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Chapter

A Potential New Mechanism for Bisphenol Molecules to Initiate Breast Cancer through Alteration of Bone Morphogenetic Protein Signaling in Stem Cells and Their Microenvironment

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Abstract

Endocrine disruptors interfere with endocrine-mediated regulations of cell or organ functions. Estrogens are one of the main hormones altered by endocrine disruptors like bisphenol A (BPA). Stem cells are active from embryogenesis to late stages of adult life. Their unique properties, such as an extended lifespan and low cycling features, render these cell privileged targets of long-term exposure to numerous factors. Therefore, stem cells are likely to be affected following exposure to endocrine disruptors. One of the major signaling pathways involved in stem cell regulation is the bone morphogenetic protein (BMP) pathway. The BMP pathway is known for its involvement in numerous physiological and pathophysiological processes. Exposure of human mammary stem cells to pollutants such as BPA initiates fundamental changes in stem cells, in particular by altering major elements of BMP signaling, such as receptor expression and localization. Lastly, BPA and its substitute bisphenol S (BPS) have similar impacts on BMP signaling despite their different ER-binding properties, supporting the hypothesis that their biological effects cannot be extrapolated only from their interaction with ERα66. We review recent discoveries in this field and discuss their implications for cancer diagnosis, prevention, and treatment, as well as their relevance for studies on endocrine disruptors.

Keywords: BMP, bisphenol, stem cells, breast cancer, microenvironment, endocrine disruptors, estrogen

1. Introduction

Breast cancer is the most common cancer in women and exhibits important phenotypic and genetic diversities associated with different prognoses. Breast cancer subtypes are clinically classified based on histological appearance and expression of hormone receptors such as estrogen (ER) and progesterone (PR) receptors, as well as on the amplification of the HER2 gene coding for a member of the EGF receptor family [1]. Based on these criteria, four major breast cancer subtypes have been defined: luminal A and luminal B (all ER+), HER+ (that can be either ER− or ER+),

and basal-like (ER−) [2, 3]. The most frequent subtype encompasses ER-positive tumors that represent almost 80% of breast cancers. In these tumors, preventing ER activation via hormone therapy is efficient. This can be achieved either by using competitive antagonists of estrogens (e.g., tamoxifen), preventing its binding to and subsequent activation of ER, by using drugs blocking estrogen synthesis (antiaromatase) in postmenopausal women, or by luteinizing hormone-releasing hormone (LHRH) analogs, inhibiting release of female hormones by the ovaries [4].

Breast cancer is a multifactorial disease, and evidences of the involvement of extrinsic factors in the increase of breast cancer risk have been described, such as the environment or lifestyle. Indeed, lack of physical activity, elevated tobacco or alcohol consumption, and the use of contraceptive pills or hormone-replacement therapy (for postmenopausal women) have been shown to increase breast cancer risk [5]. Hormonal status has also been described to play a major role in breast cancer risk. It has been shown that a premature or extensive exposure to endogenous estrogens (due to an early menarche, nulliparity, late age for first full-term pregnancy, or late menopause) increases the risk of breast cancer development.

Several chemical pollutants have been classified as endocrine-disrupting chemicals (EDCs) based on the following definition: "an endocrine disruptor is an exogenous substance or mixture that alters any function(s) of hormone actions and consequently causes adverse health effects in an intact organism, or its progeny, or (sub)populations" [6–11]. Estrogens are one of the main hormones altered by EDCs. Perturbations in estrogen functions have been identified in a wide spectrum of pathologies, including metabolic, bone, and reproductive disorders, as well as breast, endometrial, or ovarian cancers. Therefore, it is important to consider that the mammary gland is exposed throughout life not only to endogenous hormones but also to EDCs, molecules present in the environment and able to mimic these hormones.

Interest in EDCs is growing rapidly, owing notably to their extensive use in manufactured goods and their release in our environment. Among these environmental pollutants, bisphenol molecules are being increasingly studied in breast cancer due to their estrogen-mimetic properties, enabling them to activate estrogen signaling through their binding to the ER, in particular, bisphenol A (BPA) [12, 13]. Despite rising concerns about its safety [14] and progressive restrictions on its use, several million tons of BPA are still produced worldwide.

2. The major effects of bisphenols on BMP signaling and stem cells

2.1 BPA and breast cancer

2.1.1 BPA and estrogen signaling

BPA is an aromatic organic compound used by the plastic industry as a monomer in the synthesis of polycarbonates and epoxy resins. Polycarbonates are found in consumer plastic-like water bottles, food packaging materials, sport equipment or toys, while epoxy resins are used to coat the inside of food or beverage containers. BPA can also be found in thermal paper. BPA monomers from these compounds can be released into the environment by hydrolysis. At the structural level, BPA is a diphenyl compound with two hydroxyl groups in a "para" position rendering it highly similar to synthetic estrogen (diethylstilbestrol). This thus allows BPA to interact with various physiological receptors similar to estrogen, including ERs.

The classical genomic estrogen signaling pathway is triggered by the binding of estrogen to its α or β receptors that act as transcription factors in the nucleus. In the absence of ligands, these receptors are complexed with inhibitory molecules either

in the cytoplasm or in the nucleus of the cell. Upon ligand binding, these complexes dissociate resulting in conformational changes that allow DNA binding and recruitment of cofactors to regulate expression of target genes [15]. Both ERα and ERβ are also able to initiate a nongenomic signaling pathway outside of the nucleus depending on their subcellular localization [16]. Moreover, estrogen signaling can also be mediated by other receptors, such as GPR30, EGFR, to list only a few [15, 17].

In line with the current definition of EDCs, BPA was shown to exert its activity by disrupting the estrogen signaling pathway that uses ER as a transcription factor binding to estrogen response element (ERE) sites on DNA [15]. Consequently, estrogen-mimetics (e.g., BPA) were mechanistically thought to primarily act through their binding to ERα66, the main canonical (nuclear) estrogen receptor. This nuclear receptor initiates signaling pathways at the cell membrane and transcriptional responses in the cell nucleus. BPA also upregulates the level of steroid receptor coactivators (SRC-1, SRC-3) and promotes the activity of EREs [18]. However, BPA has also been shown to bind to a number of distinct nuclear and membrane receptors, namely estrogen receptors ERα/β, androgen receptor (AR), G protein-coupled ER (GPER, GPR30), PPAR (especially PPARγ), insulin-like growth factor-1 (IGF1-R) [17, 19, 20]. BPA stimulates the release of EGFR ligands by directly targeting other molecules than ER, like ADAM17 or ADAM10 [21]. Furthermore, the impact of BPA on Ca^{2+} release or ERK signaling has been highlighted in the pancreas [15]. Altogether, these results indicate that BPA, in addition to its effects on the canonical estrogen pathway, is able to perturb numerous physiological processes through estrogen genomic and nongenomic signaling, as well as nonestrogen-related pathways [19, 22]. Importantly, BPA is at the origin of toxic derivatives (chlorinated bisphenols) and is also processed by cellular and biochemical mechanisms to generate a number of different BPA metabolites. All these BPA derivatives have been reported to have similar or higher toxic effects than BPA [19, 20]. In the context of the mammary gland, it is thus of utmost importance to further elucidate how BPA, its derivatives or metabolites, modulate estrogen- or nonestrogen-related signaling. This should improve our understanding of the tumorigenic potential of BPA, firstly in the luminal breast cancer subtype, and subsequently in other tumor types.

2.1.2 BPA involvement in breast cancer

Evidence gathered from studies in experimental models and human populations has already confirmed that EDCs, including BPA, contribute to increased risk of disease [23, 24]. A positive relationship between exposure to BPA and cancer development is reported in the literature [25]. However, whether BPA is actually harmful for human health remains understudied, similar to our understanding of the molecular mechanisms underlying BPA-dependent effects in cancer development.

Given the significant involvement of estrogens in both normal and pathological conditions, EDCs able to interfere with the homeostasis of the estrogen endocrine system are a potential source of several health disorders. In this context, a human population-based study detected a significant increase in serum levels of BPA and established a correlation with breast tissue density measured in mammographies [26]. This finding was attributed to the ability of BPA to increase proliferation of mammary epithelial cells from either normal or breast cancer tissues [27, 28]. Epigenetic data from human tumors or cells exposed to BPA *in vitro* revealed the ability of this EDC to directly induce mammary epithelial cell transformation [29].

Moreover, BPA was correlated with breast cancer patients with high risk profiles and therefore with increased disease relapse [30]. This may be due to the

implication of BPA in breast cancer metastasis. This process has traditionally been associated with late stages of cancer development, though a new hypothesis on its origin has progressively emerged suggesting that it could be an inherent mark of tumor cell [31, 32]. Metastatic dissemination is a dynamic process that involves several steps: local invasion of cells from the primary tumor, intravasation leading to dissemination through the blood or lymph, extravasation to invade new tissues, implantation, and finally new tumor growth. Numerous signaling pathways and programs are activated during this process such as epithelial-to-mesenchymal transition (EMT), anoïkis, migration, and proliferation among others (for review: [33, 34]). It has been shown that ER-negative breast cancers are associated with an increased risk of developing metastases [35]. Indeed, these breast cancers express more mesenchymal markers such as vimentin and N-cadherin or EMT-transcription factors that are required for metastatic initiation. Conversely, ER-positive tumors are associated with a more differentiated luminal phenotype, expressing epithelial markers (E-cadherin, ER, FOXA1 for instance). Accordingly, a downregulation of the luminal-specific transcription factor FOXA1 is induced after BPA treatment in triple-negative tumor cell lines, leading to the induction of EMT and increasing cell motility [36]. In this study, BPA treatment was shown to activate the PI3K/AKT pathway, leading to a downregulation of epithelial genes alongside an upregulation of mesenchymal genes. Another study demonstrated that BPA promotes migration and invasion via GPER, which transduces FAK, Src, and ERK2 signaling pathway activation [37]. Promotion of GPER-induced migration by BPA or BPS occurs via different signaling pathways. Indeed, in contrast to BPA, which acts via the FAK/Scr/ERK2 pathway, it has been shown that BPS induces GPER/Hippo-YAP-dependent migration [38]. Effects of BPA, BPS, and BPF on migration and EMT properties of ER-positive tumor cell lines were compared [39]. After treatment, cells lost cell/cell contacts and acquired a fibroblast-like morphology associated with an EMT phenotype. This was further confirmed after analysis of EMT-associated protein expression showing a decrease in E-cadherin and an increase in N-cadherin. Moreover, BPA-, BPS-, and BPF-treated cells displayed a stronger migratory ability. All of these modifications were inhibited after administration of an ER antagonist, demonstrating the ER-dependent effects of these bisphenols [39].

At the mechanistic level, a large number of *in vivo* and *in vitro* studies have highlighted the ability of BPA to disrupt several key signaling pathways that are known to be involved in breast cancer [19, 40]. However, the direct involvement of BPA in breast cancer incidence is difficult to establish and remains controversial [26, 41], owing possibly to the fact that different mechanisms are depicted in either ER-positive or -negative tumors, reflecting the variety of biological effects arising from exposure to BPA [20, 28, 42]. In addition, the combinatorial effects of different pollutants encountered over a life time also complicate these studies. Hence, scientists are faced with a huge challenge in order to formally establish the transforming power of BPA, owing to the different contexts and mechanistic cascades of alterations occurring in the human breast tissue during such long-term exposure.

2.2 BPA target cells

2.2.1 Stem cells in mammary gland

Mammary gland development takes place during embryogenesis and is composed of a rudimentary ductal system blocked until puberty. Then, two master reproductive hormones are secreted, namely estrogens and progesterone.

Estrogens control the growth of ducts from their distal extremity called terminal end buds (TEBs) [43–45], while progesterone is involved in lateral branch development [46, 47]. One of the major hormones involved in mammary gland development is estrogen, mostly produced by the ovaries (but also by other tissues). Estrogens, in combination with other hormones, orchestrate the growth of the ductal system and adipose tissue accumulation during puberty and at further stages of development [43–45].

In adults, the mammary gland is formed of ducts and lobules of secreting luminal epithelial cells surrounded by contractile myoepithelial cells. These epithelial cells are embedded in a stroma mainly formed of fibroblasts and adipocytes that secrete several soluble molecules regulating epithelial cell function and differentiation. Epithelial cells of the mammary gland are generated by mammary stem cells (MaSCs) and the stromal compartment by mesenchymal stem cells (MSCs) [48–51]. During adulthood, the mammary gland undergoes functional and structural changes that alternate between phases of proliferation, differentiation, and apoptosis controlled by cyclic hormonal variations due to the estrous/menstrual cycle modulating the stem cell compartment [52]. However, this postpubertal mammary tree remains immature and only achieves full maturation during pregnancy and lactation. These final steps involve alveogenesis and milk production, which take place mostly under the control of progesterone and prolactin [53, 54]. Studies indicate that estrogens do not directly stimulate proliferation of ER-positive luminal cells but act via a paracrine process [55, 56]. Indeed, estrogen acts on luminal ER/PR-positive cells, leading to the cleavage and liberation of amphiregulin [57, 58], which then affects neighboring ER/PR-negative cells. These ER/PR-negative cells display characteristics of stem cells, in that, their asymmetric division is controlled by growth factors released by stromal cells [59–62]. Conversely, estrogen treatment induces a deficient asymmetric division of a human MaSC cell line (MCF10F) [63]. Ovariectomized mice (or letrozole treated to inhibit endogenous estrogen synthesis and provide a normal stromal and hormonal environment for all other hormones) show a decrease in the ability of MaSCs to repopulate a mammary fat pad and to generate ductal growth and expansion without impacting the size of the MaSCs-enriched subpopulation [52]. Collectively, these studies highlight the importance of the estrogen pathway on MaSC regulation through direct and indirect effects and consequently suggest potential sensitivity of these cells to estrogen-mimetics like BPA. Furthermore, stem cells are a unique category of cells active from embryogenesis up to late stages of human adult life, and are thus more prone to be exposed to EDCs, likely altering their normal functions [64–68].

2.2.2 BPA, stem cells, and breast cancer

It has been shown that exposure to EDCs occurs throughout life and even during embryogenesis, at the stage of mammary gland establishment. For instance, BPA has been detected in urinary samples but also in maternal and fetal plasma, in colostrum, and in placental tissue at birth. Several studies demonstrated that a prenatal exposure to BPA induces changes in fetal mouse mammary gland, in the epithelial as well as stromal compartments, favoring fat pad maturation and increasing the mammary gland susceptibility to carcinogens [69–71]. This is accompanied by transcriptome modifications, in particular, an increase in the expression of genes belonging to the antiapoptotic family, myoepithelial differentiation, and adipogenesis, and a decrease in those involved in cell adhesion [71]. Exposure to BPA at puberty alters the function of MaSCs, leading to the appearance in the regenerated glands of early neoplastic lesions with molecular alterations similar to those

detected in early neoplastic breast cancer tissues [72]. In a physiological model in which mice were treated at puberty with BPA, estrogen-dependent transcriptional events were perturbed and the number of terminal end buds was altered in a dose-dependent fashion [27]. *In vitro* exposure of normal human mammary epithelial cells to BPA was shown to induce their proliferation due to the secretion of autocrine growth factors and allow them to generate bigger mammospheres [73]. Treated cells displayed an increase in DNA hypermethylation of tumor suppressor genes, such as Brca1. These data support that BPA can promote early pretumoral stages corroborating findings in normal human breast epithelial cells (MCF-10F) [29, 64]. Indeed, BPA-treated human MaSC lines, such as MCF-10F, increase their expression of genes involved in DNA repair and decrease proapoptotic gene expression [74]. Chronic exposure of MCF10A cells to BPA at doses similar to those measured in contaminated water lead to major MaSC modifications affecting their stem cell properties and regulation [64]. Importantly, BPA treatment increases stem-like features by inducing the expression of ALDH1 and SOX2 genes, a human MaSCs marker and a master regulator of pluripotency in embryonic stem cells, respectively [75]. BPA also perturbs signals involved in human mammary stem cell (ERα66 negative cells) regulation, like the bone morphogenetic protein (BMP) pathway, which has been identified in their transformation [76], partly by changing BMP membrane receptor availability and priming cells to BMP signaling [64]. These data raised the hypothesis that in ER-positive tumors, under tamoxifen treatment and in a BPA-containing environment, some cells could acquire resistance to treatment by a switch in signaling pathway favoring a stem-like phenotype characterized by a decrease in treatment cytotoxicity and a modification of the stoichiometry of the type of ER (e.g., an increase in ERRγ or ERα isoform expression).

Overall, these observations strongly support that MaSCs are directly sensitive to BPA, which could be involved in their transformation and/or treatment escape [27, 72, 74].

2.3 BMP, stem cells, and cancer

2.3.1 BMP and mammary epithelial stem cells

One of the major conserved signaling pathways involved in stem cell regulation from embryogenesis up to adult stages is BMP signaling. There are 21 different soluble BMP molecules that act through serine/threonine kinase BMP receptors (BMPRs). In the context of stem cell regulation, BMP2 and BMP4 are progressively emerging as the most important BMPs. The BMP pathway is involved in numerous physiological and pathological processes [77]. BMPs control MSC regulation, such as lineage specification of adipocytes which are one of the major elements of the mammary gland microenvironment [78–80]. Alterations in BMP signaling have been implicated in metabolic disorders such as obesity in women [81, 82].

During embryogenesis in mice, BMP4 was shown to participate in the early steps of mammary gland development by regulating the dorsoventral axis establishment [83]. The BMP pathway also plays a role in mammary bud formation and outgrowth, as well as in ductal branching morphogenesis initiation. Indeed, BMP4 is expressed in both mesenchymal and epithelial cells of the mammary bud and the use of a BMP4 inhibitor leads to a decrease in bud outgrowth [84]. A link between BMPs and progesterone receptor type A involved in branching morphogenesis during postnatal mammary gland development has also been shown [85]. In addition, BMPs are also involved in the myoepithelial compartmentalization and lumen formation [85]. The knockout of a BMP extracellular antagonist, Twisted, abrogates lumen formation and disorganizes the myoepithelial layer through a decrease in

SMAD1-5-8 phosphorylation and the repression of BMP targets (Msx1, Msx2, and Gata-3) [86]. In human cells, BMP2 regulates luminal epithelial cells by modulating the expression of *GATA-3* and *FOXA1* [76]. Finally, an *in vitro* study using sorted mouse mammary epithelial undifferentiated cells demonstrated the role of BMP signaling in final maturation steps such as lactogenic differentiation [87].

In healthy tissues, epithelial cells, as well as cells within the mammary gland environment (fibroblasts, adipose tissue cells, hematopoietic cells), contribute to the production of soluble BMP2 and BMP4 molecules [76], while distinct subpopulations of normal mammary epithelial cells sorted according to CD10 and EPCAM expression [88] express different elements of the BMP pathway. A role for BMP molecules in MaSC regulation was formally demonstrated by functional assay analyses following exposure of different human cell types to soluble BMP2 or BMP4 [76], and further substantiated by the use of TGF/BMP inhibitors allowing the expansion of immature epithelial basal cells [89]. Interestingly, as in the hematopoietic system [90], BMP2 and BMP4 molecules have distinct functional effects on MaSC regulation despite their strong homology. Indeed, while BMP4 modulates the compartment of MaSC and myoepithelial progenitors, BMP2 allows the commitment and proliferation of luminal progenitors [76]. However, the molecular mechanism by which BMPs interact with estrogen signaling to regulate MaSCs remains to be further deciphered.

2.3.2 BMP and breast cancer

BMP signaling is also a well-known highly complex pathway that orchestrates the development and homeostasis of adult tissues such as the neural system [91]. The importance of BMP signaling alterations in cancer stem cell features has been revealed in glioblastoma, breast cancer, and leukemia [90, 92–95]. The role of BMPs, especially of BMP2 and BMP4, in breast cancer has been largely documented [96, 97]. Alterations of BMP ligand expression and signaling have been reported and shown to be clinically correlated with breast cancer progression [98, 99] and to play a major role in the development of bone metastases [99–101]. Despite the fact that BMP4 transcripts are expressed at various levels in tumor tissues or breast cancer cell lines [102], high levels of BMP4 are found in 25% of the breast cancer tumors displaying a low proliferation index but high recurrence rate [98]. BMP4 has crucial functions in promoting tumor growth arrest, migration and metastasis by mediating cell cycle arrest in G1 [102], chemokine regulation [103], and inhibition of lumen formation [104] for example. However, the biological effects of BMP4 largely depend on cell context, as they were reported to be either proliferative or antiproliferative in mammary epithelial cells according to cellular density and cooperative factors [105, 106]. The microenvironment of human primary luminal breast tumors produces abnormally high amounts of soluble BMP2 compared to healthy tissue, while higher BMPR1B levels were detected in tumor cells [76, 107]. Chronic exposure to high BMP2 concentrations was demonstrated to initiate MaSC transformation toward a luminal tumor phenotype dependent on a BMPR1B-initiated signaling cascade involved in luminal commitment of normal MaSC. This leads to a FOXA1/FOXC1 transcription factor balance switch in favor of FOXA1, simultaneously with an upregulation of GATA3 [76]. However, while an increase in soluble BMP2 in the tumor microenvironment has been shown in luminal ER-positive tumors where it is correlated with a high BMPR1B tumor expression [76], a strong decrease in BMP2 transcripts was found in ER-negative breast tumors [108]. Also, a downmodulation of the BMPR1B (Alk6) in a basal cell line (MDA-MB-231) increased cell growth *in vitro* [109], suggesting an antiproliferative function for BMPR1B in ER-negative tumors. Interestingly, downregulation of BMPR1A (ALK3)

in MDA-MB231D (a bone metastatic clone of MDA-MB231) basal ER-negative cells inhibited their migration and bone metastatic properties [110]. Therefore, it is very likely that the BMP2/BMPR1B signal is overactivated in the context of ER-positive tumors, while being repressed in ER-negative tumors.

Some of the first steps of carcinogenesis are an increase in proliferation, evasion of apoptosis, and activation of survival signaling pathways. To achieve this, several tumor suppressor genes, like p53 or BRCA1 for instance, need to be inactivated by different mechanisms including epigenetic changes. Modulation of BMP signaling by epigenetic mechanisms [111], such as methylation of BMP-receptor promoters, has been of particular clinical interest to further stratify glioblastoma patients and propose new therapeutic strategies [92]. While different genetic alterations progressively appear following different oncogenic signals, heredity likely accounts for only 10–30% of breast cancers. Based on epidemiological studies, different factors increasing the risk of breast cancer development have been highlighted. They can be intrinsic, like mutations in BRCA1 or 2, Tp53, ATM, or also PTEN, or extrinsic, like environmental factors or lifestyle [112, 113]. In breast cancers with a genetic origin, the most commonly mutated genes are *BRCA1* and *BRCA2,* associated with an increase in cancer risk. BRCA1 and 2 are two major regulators of double-strand breaks (DSB) DNA repair through homologous recombination (HR) and play a crucial role as tumor suppressor genes. In this context, it is interesting to note that a family member and negative regulator of P53, DNp63 has been reported to mediate activation of BMP signaling in order to govern epithelial cell plasticity, EMT, and tumorigenicity during breast cancer initiation and progression [114, 115]. DNp63 has also been identified as a repressor of BRCA1 expression exclusively in ER-positive breast cancer cells [116]. Moreover, a correlation between the BMP pathway and the P53-ATM signaling has been reported [117]. However, the importance of these different signaling crosstalks in the context of breast cancer, exposure to EDCs, and stem cell transformation need to be investigated.

2.4 BMP, estrogen, and bisphenols

2.4.1 BMP and ER crosstalk

The BMP signaling pathway is a dynamic and complex pathway, leading to the transduction of various signals depending on the nature of the BMP ligand and of the BMPR complex oligomerization induced (for review: [118, 119]). It has been shown that BMPs may interact with their receptors in two different ways [120, 121]: on the one hand, BMPs induce a BMPR complex formation called BISC (BMP-induced signaling complex), and on the other hand, a preformed BMPR complex is present before BMP fixation, known as PFC (preformed complex). These two different modes of BMP signal initiation lead to two different signaling cascades, namely the canonical SMAD-dependent pathway and the noncanonical SMAD-independent pathway [121]. SMAD-phosphorylated proteins then form a complex with SMAD4, leading to its translocation to the nucleus where it acts as a transcription factor on target genes [118, 122]. The SMAD-independent pathway does not simply encompass one signaling pathway but a multitude of downstream cascades, involving p38, Ras/ERK, and PI3K/AKT [123–126]. Interestingly, SMAD1-5-8 phosphorylation is more abundant in undifferentiated murine progenitors and decreases with their differentiation until it is almost fully abrogated in the differentiated cells treated with prolactin [87]. Involvement of the BMPR1A/SMAD1-5-8 pathway in lactogenic differentiation was further confirmed by the lack of expression of a

lactogenic differentiation marker (beta-casein) at the RNA and protein levels in BMPR1A knockdown mammary cell lines [87]. These data demonstrate that the BMP pathway constitutes an important regulator of the mammary gland during embryogenesis but most likely also during adulthood. However, the molecular and functional crosstalk between the BMP and estrogen signaling pathways is poorly understood. A first set of experiments describes the repression of BMP signaling by ER inhibition of BMP production through a direct interaction between SMAD1 and ER [127]. Reciprocally, a BMP2 signal was shown to upregulate the expression of ER receptors, including the induction of specific ER isoforms such as ERα36 [128, 129]. Interestingly, crosstalk between BMP4 and estrogen signaling seems to have opposite effects. Indeed, BMP4 inhibits ERα signaling by promoting receptor degradation through the proteosomal pathway, while estrogens repress BMP4 expression [130]. Similarly, estrogen represses BMP4 expression in cardiomyocytes by preventing BMP4-mediated ERβ expression and JNK activity in this system [131]. In addition, in this context, estrogen inhibition of BMP4 is independent of Smad1/5/8 activity [131]. BMP4, upon activation of its canonical pathway, represses CYP17A1 and induces the transcription of CYP19A1, involved in androgen and estrogen synthesis, respectively [132]. In a rat model of pituitary cells, estrogen stimulates the transcriptional activity of BMP4-specific SMADs through an ER-SMAD1 complex shown to stimulate prolactin production, while having no effect on the TGFβ/SMAD pathway [133]. Similarly, the inhibitory effects of estrogen signaling on the BMP pathway appear to be mediated by a direct physical interaction between ER receptors and the SMAD1 BMP signaling element in a luminal breast cancer cell line model (MCF7). The physical interaction between ERα and SMAD1 requires the DNA binding domain of ERα and this complex formation is dependent on BMP2 and estrogen [127]. Moreover, BMP signaling has also been directly identified in thyroid-lineage specification [134, 135] as well as in thyroid carcinoma [136]. Interestingly, thyroid hormone status interferes with estrogen target gene expression in breast cancer samples in menopausal women [137]. These findings highlight the need to further investigate the importance of the BMP pathway in both thyroid and estrogen signaling in a broader context of exposure to EDCs.

More recently, BMP2-mediated luminal transformation of MCF10A was shown to be accompanied by a strong activation of the estrogen signaling pathway despite the absence of ERα66 in those cells [76]. Our understanding of estrogen signaling is hindered by the existence of several isoforms generated by alternative splicing and different promoter usage [138]. Interaction of these isoforms with the BMP signaling elements has not yet being investigated but could be involved in epithelial stem cell response to BMP2. Indeed, the importance of these different ERα isoforms in mammary epithelial SC features and in the context of breast cancer is only just starting to be identified [139, 140]. These isoforms can be expressed in both ERα66-positive and -negative cells and display different subcellular localizations [141, 142]. For example, unlike ERα66, ERα36 is expressed mainly at the plasma membrane and activates estrogen nongenomic signaling by activating the ERK pathway through an interplay with the MKP3 phosphatase [143]. Interestingly, in the context of EDC research, ERα36 displays altered ligand preference and causes distinct effects compared to ERα66. For instance, the tamoxifen drug used as an estrogen antagonist in ERα66 breast cancers behaves as an estrogen agonist for ERα36 [140, 144]. Collectively, these different examples illustrate how BMP signaling through its interaction with estrogen signaling is at the crossroad of a number of fundamental physiological processes. The BMP pathway is therefore directly involved in mammary stem cell regulation and transformation, yet adverse effects of EDCs, like BPA, on the BMP pathway have not been thoroughly investigated (**Figure 1**).

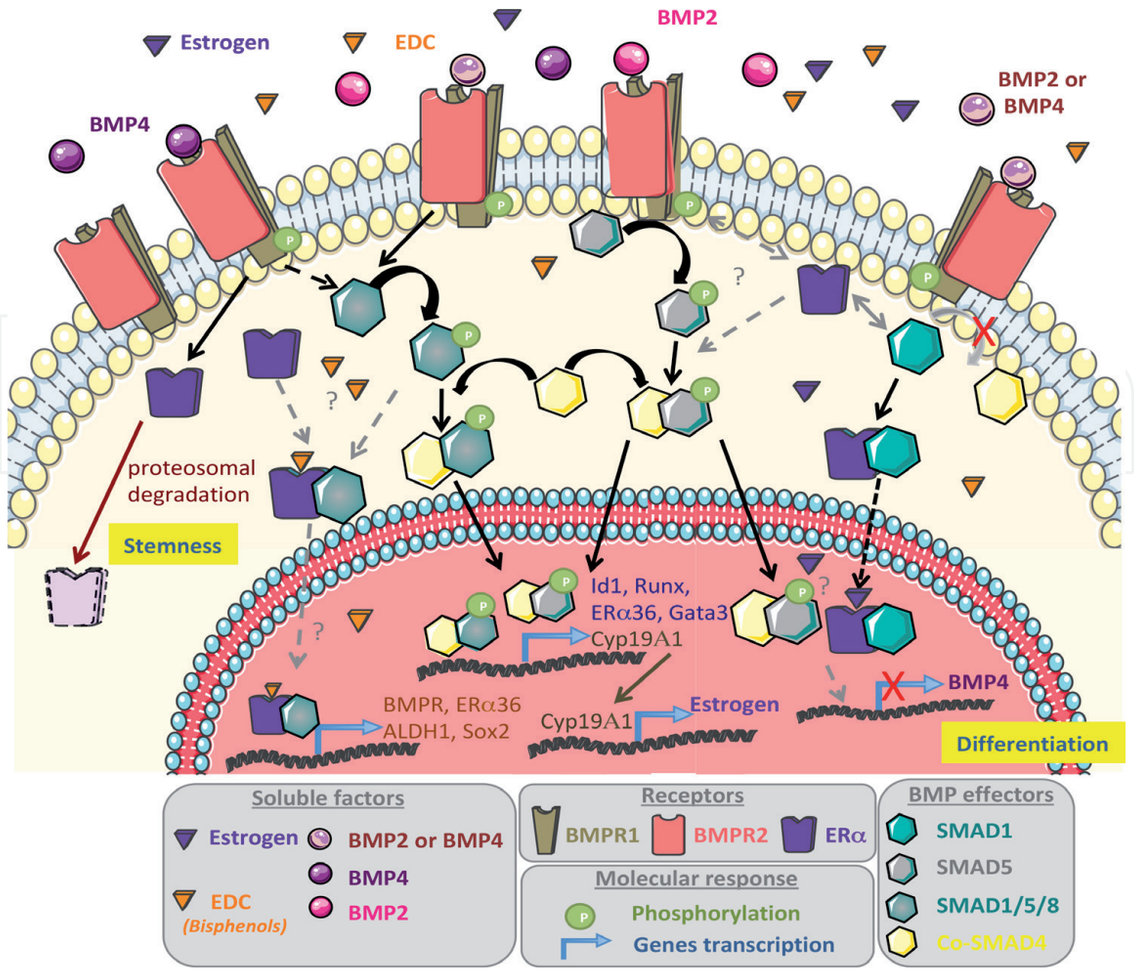

Figure 1.
Illustration of the main findings that show a crosstalk between BMP and estrogen signaling pathways.

2.4.2 BMP and bisphenols

Works from our team and others suggest that bisphenols could act on multiple cell types of the mammary gland, and their effects may converge to provoke major dysregulations of the BMP pathway that could contribute to luminal breast cancer initiation. Indeed, we observed a major impact of BPA on the mammary microenvironment (niche) equilibrium. BPA greatly increases BMP2 production by stromal cells of the human mammary SC microenvironment reaching levels comparable to those measured in luminal breast cancer [76]. Moreover, BPA treatment leads to a decrease in estrogen and BMP15 production in oocytes delaying their maturation [145]. A decrease in BMP2 production through a direct binding of BPA to ERγ was involved in bone loss through a suppression of osteoblast differentiation reverted by inhibition of ERγ [146]. This suggests that the effects and mechanisms of BPA-induced BMP ligand production depend on the estrogen receptor expression profile and are context dependent [147]. However, the molecular mechanism by which BPA induces BMP2 production by stromal cells of the mammary gland BMP2 is not yet known. On the other hand, we have demonstrated that long-term exposure (60 days) to BPA initiates fundamental changes in human mammary stem cells themselves, in particular, by altering major BMP signaling elements such as receptor expression and localization [64]. This results in the "priming" of stem cells to exogenous activating signals of the BMP pathway and sensitizes them to be more sensitive to exogenous soluble BMP ligands. We then demonstrated for the first time that nongenotoxic alterations of both the stem cells and their niche act

synergistically to initiate a transforming process mediated by the BMP signaling perturbation leading to the emergence of ER-positive tumors [76]. Interestingly, these previous studies showed that BPA impacts BMP signaling pathway members in both mammary epithelial and stromal cells that do not express ERα66. At the mechanistic level, the pathways used by BPA to induce these effects in cells remain to be deciphered, focusing notably on their reliance on other ERα isoforms or on ER-independent factors.

These questions are of great interest for understanding the effects of both BPA and estrogens since it has been reported that some cell lines respond to an estrogen signal despite their very low levels or complete absence of ER [148]. In response to accumulating evidence in favor of adverse health effects following exposure to BPA, likely mediated by its activation of ERα66, alternative bisphenols have been developed such as BPS and BPF that are considered safer due to their very low binding affinity to ERα [149–151]. However, an increasing number of studies show that these alternative bisphenol molecules are not as innocuous as anticipated, including an impact on obesity, steatosis, and reproduction [20]. In a study previously conducted in our team, assessing the impact of bisphenol on BMP2 production by stromal cells of the mammary gland, we were surprised to observe that BPA and BPS displayed very similar effects [76]. Indeed, both BPA (high affinity binding to estrogen receptors) and its substitute BPS (very weak affinity binding to estrogen receptors) induce BMP2 synthesis in the healthy breast stroma, raising concerns as to whether these bisphenols mediate their transforming effects solely through a classical ER-dependent mechanism. Since then, other studies have shown that BPS, as well as BPF, induces similar if not more potent effects than BPA [20, 152, 153]. Moreover, it was reported that BPA treatment increases aromatase expression and its activity in healthy breast fibroblasts, leading to an increase in estrogen biosynthesis and secretion. The same observations were made after treatment with BPS [154]. These results are of particular interest with regards to the important role of the microenvironment in the different steps of carcinogenesis and in the context of MaSC-driven transformation by BMP signaling. Our work thus indicates that the BMP pathway could be altered by several EDCs such as BPA and its proposed alternatives, both at the level of stem cells and their microenvironment. This suggests that early detection of increased BMP2 levels in the mammary microenvironment may constitute a reliable marker of early transformation process and could be a valuable indicator of exposure to EDCs such as bisphenols. In addition, the interplay between BMP and estrogen pathways both at the molecular and functional levels prompt us to further decipher the mechanisms underlying bisphenol- and BMP-induced transformation in mammary epithelial stem cells.

3. Conclusions

Different signaling pathways often engage in complex interactions synergistically mediating an appropriate cellular response. Estrogen signaling is no exception and it is likely involved in a crosstalk with the BMP pathway at multiple levels in the mammary gland. BMPs are secreted proteins active in a very large number of organs and tissues during development, adulthood, and pathogenesis [155]. Previous work suggested a close interaction between ER-mediated estrogen signaling and the BMP pathway in different cell types of the mammary gland. In a model of mammary epithelial stem cells, E2 or known EDCs like BPA or BPS were able to potentiate SMAD activation by BMP2 [64]. This was possibly due to a physical interaction between ERα isoforms and SMAD factors, such as that reported for ERα or ERβ, and could be associated with an increased risk of cell transformation by long-term exposure

to BMP2. Deciphering the dysregulations of the BMP signaling pathway has been remarkably useful in identifying its importance in cancer stem cell phenotypes in the neural system [92, 93]. The role of alterations of BMP signaling to sustain cancer stem cell features has been extended by us and others in breast cancer and leukemia [90, 94, 95]. We showed that chronic exposure to high concentrations of BMP2 drives the transformation of mammary stem cells toward the luminal tumor subtype [76] through binding to its BMPR1B receptor. However, downstream mechanisms and crosstalks with estrogen signaling in those mammary stem cells remained to be understood. This is especially important in the context of several studies that demonstrated the involvement of BPA in the proliferation of either ER-positive or -negative cancer cells. In addition, BPA can trigger proliferation via nonclassical estrogen receptors, including the estrogen-related receptor gamma (ERRγ) [156, 157]. We also demonstrated that long-term exposure of human mammary stem cells (ER-negative in terms of ERα-66 expression) to pollutants such as BPA initiates fundamental changes in stem cells by altering major BMP signaling components [64], thus "priming" stem cells to exogenous BMP activation. Complementary to this effect on epithelial stem cells, we revealed an impact of BPA on the tumor microenvironment through the induction of the synthesis of high levels of BMP2 by normal fibroblasts and stromal cells reaching levels similar to those measured in breast tumors [76].

Resistance and relapse can be due to tumor adaptation or evolution. Indeed, therapies elicit a selective pressure on cells, which in turn develop resistance, notably by acquiring mutations. Resistance to tamoxifen of ER-positive tumors can be caused by a loss of ER [158], its mutation, or posttranslational modification [159] among others. It was shown that BPA is involved in chemoresistance [160] and notably in resistance to tamoxifen in ER-positive tumor cell lines [161] by decreasing tamoxifen-induced apoptosis and increasing gene expression of ERRα, which contributes to resistance to tamoxifen [162] and cell proliferation [157]. Another study demonstrated that an ERα variant could be induced by BMP2 [128] and may be involved in resistance to tamoxifen [163]. The addiction of cancer cells toward BMP signaling and the crosstalk with estrogen signaling is currently under consideration as a new therapeutic avenue for ER-positive breast cancer patients [164]. At the clinical level, targeting estrogen signaling has been decisive in improving the outcome of ER-positive breast cancer patients. At the era of immunotherapy, the analysis of the impact of bisphenols on the immune system and on tumor surveillance is crucial. This will need to be pursued to improve our understanding and implementation of antiestrogen therapies in the context of their combination with new immune treatments [165]. Overall, these data indicate that disruption of BMP signaling affects both the stem cells and their niche at different stages of the disease, which could be instrumental in the management of breast cancer.

Several studies demonstrated that BPS promotes breast cancer cell proliferation, notably through an ER-cyclin D1-CDK4/6-pRb-dependent pathway, exclusively in ER-positive breast cancer cells [38, 39, 166]. Moreover, it has also been demonstrated that BPF has the same proliferative action as BPA, BPS, or estrogen treatments on transformed ER-positive cells. Similar to BPS, this proliferative effect relies on cyclin D and E expression through ER-dependent pathways [39]. BPS, as shown for BPA, can also induce epigenetic and transcriptional changes in breast cancer cells, resulting in an increase in the expression of genes implicated in proliferation, cellular attachment as well as adhesion and migration [167]. Lastly, the bioavailability of BPS substitutes might be higher than for BPA. A recent study conducted in pigs, an ideal model for mimicking the human digestive tract, demonstrated the lower plasma clearance of BPS (3.5 lower) compared to BPA and an increased oral systemic exposure exceeding 250-fold [168]. These observations draw our attention and raise concerns about replacing BPA by BPS, as this may result in an increased internal exposure to EDCs.

To conclude, BMP signaling plays a major role in the regulation of SCs and of their microenvironment (niche), in both normal and tumor contexts. Multiple abnormalities of BMP signaling have been observed in cancer, but until recently studies had mostly focused on its role in advanced disease. However, due to the number of studies describing the importance of BMP signaling throughout breast cancer development (from initiation, progression, metastasis up to resistance), we suggest that early detection of BMP signaling alterations, such as increased levels of BMP2 and/or of BMP receptors, may constitute a reliable marker of exposure to BPA. This suggests that further investigations into alterations of the BMP pathway in the context of exposure to bisphenols should improve our understanding of associated side effects.

Acknowledgements

The authors thank the following funding bodies for their support of the team's work mentioned in this review: the Association pour la Recherche contre le Cancer, La Ligue contre le Cancer, the Déchaine ton cœur association, the Région Rhône-Alpes and the Institut National du Cancer.

Conflict of interest

The authors declare no conflict of interest.

Notes/thanks/other declarations

The author thanks Brigitte Manship for English proofreading and critical reading.

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