receptors was initially somewhat confusing, but today two types of receptors are formally recognized and called AT1 and AT2 [93–95]. The human AT1 receptor is encoded by a single gene located on the q arm, band 22 of chromosome 3 and its distribution is quite wide in adult tissues [89, 94]. AT1 activation triggers an intracellular signaling cascade that promotes the phosphorylation of proteins that participate in smooth muscle contraction, aldosterone secretion, cell growth, and cell proliferation [96]. By comparison, the gene that encodes the AT2 receptor is located on the X chromosome [93], expressing itself predominantly during intrauterine development though its levels have been found to increase due to stress or tissue damage [96]. Physiologically, the activity of AT2 receptor antagonizes that of the AT1 receptor [94, 96]. Since their discovery, angiotensin receptors have been considered important therapeutic targets for hypertension, heart and kidney failure, and other types of vascular diseases [10]. Moreover, angiotensin receptors have also been involved in the development of different types of metabolic and neoplastic diseases.

One of the most important theories elaborated to explain the origin and persistence of cancer in modern societies deals with CSCs, key cellular players first isolated in the 1990s by John E. Dick from human acute myeloid leukemia cells [97]. So far, CSCs have been identified in different types of tumors as a subpopulation of cancer cells with self-renewal and multipotency properties, capable of initiating and maintaining carcinogenesis, through clones with different degrees of differentiation, and responsible for resistance to treatment strategies, metastases, and disease relapse [34, 98]. Recent evidence indicates that the RAS pathway is crucial for an appropriate tumor microenvironment and maintenance and differentiation of CSCs [36, 97–99].

Overexpression of the AT2 receptor stimulates the differentiation of mesenchymal stem cells [99], and signaling via AT1 or AT2 receptors can condition the hematopoietic lineage [98]. Expression of angiotensin receptors and other members of the RAS pathway in CSCs suggests that new therapeutic routes may emerge for several types of cancer [10, 100–102]. Human embryonic cells exposed to low

concentrations of BPA upregulate the expression of Oct4 and Nanog proteins, two early differentiation markers of mammary epithelial cells [103]. Another possible regulator of CSCs, activated by BPA, is bone morphogenetic protein [104]; it has been suggested that bone morphogenetic protein 2 initiates the transformation of stem cells toward a malignant phenotype [105]. Similarly, the presence of angiotensin II has been verified in breast cancer epithelial cells [102, 106] and the stroma [102] and overexpression of AT1 receptor in MCF-7 cells has been associated with an increased capacity for cell migration, invasion, proliferation [101, 107], and release of MMP-9 [107], responses associated with phosphorylation of ERK1/2 MAPK [107]. Interestingly, most of the effects of angiotensin II on cell proliferation and activation of the Ras-Raf-MAPK pathway and the transcription factors NF-κB and CREB can be inhibited by an AT1 interfering RNA, plus treatment with irbesartan, an AT1 pharmacological antagonist [107]. On the other hand, a study in nonmetastatic operable breast tumors determined the presence of AT2 receptors in up to 35% of cases whereas tumors expressing the AT1 receptor corresponded to stage III and showed an increased number of mitosis and vascularization [108].

Considering that inflammation and increased angiogenesis are two events directly associated with angiotensin receptors' dysregulation, these receptors have been proposed to contribute significantly to the development of neoplasia, especially if we consider the possibility that they could be activated by bisphenols [107–109].

4.5 Chemokine receptors

Evolutionarily, it is estimated that the origin of the chemokine system dates back about 650 million years ago [110]. This system has undergone great structural and functional diversification, contributing to the physiological activity of the different tissues of vertebrates [110, 111]. The first chemokine was described in 1977 by identifying the sequence and activity of platelet factor 4 (PF-4) [112]. In 1985, gamma interferon, another chemokine with high homology with PF-4 and proinflammatory activity, was discovered [113]. Subsequently, Yoshimura et al. isolated and described a monocyte chemotactic protein (MCP-1), which is currently recognized as one of the most potent monocyte activators [114]. Initially, chemokines were given names associated with their biological activity, but in order to limit the generation of a diversity of names due to the increasing amount of chemokines discovered, a nomenclature was created in the year 2000 [115]. Currently, chemokines are characterized by the presence of four cysteine residues involved in their 3-dimensional shape; chemokines are classified into four main subfamilies: CC, CXC, XC, and CX3C followed by a number (the "X" corresponds to an amino acid that can change) [115].

At the beginning of the 1990s it was determined that stimulation of leukocytes by proinflammatory chemokines induced a transient increase in intracellular calcium levels [116, 117]; this observation constituted one of the first indications of chemokine receptors' activity such as GPCRs-dependent chemokines [111, 115]. Initially it was thought that the activity of chemokine receptors was limited to modulation of certain aspects of the immune response, such as the recruitment of neutrophils during acute inflammation or of monocytes during chronic inflammation. However, it is currently considered that practically any cell type in the body can express chemokine receptors and not just leukocytes [111, 118]. Similarly, it is estimated that around 20 chemokine receptors can recognize the more than 50 chemokines studied so far [118, 119]. This opens a range of biological responses commanded by chemokine receptors and accounts for versatility of these receptors in their interaction with chemokines including a role in the pathophysiology of cancer. The first investigation that evidenced this activity used a model of murine

lymphoma and demonstrated the association between MCP-1 (current CCL2) with promotion of tissue invasion [120]. Following this finding, the activity of chemokine receptors in the initiation and progression of different types of cancers has been demonstrated [111, 121]. In breast cancer, chemokine receptors can downregulate the immune response, favoring tumor progression [119, 121] by promoting tumor growth and survival signals [119]. The chemokine system has also been related to the maintenance of CSCs, through modulation of tumor microenvironment [111, 119, 121]. Although there are still many factors to be clarified, it has been established that the chemokine system significantly strengthens carcinogenic activity by promoting angiogenesis. Actually, the chemokine receptors expressed in endothelial cells and displaying high proangiogenic activity are CXCR2 (whose ligands are CXCL1, CXCL2, CXCL3, CXCL5, CXCL6, CXCL7, and CXCL8), and CXCR1 (whose ligand is CXCL8, one of the most potent angiogenic molecules) [119]. Additionally, it is known that CXCL8 induces higher levels of MMP-2 and MMP-9 and of VEGF, supporting its role in cancer cell migration and metastasis [111]. Recently, CXCL1-3 has been negatively correlated with the prognosis and survival of breast cancer patients [122]. Furthermore, a phytoestrogen, called quercetin (a flavonoid found in high concentrations in fruits and vegetables), has been found to have an inhibitory effect on cell proliferation, promoting apoptosis in MDA-MB-231 and MCF-7 cells and increasing CXCL1-2 secretion [122].

It has been suggested that early exposure to BPA can cause deleterious immunological effects, creating over time the organic conditions for development of a variety of disorders during adulthood; thus, bisphenols can dysregulate the chemokine network altering homeostasis of the immune system. A study in which a low dose of BPA was administered intratracheally in six-week-old male mice suggests that BPA exacerbates the allergic process of the airways through the expression of CXCR4 receptors in antigen-presenting cells [123]. Additionally, it has been estimated that 10 μM BPA, BPS, and BPAF increase secretion levels of chemokines, such as CXCL8 (IL-8), reducing the viability of human macrophages [124]; this effect is partially reversed by exposure to genistein (one of the most common phytoestrogens) [124].

Notably, 17β-estradiol increases the expression of CXC12 and its receptor CXCR4 in MCF-7 cells but inhibits the expression of CXCR7, the other receptor for this chemokine. Overexpression of CXC12 and CXCR4 is important for the increase in the proliferation rate of breast cancer cells stimulated with 17β-estradiol. By contrast, high levels of CXCR7 are related to the basal growth of tumor cells [125]. These effects can be explained molecularly by the regulatory effect of 17β-estradiol on the level of chromatin compaction in the promoters of genes related to chemokines.

Furthermore, the activity of the chemokine network has been associated with a series of estrogenic compounds in estrogen-sensitive breast cancer cells. Genistein and BPA (in addition to estrogen) have been shown to stimulate CXC12 synthesis and secretion in T47D breast cancer cells [126]. Similarly, it has been observed that BPAF stimulates proliferation of T47D cells, in a dose-dependent manner, promoting transcription and secretion of CXCL12, while the use of a shRNA or selective inhibition of CXCL12 significantly reduced the activity of CXCL12 and cell proliferation [127]. Dysregulation of the chemokine network by BPs has been associated, in humans and animals, with a variety of adverse effects both on the development and on the structure of the mammary gland, highlighting the generation of intraductal hyperplasia and carcinoma *in situ* in mice exposed prenatally to BPA [128]. Thus, early exposure to BPA may increase susceptibility of the mammary gland to malignant transformation. Notably, prenatal exposure of mice to BPA induced

gene reprogramming that resulted in low expression of members of the CXC family (CXCL2, CXCL4, CXCL14, and CXCL20) and of the interferon regulatory factor 9 (IL-R9) as well as the immune response gene 1 (Irg1) and some members of genes 1 (IL-1β and IL1-RN) and genes 2 (IL-7) of the interleukin family [129]. These changes affected the normal activity of the inflammatory response, increasing the risk of developing breast cancer in the long term [129].

In perspective, the set of experimental results indicates that bisphenols, particularly BPA and BPAF, target the mammary gland, affecting the expression of chemokine receptors and their ligands, alterations that have been associated with changes in normal development. Although an important part of the research indicates a possible cross-talk between nuclear estrogen receptors, GPCRs and bisphenols to alter homeostasis of the chemokine system, this interactions have so far not been directly addressed and remain largely unknown.

4.6 Adrenergic receptors

Epinephrine and norepinephrine bind to specific GPCRs referred to as adrenergic receptors, modulating physiological responses such as metabolism, vascular tone, and cell proliferation. These receptors are classified into three types, which are subdivided into the following subtypes: α1-adrenergic (α1A, α1B, α1D), α2-adrenergic (α2A, α2B, α2C), and β-adrenergic (β1, β2, β3) [130, 131]. In general, α-adrenergic receptors have a vasoconstrictive effect and produce excitation in the uterus, heart, and blood vessels and have a relaxing effect in the intestine [132]. On the other hand, β-adrenergic receptors have a vasodilator effect, but a vasoconstrictor activity in the uterus and an excitatory effect in the myocardium [131, 132]. By binding to catecholamines, AR activate various signaling pathways that depend on heterotrimeric G proteins, which use phospholipase C and adenyl cyclase to produce second messengers that activate cytosolic kinases, which by translocating to the nucleus modulate different transcription factors [133]. Two single nucleotide polymorphisms of the α2-adrenergic receptor gene (rs1800544 and rs553668) have been considered as useful tools to predict the severity of invasive breast cancer and their relation with metabolic alterations [130]. Presence of AR has been described in human epithelial breast cells [134, 135] and in adipocytes of breast tissue [131, 136]. Furthermore, stimulation of α and β AR by catecholamines has been shown to stimulate proliferation and migration of non-tumor (MCF-10A) and neoplastic (MCF-7 and MDA-MB-231) breast epithelial cells, generating an increase in cAMP levels, effects that are reversed by the use of AR antagonists [135, 136].

Prenatal exposure of mice to BPA (10 μg/kg body weight) and its binding to α2-adrenergic receptors changed the binding affinity of adrenaline to α2-adrenergic receptors in the locus coeruleus and the medial preoptic area of the brain and eliminated the behavioral differences between males and females related to emotion and anxiety [137]. Other studies have indicated that intrauterine exposure to BPA can alter the programming of most sensitive brain regions to steroids, differentially affecting men and women [51, 138]. On the other hand, both BPA and BPS have been shown to promote lipid accumulation and differentiation of murine 3 T3-L1 adipocytes in a dose-dependent manner though BPS displayed more adipogenicity than BPA [136]. Interestingly, it has been established that alterations in the typical responses of the sympathetic nervous system and its signaling pathways alter the normal metabolic balance, generating conditions for the establishment of disorders, such as obesity and type II diabetes mellitus, and consequently increasing the risk for cancer development [133].

Although there is no conclusive evidence to establish a direct relationship between bisphenols exposure and activation of AR in the context of breast cancer, experimental evidence indicates that they are involved in the development of breast cancer at a systemic level mediated by the sympathetic nervous system and through activation of α and β adrenergic receptors that are expressed in a great variety of cell types, including epithelial cells and adipocytes of the breast. On the other hand, interactions of AR with BPA in cells of the nervous system and with BPA and BPS during adipogenesis suggest that there exists a disruptor axis in sympathetic and metabolic activity to favor the development of neoplasia [136].

5. Conclusion

Although the concern about the deleterious effects of BPA on health has been recognized by the industry, in particular its relationship with cancer, the generation of new analogs such as BPB, BPF, and BPAF, which are part of products labeled as BPA-free, has not solved the problem [129]. Indeed, *in vitro* assays have revealed that BPAF has a stronger binding affinity for estrogen receptors than BPA [80]. The evidence accumulated so far suggests that BPA and BPS may contribute to breast cancer by disrupting the organization of acinar structures and by affecting the natural development of the mammary gland [3]. To date, the effects of BPA in eukaryotic cells have been reported to be mediated primarily by steroid receptors, including ERα and ERβ, but also as we discussed in this chapter, the effects are also mediated by activation of GPCRs exposed on the cell surface (**Figure 2**) [41].

More studies regarding the effects of bisphenols on angiotensin, adrenergic, chemokines, B1R, or even GPER-1 receptors are necessary to determine the real risks of these compounds for human health and the particular risk of developing cancer.

Understanding the role of endocrine disruptors and the mechanisms involved in their action is crucial to prevent the harm that bisphenols may cause in the population and to improve public health approaches to control cancer as well as some chronic diseases that afflict adult life.

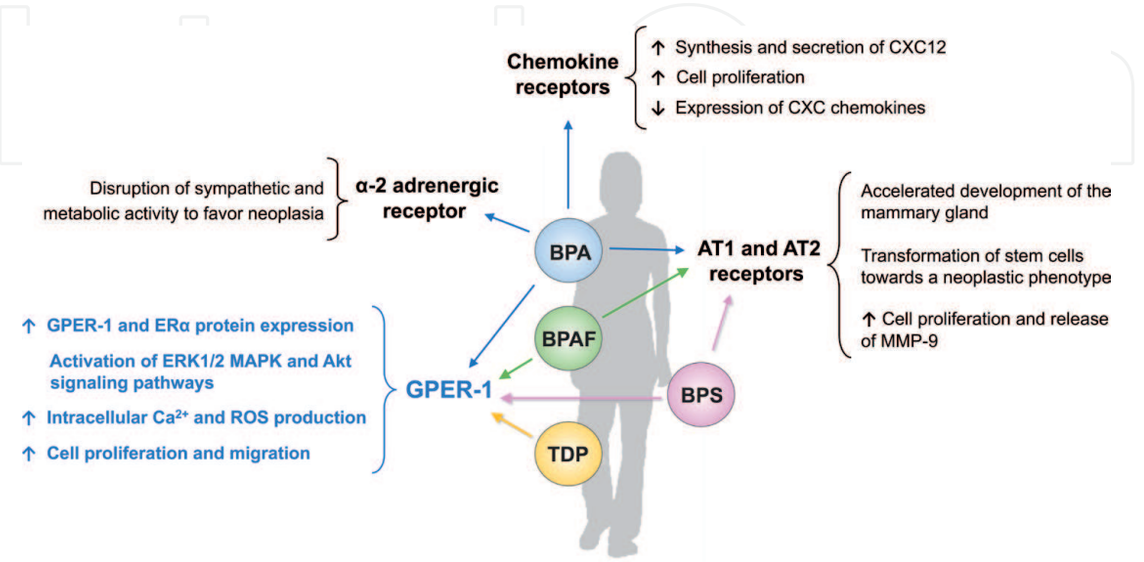

Figure 2.
Potential effects of bisphenols on GPCRs to favor development and progression of breast cancer. BPA, BPAF, BPS, bisphenols A, AF and S; GPER-1, G protein coupled estrogen receptor 1; AT, angiotensin; Erα, estrogen receptor alpha; TDP, 4,4′-thiodiphenol; ROS, reactive oxygen species.

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References

[1] Dumitrascu MC, Mares C, Petca RC, Sandru F, Popescu RI, Mehedintu C, et al. Carcinogenic effects of bisphenol A in breast and ovarian cancers. Oncology Letters. 2020;**20**:282-289. DOI: 10.3892/ol.2020.12145

[2] Liao C, Kannan K. Widespread occurrence of bisphenol A in paper and paper products: Implications for human exposure. Environmental Science & Technology. 2011;**45**:9372-9379

[3] Feldman D, Krishnan A. Estrogens in unexpected places: Possible implications for researchers and consumers. Environmental Health Perspectives. 1995;**103**:129-133

[4] Hengstler JG, Foth H, Gebel T, Kramer PJ, Lilienblum W, Schweinfurth H, et al. Critical evaluation of key evidence on the human health hazards of exposure to bisphenol A. Critical Reviews in Toxicology. 2011;**41**:263-291

[5] Eladak S, Grisin T, Moison D, Guerquin MJ, N'Tumba-Byn T, Pozzi-Gaudin S, et al. A new chapter in the bisphenol a story: Bisphenol S and bisphenol F are not safe alternatives to this compound. Fertility and Sterility. 2015;**103**:11-21

[6] Cheryl S. Rosenfeld. Frontiers in Neuroendocrinology. 2017;**47**:123-133

[7] Pouzaud F, Thierry-Mieg M, Burga K, Vérines-Jouin L, Fiore K, et al. ANSES's Working Group on « Endocrine disruptors », ANSES's Expert Committee on « Chemicals covered by the REACh and CLP Regulations », Concerns related to ED-mediated effects of Bisphenol A and their regulatory consideration. Molecular and Cellular Endocrinology. 2018;**475**:92-106. DOI: 10.1016/j.mce.2018.02.002

[8] Kahn LG, Philippat C, Nakayama SF, Slama R, Trasande L. Endocrine-disrupting chemicals: Implications for human health. The Lancet Diabetes and Endocrinology. 2020;**8**:703-718

[9] Atlas E, Dimitrova V. Bisphenol S and Bisphenol A disrupt morphogenesis of MCF-12A human mammary epithelial cells. Scientific Reports. 2019;**9**:1-10. DOI: 10.1038/s41598-019-52505-x

[10] Dhanachandra Singh K, Karnik SS. Angiotensin receptors: Structure, function, signaling and clinical applications. Journal of Cellular Signaling. 2017;**01**:1-8

[11] Zincke T, Walter W. II. Ueber die Einwirkung von Brom und von Chlor auf Phenole: Substitutionsproducte, Pseudobromide und Pseudochloride. XI. Ueber die Einwirkung von Brom auf p-Oxydiphenylmethan. Justus Liebigs Annalen der Chemie. 1904;**334**:367-385

[12] Dodds. Endocrine-dirsupting chemical. Nature. 1936;**137**:996

[13] Casajuana N, Lacorte S. New methodology for the determination of phthalate esters, bisphenol A, bisphenol A diglycidyl ether, and nonylphenol in commercial whole milk samples. Journal of Agricultural and Food Chemistry. 2004;**52**:3702-3707

[14] Dodds EC, Goldberg L, Lawson W, Robinson R. Synthetic oestrogenic compounds related to stilbene and diphenylethane. Part I. Proceedings of the Royal Society B. 1939;**127**:140-167

[15] Krishnan V, Stathis P, Permuth SF, Tokes L, Feldman D. Bisphenol-A: Polycarbonate. Endocrinology. 1993;**6**:2279-2286. DOI: 10.1210/endo.132.6.8504731

[16] Pu Y, Gingrich JD, Steibel JP, Veiga-Lopez A. Sex-specific modulation of fetal adipogenesis by gestational Bisphenol A and Bisphenol S exposure. Endocrinology. 2017;**158**:3844-3858

[17] Diamanti-Kandarakis E, Bourguignon JP, Giudice LC, Hauser R, Prins GS, Soto AM, et al. Endocrine-disrupting chemicals: An Endocrine Society scientific statement. Endocrine Reviews. 2009;**30**:293-342

[18] VandeVoort CA, Gerona RR, Vom Saal FS, Tarantal AF, Hunt PA, Hillenweck A, et al. Maternal and fetal pharmacokinetics of oral radiolabeled and authentic bisphenol a in the rhesus monkey. PLoS One. 2016;**11**:1-16

[19] Mas S, Egido J, González-Parra E. The importance of bisphenol A, an uraemic toxin from exogenous sources, in haemodialysis patients. Nefrologia [Internet]. Sociedad Española de Nefrología. 2017;**37**:229-234. DOI: 10.1016/j.nefroe.2017.06.004

[20] Bousoumah R, Leso V, Iavicoli I, Huuskonen P, Viegas S, Porras SP, et al. Biomonitoring of occupational exposure to bisphenol A, bisphenol S and bisphenol F: A systematic review. Science of the Total Environment. 2021;**783**:146905. DOI: 10.1016/j.scitotenv.2021.146905

[21] Sarigiannis DA, Karakitsios SP, Handakas E, Simou K, Solomou E, Gotti A. Integrated exposure and risk characterization of bisphenol-A in Europe. Food and Chemical Toxicology. 2016;**98**:134-147. DOI: 10.1016/j.fct.2016.10.017

[22] Ullah A, Pirzada M, Jahan S, Ullah H, Shaheen G, Rehman H, et al. Bisphenol A and its analogs bisphenol B, bisphenol F, and bisphenol S: Comparative in vitro and in vivo studies on the sperms and testicular tissues of rats. Chemosphere. 2018;**209**:508-516. DOI: 10.1016/j.chemosphere.2018.06.089

[23] Le Fol V, Aït-Aïssa S, Sonavane M, Porcher JM, Balaguer P, Cravedi JP, et al. In vitro and in vivo estrogenic activity of BPA, BPF and BPS in zebrafish-specific assays. Ecotoxicology and Environmental Safety. 2017;**142**:150-156

[24] Bilancio A, Bontempo P, Di Donato M, Conte M, Giovannelli P, Altucci L, et al. Bisphenol a induces cell cycle arrest in primary and prostate cancer cells through EGFR/ERK/p53 signaling pathway activation. Oncotarget. 2017;**8**:115620-115631

[25] Rochester JR, Bolden AL. Bisphenol S and F: A systematic review and comparison of the hormonal activity of bisphenol a substitutes. Environmental Health Perspectives. 2015;**123**:643-650

[26] Matsushima A, Liu X, Okada H, Shimohigashi M, Shimohigashi Y. Bisphenol AF is a full agonist for the estrogen receptor ERα but a highly specific antagonist for ERβ. Environmental Health Perspectives. 2010;**118**:1267-1272

[27] Tharp AP, Maf MV, Hunt PA, Vandevoort CA, Sonnenschein C, Soto AM. Bisphenol A alters the development of the rhesus monkey mammary gland. Proceedings of the National Academy of Sciences of the United States of America. 2012;**19**:8190-8195. DOI: 10.1073/pnas.1120488109

[28] Wetherill YB, Akingbemi BT, Kanno J, McLachlan JA, Nadal A, Sonnenschein C, et al. In vitro molecular mechanisms of bisphenol A action. Reproductive Toxicology. 2007;**24**:178-198

[29] Fernandez SV, Huang Y, Snider KE, Zhou Y, Pogash TJ, Russo J. Expression and DNA methylation changes in human breast epithelial cells after bisphenol A exposure. International Journal of Oncology. 2012;**41**:369-377. DOI: 10.3892/ijo.2012.1444

[30] Dairkee SH, Luciani-Torres MG, Moore DH, Goodson WH. Bisphenol-A-induced inactivation of the p53 axis underlying deregulation of proliferation

kinetics, and cell death in non-malignant human breast epithelial cells. Carcinogenesis. 2013;**34**:703-712

[31] LaPensee EW, Tuttle TR, Fox SR, Ben-Jonathan N. Bisphenol A at low nanomolar doses confers chemoresistance in estrogen receptor-α-positive and -negative breast cancer cells. Environmental Health Perspectives. 2009;**117**:175-180

[32] Buteau-Lozano H, Velasco G, Cristofari M, Balaguer P, Perrot-Applanat M. Xenoestrogens modulate vascular endothelial growth factor secretion in breast cancer cells through an estrogen receptor-dependent mechanism. The Journal of Endocrinology. 2008;**196**:399-412

[33] Zhang W, Fang Y, Shi X, Zhang M, Wang X, Tan Y. Effect of bisphenol A on the EGFR-STAT3 pathway in MCF-7 breast cancer cells. Molecular Medicine Reports. 2012;**5**:41-47

[34] Lillo MA, Nichols C, Seagroves TN, Miranda-Carboni GA, Krum SA. Bisphenol A induces Sox2 in ER+ breast cancer stem-like cells. Hormones and Cancer. 2017;**8**:90

[35] O'Hayre M, Vázquez-Prado J, Kufareva I, Stawiski EW, Handel TM, Seshagiri S, et al. The emerging mutational landscape of G proteins and G-protein-coupled receptors in cancer. Nature Reviews. Cancer. 2013;**13**:412-424. Available from: https://www.nature.com/articles/nrc3521

[36] Young D, Waitches G, Birchmeier C, Fasano O, Wigler M. Isolation and characterization of a new cellular oncogene encoding a protein with multiple potential transmembrane domains. Cell. 1986;**45**:711-719. Available from: https://pubmed.ncbi.nlm.nih.gov/3708691/

[37] Acconcia F. The network of angiotensin receptors in breast cancer. Cell. 2020;**9**:1-14

[38] Maehle AH. A binding question: the evolution of the receptor concept. Endeavour. 2009;**33**:135-140. Available from:. DOI: 10.1016/j.endeavour.2009.09.001

[39] Maehle AH. "Receptive substances": John Newport Langley (1852-1925) and his path to a receptor theory of drug action. Medical History. 2004;**48**:153-174

[40] Lefkowitz RJ, Mukherjee C, Coverstone M, Caron MG. Stereospecific [3h](−)-alprenclol binding sites, e-adrenergic receptors and adenylate cyclase Robert. Biochemical and Biophysical Research Communications. 1974;**60**:703-709

[41] Caron MG, Srinivasan Y, Pitha J, Kociolek K, Lefkowitz RJ. Affinity chromatography of the β adrenergic receptor. The Journal of Biological Chemistry. 1979;**254**:2923-2927

[42] Cerione RA, Sibley DR, Codina J, Benovic JL, Winslow J, Neer EJ, et al. Reconstitution of a hormone-sensitive adenylate cyclase system. The pure β-adrenergic receptor and guanine nucleotide regulatory protein confer hormone responsiveness on the resolved catalytic unit. The Journal of Biological Chemistry. 1984;**259**:9979-9982

[43] Hanson MA, Stevens RC. Discovery of new GPCR biology: One receptor structure at a time. Structure. 2009;**17**:8-14. DOI: 10.1016/j.str.2008.12.003

[44] Palczewski K, Kumasaka T, Hori T, Behnke CA, Motoshima H, Fox BA, et al. Crystal structure of rhodopsin: A G protein-coupled receptor. Science. 2000;**289**:739-745

[45] Heifetz A, Schertler GFX, Seifert R, Tate CG, Sexton PM, Gurevich VV, et al. GPCR structure, function, drug discovery and crystallography: report from Academia-Industry International

Conference (UK Royal Society) Chicheley Hall, 1-2 September 2014. Naunyn-Schmiedeberg's Archives of Pharmacology. 2015;**388**:883-903

[46] Fredriksson R, Lagerström MC, Lundin LG, Schiöth HB. The G-protein-coupled receptors in the human genome form five main families. Phylogenetic analysis, paralogon groups, and fingerprints. Molecular Pharmacology. 2003;**63**:1256-1272

[47] Gacasan SB, Baker DL, Parrill AL. G protein-coupled receptors: The evolution of structural insight. AIMS Biophys [Internet]. American Institute of Mathematical Sciences. 2017;**4**:491-527. Available from: http://www.aimspress.com/article/doi/10.3934/biophy.2017.3.491

[48] Fredriksson R, Schiöth HB. The repertoire of G-protein-coupled receptors in fully sequenced genomes. Molecular Pharmacology. 2005; **67**:1414-1425

[49] Dunn HA, Orlandi C, Martemyanov KA. Beyond the ligand: Extracellular and transcellular G protein-coupled receptor complexes in physiology and pharmacology. Pharmacological Reviews. 2019; **71**:503-519

[50] Molina L, Figueroa CD, Bhoola KD, Ehrenfeld P. GPER-1/GPR30 a novel estrogen receptor sited in the cell membrane: Therapeutic coupling to breast cancer. Expert Opinion on Therapeutic Targets. 2017;**21**:755-766. DOI: 10.1080/14728222.2017.1350264

[51] Bustamante-Barrientos FA, Méndez-Ruette M, Ortloff A, Luz-Crawford P, Rivera FJ, Figueroa CD, et al. The impact of estrogen and estrogen-like molecules in neurogenesis and neurodegeneration: Beneficial or harmful? Frontiers in Cellular Neuroscience. 2021;**15**:1-19

[52] Durando M, Kass L, Perdomo V, Bosquiazzo VL, Luque EH, Muñoz-De-Toro M. Prenatal exposure to bisphenol A promotes angiogenesis and alters steroid-mediated responses in the mammary glands of cycling rats. The Journal of Steroid Biochemistry and Molecular Biology. 2011;**127**:35-43

[53] Tucker DK, Bouknight SH, Brar SS, Kissling GE, Fenton SE. Evaluation of prenatal exposure to bisphenol analogues on development and long-term health of the mammary gland in female mice. Environmental Health Perspectives. 2018;**126**(**8**):087003. DOI: 10.1289/EHP3189

[54] Cao LY, Ren XM, Li CH, Zhang J, Qin WP, Yang Y, et al. Bisphenol AF and Bisphenol B exert higher estrogenic effects than Bisphenol A via G Protein-coupled estrogen receptor pathway. Environmental Science & Technology. 2017;**51**:11423-11430

[55] Szego CM, Davis JS. Adenosine 3′,5′-monophosphate in rat uterus: acute elevation by estrogen. Proceedings of the National Academy of Sciences of the United States of America. 1967; **58**:1711-1718

[56] Toran-Allerand CD, Guan X, MacLusky NJ, Horvath TL, Diano S, Singh M, et al. ER-X: A novel, plasma membrane-associated, putative estrogen receptor that is regulated during development and after ischemic brain injury. The Journal of Neuroscience. 2002;**22**:8391-8401

[57] Boulware MI, Weick JP, Becklund BR, Kuo SP, Groth RD, Mermelstein PG. Estradiol activates group I and II metabotropic glutamate receptor signaling, leading to opposing influences on cAMP response element-binding protein. The Journal of Neuroscience. 2005;**25**:5066-5078

[58] Carmeci C, Thompson DA, Ring HZ, Francke U, Weigel RJ.

Identification of a gene (GPR30) with homology to the G-protein-coupled receptor superfamily associated with estrogen receptor expression in breast cancer. Genomics. 1997;**617**:-607, 17. DOI: 10.1006/geno.1997.4972

[59] Thomas P, Pang Y, Filardo EJ, Dong J. Identity of an estrogen membrane receptor coupled to a G protein in human breast cancer cells. Endocrinology. 2005;**146**:624-632

[60] Revankar CM, Cimino DF, Sklar LA, Arterburn JB, Prossnitz ER. A transmembrane intracellular estrogen receptor mediates rapid cell signaling. Science. 2005;**307**:1625-1630

[61] Prossnitz ER, Arterburn JB. International union of basic and clinical pharmacology. XCVII. G protein–coupled estrogen receptor and its pharmacologic modulators. Pharmacological Reviews. 2015; **67**:505-540

[62] Sharma G, Hu C, Staquicini DI, Brigman JL, Liu M, Mauvais-Jarvis F, et al. Preclinical efficacy of the GPER-selective agonist G-1 in mouse models of obesity and diabetes. Science Translational Medicine. 2020; **12**:eaau596. Available from: https://pubmed.ncbi.nlm.nih.gov/31996464/

[63] Revankar CM, Cimino DF, Sklar LA, Arterburn JB, Prossnitz ER. A transmembrane intracellular estrogen receptor mediates rapid cell signaling. Science. 2005;**307**: 1625-1630

[64] Molina L, Bustamante F, Ortloff A, Ramos I, Ehrenfeld P, Figueroa CD. Continuous exposure of breast cancer cells to tamoxifen upregulates GPER-1 and increases cell proliferation. Frontiers in Endocrinology. 2020; **1**:563165. Available from: https://www.frontiersin.org/article/10.3389/fendo.2020.563165/full

[65] Martensson UEA, Salehi SA, Windahl S, Gomez MF, Swärd K, Daszkiewicz-Nilsson J, et al. Deletion of the G protein-coupled receptor 30 impairs glucose tolerance, reduces bone growth, increases blood pressure, and eliminates estradiol-stimulated insulin release in female mice. Endocrinology. 2009;**150**:687-698

[66] Delbeck M, Golz S, Vonk R, Janssen W, Hucho T, Isensee J, et al. Impaired left-ventricular cardiac function in male GPR30-deficient mice. Molecular Medicine Reports. 2011;**4**:37-40

[67] Notas G, Kampa M, Castanas E. G protein-coupled estrogen receptor in immune cells and its role in immune-related diseases. Frontiers in Endocrinology. 2020;**11**:1-9

[68] Feldman RD, Limbird LE. GPER (GPR30): A nongenomic receptor (GPCR) for steroid hormones with implications for cardiovascular disease and cancer. Annual Review of Pharmacology and Toxicology. 2017;**57**:567-584

[69] Ignatov A, Ignatov T, Weienborn C, Eggemann H, Bischoff J, Semczuk A, et al. G-protein-coupled estrogen receptor GPR30 and tamoxifen resistance in breast cancer. Breast Cancer Research and Treatment. 2011;**128**:457-466

[70] Ignatov T, Claus M, Nass N, Haybaeck J, Seifert B, Kalinski T, et al. G-protein-coupled estrogen receptor GPER-1 expression in hormone receptor-positive breast cancer is associated with poor benefit of tamoxifen. Breast Cancer Research and Treatment. 2019;**174**:121-127. DOI: 10.1007/s10549-018-5064-8

[71] Zhou X, Lei Q, Guan K, Zhou X, Wang S, Wang Z, et al. Estrogen regulates Hippo signaling via GPER in breast cancer. The Journal of Clinical Investigation. 2015;**125**:2123-2135

[72] Piccolo S, Dupont S, Cordenonsi M. The biology of YAP/TAZ: Hippo signaling and beyond. Physiological Reviews. 2014;**94**:1287-1312

[73] Chan YT, Lai ACY, Lin RJ, Wang YH, Wang YT, Chang WW, et al. GPER-induced signaling is essential for the survival of breast cancer stem cells. International Journal of Cancer. 2020; **146**:1674-1685

[74] Luo H, Yang G, Yu T, Luo S, Wu C, Sun Y, et al. GPER-mediated proliferation and estradiol production in breast cancer-associated fibroblasts. Endocrine-Related Cancer. 2014; **21**:355-369

[75] Thomas P, Dong J. Binding and activation of the seven-transmembrane estrogen receptor GPR30 by environmental estrogens: A potential novel mechanism of endocrine disruption. The Journal of Steroid Biochemistry and Molecular Biology. 2006;**102**:175-179

[76] Ge LC, Chen ZJ, Liu HY, Zhang KS, Liu H, Huang HB, et al. Involvement of activating ERK1/2 through G protein coupled receptor 30 and estrogen receptor α/β in low doses of bisphenol A promoting growth of Sertoli TM4 cells. Toxicology Letters. 2014;**226**:81-89. DOI: 10.1016/j.toxlet.2014.01.035

[77] Pouzaud F, Thierry-Mieg M, Burga K, Vérines-Jouin L, Fiore K, Beausoleil C, et al. Concerns related to ED-mediated effects of Bisphenol A and their regulatory consideration. Molecular and Cellular Endocrinology. 2018;**475**:92-106

[78] Sheng Z, Wang C, Ren F, Liu Y, Zhu B. Molecular mechanism of endocrine-disruptive effects induced by Bisphenol A: The role of transmembrane G-protein estrogen receptor 1 and integrin α v β 3. Journal of Environmental Sciences. 2018;**75**:1-13. DOI: 10.1016/j.jes.2018.05.002

[79] Deng Q, Jiang G, Wu Y, Li J, Liang W, Chen L, et al. GPER / Hippo-YAP signal is involved in Bisphenol S induced migration of triple negative breast cancer (TNBC) cells. Journal of Hazardous Materials. 2018;**355**:1-9. DOI: 10.1016/j.jhazmat.2018.05.013

[80] Lei B, Sun S, Zhang X, Feng C, Xu J, Wen Y, et al. Bisphenol AF exerts estrogenic activity in MCF-7 cells through activation of Erk and PI3K/Akt signals via GPER signaling pathway. Chemosphere. 2019;**220**:362-370. DOI: 10.1016/j.chemosphere.2018.12.122

[81] Lei B, Peng W, Xu G, Wu M, Wen Y, Xu J, et al. Activation of G protein-coupled receptor 30 by thiodiphenol promotes proliferation of estrogen receptor α-positive breast cancer cells. Chemosphere. 2017;**169**:204-211. DOI: 10.1016/j.chemosphere.2016.11.066

[82] Xu F, Wang X, Wu N, He S, Yi W, Xiang S, et al. Bisphenol A induces proliferative effects on both breast cancer cells and vascular endothelial cells through a shared GPER-dependent pathway in hypoxia. Environmental Pollution. 2017;**231**:1609-1620. DOI: 10.1016/j.envpol.2017.09.069

[83] Segovia-Mendoza M, Gómez de León CT, García-Becerra R, Ambrosio J, Nava-Castro KE, Morales-Montor J. The chemical environmental pollutants BPA and BPS induce alterations of the proteomic profile of different phenotypes of human breast cancer cells: A proposed interactome. Environmental Research. 2020;**191**:109960-109972. DOI: 10.1016/j.envres.2020.109960

[84] Figueroa CD, Ehrenfeld P, Bhoola KD. Kinin receptors as targets for cancer therapy. Expert Opinion on Therapeutic Targets. 2012;**16**:299-312

[85] Molina L, Matus CE, Astroza A, Pavicic F, Tapia E, Toledo C, et al. Stimulation of the bradykinin B1

receptor induces the proliferation of estrogen-sensitive breast cancer cells and activates the ERK1/2 signaling pathway. Breast Cancer Research and Treatment. 2009;**118**:499-510

[86] Ehrenfeld P, Conejeros I, Pavicic MF, Matus CE, Gonzalez CB, Quest AFG, et al. Activation of kinin B1 receptor increases the release of metalloproteases-2 and -9 from both estrogen-sensitive and -insensitive breast cancer cells. Cancer Letters. 2011;**301**:106-118. DOI: 10.1016/j.canlet.2010.09.020

[87] Feigin ME, Xue B, Hammell MC, Muthuswamy SK. G-protein-coupled receptor GPR161 is overexpressed in breast cancer and is a promoter of cell proliferation and invasion. Proceedings of the National Academy of Sciences of the United States of America. 2014;**111**:4191-4196

[88] Bumpus FM, Smeby RR, Page IH, Khairallah PA. Distribution and metabolic fate of angiotensin II and various derivatives. Canadian Medical Association Journal. 1964;**90**:190-193

[89] Cherne PN, Young P. Historia del sistema renina angiotensina: Grandes hombres, un gran descubrimiento. Revista Médica de Chile. 2014; **142**:1210-1216

[90] Lin SYGT. Angiotensin receptors. The American Journal of Physiology. 1970;**218**:1319-1328

[91] Peach MJ. Renin-angiotensin system: Biochemistry and mechanisms of action. Physiological Reviews. 1977;**57**:313-370

[92] Marie-Aude D, Meyer P. Commentary angiotensin receptors. Biochemical Pharmacology. 1978;**27**:1-5

[93] Dasgupta C, Zhang. Angiotensin II receptors and drug discovery in cardiovascular disease. Drug Discovery Today. 2011;**16**:22-34. Available from: https://pubmed.ncbi.nlm.nih.gov/21147255/

[94] de Gasparo M, Catt KJ, Inagami T, Wright JWUT. International union of pharmacology. XIII. Pharmacological Reviews. 2000;**52**:415-472

[95] Allen AM, Zhuo J, Mendelsohn FAO. Localization and function of angiotensin AT1 receptors. American Journal of Hypertension. 2000;**13**:31-38

[96] Carey RM. Update on angiotensin AT2 receptors. Current Opinion in Nephrology and Hypertension. 2017;**26**:91-96

[97] Dick JE. Normal and leukemic human stem cells assayed in SCID mice. Seminars in Immunology. 1996; **8**:197-206

[98] Hubert C, Savary K, Gasc J, Corvol P. The hematopoietic system : a new niche for the renin-angiotensin system. Review Criteria in Humans. 2006;**3**:80-85

[99] Matsushita K, Wu Y, Okamoto Y, Pratt RE, Dzau VJ. Local renin angiotensin expression regulates human mesenchymal stem cell differentiation to adipocytes. Hypertension. 2006; **48**:1095-1102

[100] Roth IM, Wickremesekera AC, Wickremesekera SK, Davis PF, Tan ST. Therapeutic targeting of cancer stem cells via modulation of the renin-angiotensin system. Frontiers in Oncology. 2019;**9**:1-12

[101] Du N, Feng J, Hu L, Sun XIN, Sun H, Zhao Y, et al. Angiotensin II receptor type 1 blockers suppress the cell proliferation effects of angiotensin II in breast cancer cells by inhibiting AT1R signaling. Oncology Reports. 2012;**27**:1893-1903

[102] Vinson GP, Barker S, Puddefoot JR. The renin-angiotensin system in the

breast and breast cancer. Endocrine-Related Cancer. 2012;**19**:1-19

[103] Yang L, Luo L, Ji W, Gong C, Wu D, Huang H, et al. Effect of low dose bisphenol A on the early differentiation of human embryonic stem cells into mammary epithelial cells. Toxicology Letters. 2013;**218**:187-193. DOI: 10.1016/j.toxlet.2013.01.026

[104] Chapellier M, Maguer-Satta V. BMP2, a key to uncover luminal breast cancer origin linked to pollutant effects on epithelial stem cells niche. Molecular & Cellular Oncology. 2016;**3**:3-5

[105] Winz C, Suh N. Understanding the mechanistic link between bisphenol A and cancer stem cells: A cancer prevention perspective. Journal of Cancer Prevention. 2021;**26**:18-24

[106] Kilmister EJ, Tan ST. The role of the renin–angiotensin system in the cancer stem cell niche. Journal of Histochemistry and Cytochemistry. 2021;**24**:221554211026295-221554211026308. DOI: 10.1369/00221554211026295

[107] Oh E, Kim JY, Cho Y, An H, Lee N, Jo H, et al. Overexpression of angiotensin II type 1 receptor in breast cancer cells induces epithelial-mesenchymal transition and promotes tumor growth and angiogenesis. Biochimica et Biophysica Acta. 2016;**1863**:1071-1081. DOI: 10.1016/j.bbamcr.2016.03.010

[108] Arrieta O, Villarreal-Garza C, Vizcaíno G, Pineda B, Hernández-Pedro N, Guevara-Salazar P, et al. Association between AT1 and AT2 angiotensin II receptor expression with cell proliferation and angiogenesis in operable breast cancer. Tumor Biology. 2015;**36**:5627-5634

[109] Smith GR, Missailidis S. Cancer, inflammation and the AT1 and AT2 receptors. Journal of Inflammation. 2004;**1**:1-12

[110] DeVries ME, Kelvin AA, Xu L, Ran L, Robinson J, Kelvin DJ. Defining the origins and evolution of the chemokine/chemokine receptor system. Journal of Immunology. 2006; **176**:401-415

[111] Chen K, Bao Z, Tang P, Gong W, Yoshimura T, Wang JM. Chemokines in homeostasis and diseases. Cellular & Molecular Immunology. 2018;**15**:324-334

[112] Deuel TF, Keim PS, Farmer M, Heinrikson RL. Amino acid sequence of human platelet factor 4. Proceedings of the National Academy of Sciences of the United States of America. 1977; **74**:2256-2258

[113] Luster AD, Unkeless JC, Ravetch JV. γ-Interferon transcriptionally regulates an early-response gene containing homology to platelet proteins. Nature. 1985;**315**:672-676

[114] Yoshimura T, Matsushima K, Tanaka S, Robinson EA, Appella E, Oppenheim JJ, et al. Purification of a human monocyte-derived neutrophil chemotactic factor that has peptide sequence similarity to other host defense cytokines. Proceedings of the National Academy of Sciences of the United States of America. 1987;**84**:9233-9237

[115] Zlotnik A, Yoshie O. Chemokines: A new classification system and their role in immunity. Journal of Cultural Heritage. 2000;**1**:121-127

[116] Holmes WE, Lee J, Kuang WJ, Rice GC, Wood WI. Structure and functional expression of a human interleukin-8 receptor. Science. 1991;**253**:1278-1280

[117] Neote K, DiGregorio D, Mak JY, Horuk R, Schall TJ. Molecular cloning, functional expression, and signaling characteristics of a C-C chemokine receptor. Cell. 1993;**72**:415-425

[118] Monteagudo C, Pellín-Carcelén A, Martín JM, Ramos D. Papel de las

quimiocinas en la progresión del melanoma. Actas Dermo-Sifiliográficas. 2011;**102**:498-504

[119] King J, Mir H, Singh S. Association of cytokines and chemokines in pathogenesis of breast cancer. Progress in Molecular Biology and Translational Science. 2017;**151**:113-136. DOI: 10.1016/bs.pmbts.2017.07.003

[120] Wang JM, Chertov O, Proost P, Li JJ, Menton P, Xu L, et al. Purification and identification of chemokines potentially involved in kidney-specific metastasis by a murine lymphoma variant: Induction of migration and NFκB activation. International Journal of Cancer. 1998;**75**:900-907

[121] Korbecki J, Grochans S, Gutowska I, Barczak K, Baranowska-Bosiacka I. Cc chemokines in a tumor: A review of pro-cancer and anti-cancer properties of receptors ccr5, ccr6, ccr7, ccr8, ccr9, and ccr10 ligands. International Journal of Molecular Sciences. 2020;**21**:1-34

[122] Wang F, Yuan C, Wu HZ, Liu B, Yang YF. Bioinformatics, molecular docking and experiments in vitro analyze the prognostic value of CXC chemokines in breast cancer. Frontiers in Oncology. 2021;**11**:1-17

[123] Koike E, Yanagisawa R, Win-Shwe TT, Takano H. Exposure to low-dose bisphenol A during the juvenile period of development disrupts the immune system and aggravates allergic airway inflammation in mice. International Journal of Immunopathology and Pharmacology. 2018;**32**:2058738418774897. DOI: 10.1177/2058738418774897

[124] Chen Y, Xu HS, Guo TL. Modulation of cytokine/chemokine production in human macrophages by bisphenol a: A comparison to analogues and interactions with genistein. Journal of Immunotoxicology. 2018;**15**:96-103. DOI: 10.1080/1547691X.2018.1476629

[125] Boudot A, Kerdivel G, Habauzit D, Eeckhoute J, Le Dily F, Flouriot G, et al. Differential estrogen-regulation of CXCL12 chemokine receptors, CXCR4 and CXCR7, contributes to the growth effect of estrogens in breast cancer cells. PLoS One. 2011;**6**:2-13

[126] Habauzit D, Boudot A, Kerdivel G, Flouriot G. Development and validation of a test for environmental estrogens: Checking xeno-estrogen activity by CXCL12 secretion in breast cancer cell lines. Environmental Toxicology. 2010;**25**:495-503 Available from: https://pubmed.ncbi.nlm.nih.gov/20549624/

[127] Li M, Han X, Gao W, Chen F, Shao B. Bisphenol AF stimulates transcription and secretion of C-X-C chemokine ligand 12 to promote proliferation of cultured T47D breast cancer cells. Toxicology. 2015;**338**:30-36. DOI: 10.1016/j.tox.2015.09.007

[128] Murray TJ, Maffini MV, Ucci AA, Sonnenschein C, Soto AM. Induction of mammary gland ductal hyperplasias and carcinoma in situ following fetal bisphenol A exposure. Reproductive Toxicology. 2007;**23**:383-390. DOI: 10.1016/j.reprotox.2006.10.002

[129] Fischer C, Mamillapalli R, Goetz LG, Jorgenson E, Ilagan Y, Taylor HS. Bisphenol A (BPA) exposure in utero leads to immunoregulatory cytokine dysregulation in the mouse mammary gland: A potential mechanism programming breast cancer risk. Hormones and Cancer. 2016; **7**:241-251

[130] Kaabi B, Belaaloui G, Benbrahim W, Hamizi K, Sadelaoud M, Toumi W, et al. ADRA2A germline gene polymorphism is associated to the severity, but not to the risk, of breast cancer. Pathology Oncology Research. 2016;**22**:357-365

[131] Collins S, Surwit RS. The β-adrenergic receptors and the control

of adipose tissue metabolism and thermogenesis. Recent Progress in Hormone Research. 2001;**56**:309-328

[132] Ahlquist RP. A study of the adrenotropic receptors. The American Journal of Physiology. 1948;**153**:586-600. DOI: 10.1152/ajplegacy.1948.153.3.586

[133] Dieterich LC, Bikfalvi A. The tumor organismal environment: Role in tumor development and cancer immunotherapy. Seminars in Cancer Biology. 2020;**65**:197-206. DOI: 10.1016/j.semcancer.2019.12.021

[134] Vázquez SM, Mladovan AG, Pérez C, Bruzzone A, Baldi A, Lüthy IA. Human breast cell lines exhibit functional α2-adrenoceptors. Cancer Chemotherapy and Pharmacology. 2006;**58**:50-61

[135] Amaro F, Silva D, Reguengo H, Oliveira JC, Quintas C, Vale N, et al. B-Adrenoceptor activation in breast Mcf-10a cells induces a pattern of catecholamine production similar to that of tumorigenic Mcf-7 cells. International Journal of Molecular Sciences. 2020;**21**:1-16

[136] Ahmed S, Atlas E. Bisphenol S- and bisphenol A-induced adipogenesis of murine preadipocytes occurs through direct peroxisome proliferator-activated receptor gamma activation. International Journal of Obesity. 2016;**40**:1566-1573

[137] Ponzi D, Gioiosa L, Parmigiani S, Palanza P. Effects of prenatal exposure to a low-dose of bisphenol a on sex differences in emotional behavior and central alpha2-adrenergic receptor binding. International Journal of Molecular Sciences. 2020;**21**:3269-3283. DOI: 10.3390/ijms21093269

[138] Palanza P, Nagel SC, Parmigiani S, vom Saal FS. Perinatal exposure to endocrine disruptors: Sex, timing and behavioral endpoints. Current Opinion in Behavioral Sciences. 2016;**7**:69-75. DOI: 10.1016/j.cobeha.2015.11.017