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Endocrine disruptor actions through receptor crosstalk

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ABSTRACT

Endocrine disruptors interfere with hormonal action through receptors and signaling pathways, but receptor crosstalk involved in the actions of endocrine disruptors has not yet been well documented. This review summarizes what is known about the actions of endocrine disruptors through receptor crosstalk, focusing on three model cases: crosstalk involving the estrogen receptor, the androgen receptor, and the thyroid hormone receptor. Here, crosstalk is categorized as bidirectional or unidirectional, with the latter category further subdivided into ligand-dependent or –independent crosstalk. More research needs to be done to develop a clearer understanding of the involvement of receptor crosstalk in cell signaling that is induced by endocrine disruptors. This understanding will help to develop *in vitro* and *in silico* assays that can replace animal tests.

ABBREVIATIONS

AhR	aryl hydrocarbon receptor
AR	androgen receptor
CCR	C-C chemokine receptor
CREB	cAMP response element-binding protein
DDE	dichlorodiphenyldichloroethylene
DDT	dichlorodiphenyltrichloroethane
DEHP	di-(2-ethylhexyl)-phthalate
DMBA	7,12-dimethylbenz[*a*]anthracene
E_2	17β-estradiol
EGF	epidermal growth factor
EGFR	epidermal growth factor receptor
ER	estrogen receptor
ERK	extracellular-signal-regulated kinase
ERR	estrogen-related receptor

GF	growth factor
GPCR	G protein-coupled receptor
GPER	G protein-coupled estrogen receptor 1
hCG	human chorionic gonadotropin
HDAC1	histone deacetylase 1
HER2	human EGFR2
IFN	interferon
IGF-1	insulin-like growth factor 1
IGF-1R	insulin-like growth factor 1 receptor
IL-6R	interleukin 6 receptor
LXR	liver X receptor
MAPK	mitogen-activated protein kinase
MNAR	modulator of non-genomic action of estrogen receptor
mTOR	mammalian target of rapamycin
ObR	leptin receptor
PI3K	phosphoinositide 3-kinase
PPAR	peroxisome proliferator-activated receptor
PR	progesterone receptor
pRb	retinoblastoma protein
PXR	pregnane and xenobiotic receptor
p-XSC	1,4-phenylenebis(methylene)selenocyanate
RAR	retinoic acid receptor
T3	3,5,3'-triiodo-L-thyronine
TAM	tamoxifen
TCDD	2,3,7,8-tetrachlorodibenzo-*p*-dioxin
TGF-β	transforming growth factor β
TNF-α	tumor necrosis factor-α
TR	thyroid hormone receptor
TR4	testicular orphan receptor 4

INTRODUCTION

Endocrine disruptors are defined as "an exogenous chemical, or mixture of chemicals, that can interfere with any aspect of hormone action" (Zoeller et al. 2012). They are present outside of organisms (i.e. they are xenobiotics) and affect the production, release, transport, metabolism, binding, and elimination of natural hormones in the body, which are responsible for maintaining homeostasis and regulating developmental processes (Kavlock et al. 1996). Definitions differ as to what constitutes an endocrine disruptor, based on the kinds of adverse outcomes that are stipulated (Schug et al. 2012). The assessment of endocrine disruptors was initiated with mainly estrogenic chemicals and subsequently expanded to include androgenic and thyroid-hormone–like chemicals (Tabb and Blumberg 2006). Estrogenic, androgenic, and thyroid-hormone–like chemicals were initially recommended for tiered testing of their endocrine disrupting actions (Charles 2004), and this approach is also used in recent endocrine disruptor studies (Du et al. 2010; Hu et al. 2011; Scholz et al. 2013; Sun et al. 2012).

In the face of skepticism (Safe 2000) and controversies (Vandenberg et al. 2009) surrounding the actions of endocrine disruptors, concerted efforts have been made in the past few decades to elucidate the underlying mechanisms of their effects. It is a challenge to demonstrate the endogenous effects of these substances because of difficulties specifying the animals, the outcomes, and the strength of the effects required for the assessment. However, a deeper understanding of the mechanisms of endocrine disruption is not only interesting from a scientific point of view, but important for reducing or refining animal tests, or even replacing them with *in vitro* or *in silico* assays (reviewed in Kiyama et al. 2014; Kiyama and Wada-Kiyama 2015).

Information on the molecular mechanisms underlying the actions of endocrine disruptors is very limited due to the variety of chemicals and the complexity of the molecular mechanisms to be examined; this is particularly the case when the mechanisms involve multiple actions of endocrine-disrupting chemicals and a large number of intracellular and/or intercellular signaling pathways. Many of the hundreds of thousands of chemicals around us have not yet been examined toxicologically, and the complexities of the cell signaling pathways induced by these chemicals currently remain unclear.

Interest in receptor-mediated crosstalk between signaling pathways and hormone/growth factor (GF) networks is increasing due to advances in the development of biotechnological methods, tools, and devices. Crosstalk has been described at various levels, for example, in homeostatic interactions (Benmouloud et al. 2014), cell functional interactions (Le et al. 2014), cell-cell interactions (Hollmén et al. 2015; Lu et al. 2012), interactions among cellular apparatuses (Totta et al. 2014), interactions between genomic and non-genomic pathways (Michels and Hoppe 2008; Silva et al. 2010), interactions between signal mediators (Bratton et al. 2012), and receptor interactions (Ernst et al. 2014). Receptor-mediated crosstalk involves receptors and their signal mediators.

Here, we focus on receptor crosstalk involved in the actions of endocrine disruptors, which has not yet been examined in detail. For example, bisphenol A, a well-studied endocrine disruptor, is known to interact with various receptors, such as estrogen receptor α (ERα), ERβ, estrogen-related receptor γ (ERRγ), membrane-bound ER, G-protein–coupled estrogen receptor 1 (GPER), aryl hydrocarbon receptor (AhR), thyroid hormone receptor (TR), and androgen receptor (AR) (Schug et al. 2012), suggesting that there is either direct crosstalk between signaling pathways or at least broad functional associations or interactions between them.

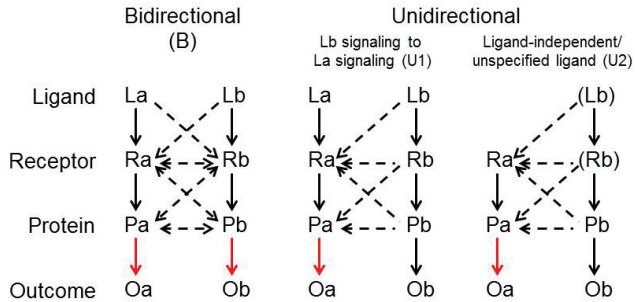

Figure 1. Simplified diagrams of receptor crosstalk.
Diagrams of receptor crosstalk, involving ligands (L), receptors (R), signal-mediating proteins (P), and functional outcomes (O) for two different signaling pathways (types a and b), are categorized by the direction (bi- or unidirectional) and also by the involvement of additional ligands/receptors. Solid arrows indicate simplified pathways, while hatched arrows indicate potential pathways (not necessarily existing). The pathways affecting outcomes are shown in red.

Receptor crosstalk has been categorized into bidirectional and unidirectional signaling pathways, in which signaling among ligands (La and Lb), receptors (Ra and Rb), signal-mediating proteins (Pa and Pb), and functional outcomes (Oa and Ob) are involved (Figure 1). Cases of bidirectional signaling pathways have been reported (Giuliano et al. 2013; Thorne and Lee 2003), such as those between the ER, AR, and TR, between just two of these receptor-mediated signaling pathways, or between one of them and other hormone/GF signaling pathways. Unidirectional signaling pathways, in which a particular hormone response is affected unidirectionally by other hormones/GFs (type U1 in Figure 1), have also been described (Bratton et al. 2012; Garay et al. 2012). Unidirectional crosstalk may be regarded as ligand-independent crosstalk (type U2), in which the receptors activated in a ligand-independent manner crosstalk with other signaling pathways (Culig 2004; Thorne and Lee 2003). Mutations or epigenetic alterations may change the status of receptors and/or their signal mediators, further affecting hormone signaling and its outcomes. The directions of crosstalk involving the ER, AR, and TR are discussed in the section "Directionality of crosstalk".

OUTLINE OF RECEPTOR CROSSTALK

Receptor-mediated mechanisms underlying endocrine disruptor actions

Estrogens, androgens, and thyroid hormones are considered to be involved in the actions of endocrine disruptors; however, other hormones may be involved, such as those secreted by the hypothalamus, pituitary gland, and pancreas (Khetan 2014). These hormones collaborate with other hormones and cytokines/GFs inside or outside cells in homeostatic networks, in which receptor crosstalk plays an important role.

Table 1. Summary of receptor crosstalk.

Crosstalk between receptors/pathways	Function analyzed or subject examined	Reference (reviews)
ER		
ER:AhR	Endocrine disruptor action/antiestrogenicity	Safe et al. 1998; Safe and Wormke 2003
ER:Cytokine/GF signaling	Breast cancer	Massarweh and Schiff 2006; Osborne et al. 2005; Schiff et al. 2005; Thakkar and Mehta 2011
ER:Cytokine/GF signaling	Hormone-regulated transcription	Smith 1998
ER:Cytokine/GF signaling	Lung cancer	Stabile and Siegfried 2004
ER:Cytokine/GF signaling	Target for selective estrogen receptor modulators	Härkönen and Väänänen 2006
ER:ERRα signaling	Therapeutic target in cancer	Stein and McDonnell 2006
ER:HER2 signaling	Breast cancer	Bender and Nahta 2008; Giuliano et al. 2013; Johnston 2006; Nahta and O'Regan 2012; Osborne and Schiff 2011
ER:HER family signaling	Endocrine-resistant tumor growth	Arpino et al. 2008
ER:IGF-1 signaling	Breast cancer	Fagan and Yee 2008; Lanzino et al. 2008; Surmacz and Bartucci 2004; Thorne and Lee 2003;
ER:MNAR signaling	Estrogen-induced cardio-/neuro-/osteo-protection	Cheskis et al. 2008
ER:NF-κB signaling	Inflammation	Harnish 2006
ER:NF-κB signaling	Endocrine-resistant breast cancer	Zhou et al. 2005
ER:PI3K/Akt/mTOR signaling	Cancer cell proliferation/metabolism/survival	Fu et al. 2013
ER:PR signaling	Regulation of gene expression/cell proliferation	Katzenellenbogen 2000
ER:TGF-β signaling	Breast cancer	Band and Laiho 2011
ER-α36:Other ER signaling	Breast cancer	Wang and Yin 2015
GPER:Other ER signaling	Breast cancer	Barton 2012
AR		
AR:Cytokine/GF signaling	Prostate cancer	Koochekpour 2010; Mellado et al. 2009, 2013
AR:EGFR signaling	Prostate cancer	Bonaccorsi et al. 2008
AR:ER signaling	Breast cancer	Fioretti et al. 2014
AR:IL-6 signaling	Prostate cancer	Culig 2004
AR:Notch signaling	Prostate cancer	Villaronga et al. 2008
AR:PI3K/Akt signaling	Prostate cancer	Wang et al. 2007
AR:PI3K, pRb, Ras/Raf/MAPK/ERK signaling	Prostate cancer	Georgi et al. 2014
AR:PI3K/Akt, MAPK, Wnt/β-catenin signaling	Prostate cancer	Zhang et al. 2011
AR:Prolactin receptor	Prostate cancer	Goffin et al. 2011
AR:Redox signaling	Prostate cancer	Rajendran et al. 2010
AR:TGF-β signaling	Prostate cancer	Zhu and Kyprianou 2005
AR:Wnt/β-catenin signaling	Prostate cancer	Verras and Sun 2006
AR:Wnt/β-catenin signaling	Cell growth/proliferation/differentiation/apoptosis	Beildeck et al. 2010
TR		
TR:ER	Endocrine disruptor	Zhang and Trudeau 2006
TR:PPARs	Fatty acid catabolism/inflammatory response	Hihi et al. 2002
TR:Steroid hormone receptors	Endocrine disruptor	Duarte-Guterman et al. 2014

*Abbreviations; AhR: aryl hydrocarbon receptor; AR: androgen receptor; EGFR: epidermal growth factor receptor (HER1 in humans); ER: estrogen receptor; ERK: extracellular-signal-regulated kinase; ERR: estrogen-related receptor; GF: growth factor; GPER: G protein-coupled estrogen receptor 1; HER2: human EGFR2; IGF-1: insulin-like growth factor 1; IGF-1R: insulin-like growth factor 1 receptor; MAPK: mitogen-activated protein kinase; MNAR: modulator of non-genomic action of estrogen receptor; mTOR: mammalian target of rapamycin; PI3K: phosphoinositide 3-kinase; PPAR: peroxisome proliferator-activated receptor; PR: progesterone receptor; pRb: retinoblastoma protein; TGF-β: transforming growth factor β; TR: thyroid hormone receptor.

Studies on receptor crosstalk are summarized in Table 1. Table 1 includes early studies on signal transduction, which are useful for examining the outline of receptor crosstalk although they sometimes lack details about mediators and the types of crosstalk. Reviews with comprehensive lists of references are available that describe crosstalk between the ER, AR, or TR and other signaling pathways. These other signaling pathways are initiated or mediated by receptors, such as the AhR, ERRα, the epidermal growth factor receptor (EGFR), HER2, Notch, peroxisome proliferator-activated receptors (PPARs), the progesterone receptor (PR), and prolactin receptor; or by cytokines/GFs, such as insulin-like growth factor 1 (IGF-1), interleukin 6 (IL-6), and transforming growth factor β (TGF-β); or by signal-related proteins, such as NF-κB, phosphoinositide 3-kinase (PI3K)/Akt/mTOR, Retinoblastoma protein (pRb), Ras/Raf/mitogen-activated protein kinase (MAPK)/ERK, redox proteins, and Wnt/β-catenin. These signaling pathways are associated with cancer (such as breast, lung, and prostate cancers), cellular functions/responses (such as cell growth/proliferation/differentiation/apoptosis, inflammation, and metabolism), endocrine disruptor actions, functional regulation (such as transcriptional and expressional regulation), and drug targets (such as those for selective estrogen receptor modulators and therapeutic targets).

Crosstalk involving the ER

Estrogen is a female hormone that is responsible for menstrual and estrous reproductive cycles. The signals induced by estrogens and estrogenic endocrine disruptors are mediated by ERs, which comprise nuclear ERs, ERα and ERβ, membrane ERs (such as GPER and ERX), and variant ERs (such as ERα-36) (Kiyama and Wada-Kiyama 2015). In the genomic pathway, these ERs function as transcription factors that up-regulate or down-regulate the expression of target genes; in the non-genomic pathway, they function as signal mediators that activate or suppress estrogen signaling via crosstalk with other receptors, often forming extracellular networks with the same cell, nearby cells, or distant cells.

Of the papers on crosstalk and ER-mediated signaling that we review here, those that concern breast cancer comprise the largest group. These papers discuss crosstalk involving the ER and cytokines, GFs, and receptors (Table 1), as well as therapeutic strategies for endocrine-resistant, GF-activated cancers, such as cancers with activated HER2 (human EGFR2), and ER-positive and PR-negative cancer (Massarweh and Schiff 2006; Osborne et al. 2005; Schiff et al. 2005; Thakkar and Mehta 2011). Estrogen and other hormones/GFs regulate apoptosis and other cell functions through two major pathways: the PI3K/Akt and Ras/MEK/ERK pathways, in normal breast cells (Nahta and O'Regan 2012), and this regulation is abolished by the depletion of receptor functions, resulting in the deregulation of these pathways and substitution with other signaling pathways, along with the constitutive activation of growth- and cell cycle-regulating pathways through receptor crosstalk in cancer cells.

Crosstalk between the ER and HER2 has been associated with breast cancer (Bender and Nahta 2008; Giuliano et al. 2013; Johnston 2006; Nahta and O'Regan 2012; Osborne and Schiff 2011), and endows cells with endocrine resistance, such as that by selective estrogen receptor modulators (SERMs). HER2 is a member of the HER family of proteins, which includes HER1 (or EGFR), HER3, and HER4; it exhibits receptor tyrosine kinase activity; and it contributes to tumorigenesis by forming complexes with or phosphorylating HER3 (Bender and Nahta 2008). Intercellular small-molecule inhibitors against breast cancer have been developed based on the signaling pathways identified to date (Johnston 2006). Bidirectional crosstalk between ER and HER2 may require the simultaneous blocking of both signaling pathways (Giuliano et al. 2013). Thus, information on receptor crosstalk provides oncologists with the opportunity to develop effective strategies that block, downgrade, or deprive receptor functions, and, because of the absence of appropriate targets, triple-negative (ER^-, $HER2^-$ and PR^-) breast cancer has the poorest prognosis (Thakkar and Mehta 2011).

Additional crosstalk involving ERs has been discussed in association with specific cell functions, such as the regulation of gene expression (at the levels of transcription, translation, transport, and further processing/metabolism/degradation) and cell growth/proliferation as well as specific physiological outcomes, such as anti-estrogenicity, inflammation, and cardio-/neuro-/osteo-protection, in which the pathways for various hormones (including membrane and variant ERs), cytokines, GFs, and signal mediators, such as AhR, ERRα, IGF-1, NF-κB, and TGF-β signaling, are involved (Table 1). Information on crosstalk has been used in order to identify new targets for cancer treatments (combination treatments for breast cancer using inhibitors of ERRα, IGF-1, or TGF-β signaling; Band and Laiho 2011; Fagan and Yee 2008; Stein and McDonnell 2006), hormone therapy (suppression of estrogen-mediated functions by membrane/variant ERs; Barton 2012; Wang and Yin 2015) and drug development (drugs for the treatment of pathogenic inflammation; Harnish 2006), or to identify prognostic markers (NF-κB activity for breast cancer; Zhou et al. 2005) .

Crosstalk involving the AR

The AR is a nuclear receptor, and like the ER, the AR also has two known modes of action: genomic and non-genomic. In the genomic mode, the AR binds with the physiological androgens, testosterone or dihydrotestosterone, in the cytoplasm. After this, it is translocated into the nucleus, where it acts as a transcription factor that controls the expression of the genes critical for the development and maintenance of the male sexual phenotype (Mooradian et al. 1987; Roy et al. 1999). In the non-genomic mode, membrane ARs rapidly activate kinase-signaling pathways, such as the MAPK signaling pathway, but do not directly regulate gene transcription (Heinlein and Chang 2002; Wang et al. 2014). Androgenic endocrine disruptors include industrial chemicals, such as bisphenol A, dichlorodiphenyltrichloroethane (DDT),

dichlorodiphenyldichloroethylene (DDE), diphenylmethanes, methoxychlor, organochlorines, and phthalates (Luccio-Camelo and Prins 2011). These endocrine disruptors interfere with the biosynthesis, metabolism, and/or effects of androgens, resulting in abnormal male development and abnormal growth and function of the reproductive tract.

Prostate cancer is associated with crosstalk between the AR and receptor-mediated pathways, such as the EGFR pathway, cytokines and growth factors, or other signaling pathways, including the IL-6, Notch, PI3K/Akt, pRb, Ras/Raf/MAPK/ERK, redox, TGF-β, and Wnt/β-catenin signaling pathways (Table 1). Carcinogenesis and metastatic or androgen-independent (castration-resistant) progression of prostate cancer involve crosstalk between the AR and growth factors, neurotrophic peptides, cytokines or non-androgenic hormones (Koochekpour 2010; Mellado et al. 2009, 2013). This type of crosstalk is associated with somatic and germline mutations in the AR, such as those detected in its ligand-binding and DNA-binding domains. This crosstalk can be classified into three categories: 1) the AR interacts with other receptors, such as EGFR, at the plasma membrane (Bonaccorsi et al. 2008); 2) the AR interacts with β-catenin in the nucleus (Verras and Sun 2006; Zhang et al. 2011), 3) the AR is activated in a ligand-independent manner by MAPK or other signal mediators in response to IL-6 (Culig 2004). The growth of androgen-independent prostate cancer may be induced by the overexpression of HER2, a receptor tyrosine kinase, and advanced androgen-independent prostate cancer has been associated with deregulation of the Wnt/β-catenin pathway (Zhang et al. 2011). In both of these cases, crosstalk may occur in many locations: in the intracellular space, at the cell membrane, in the cytoplasm, and within the nucleus (Beildeck et al. 2010). In addition, the crosstalk of the AR with female hormones, such as prolactin (Goffin et al. 2011) and estrogen (Fioretti et al. 2014), through their receptor-mediated pathways plays significant roles in the initiation, progression, and malignancy of cancer.

Crosstalk involving the TR

Thyroid hormone plays significant roles in lipid/glucose metabolism and the development of tissues in the nervous, skeletal, pulmonary, and cardiovascular systems. A key step in its regulation is the activation of the prohormone, thyroxine (T4), to the active form, triiodothyronine (T3) (Brent 2012; Cheng et al. 2010; Harvey and Williams 2002; Mullur et al. 2014; Yen 2001). The TR has two isoforms, TRα and TRβ, which are differentially expressed in tissues and have distinct roles in thyroid hormone signaling. Crosstalk between the TR and other receptors or signaling pathways has been investigated in association with metabolic processes, such as basal/adaptive metabolism, bile acid/cholesterol/fatty acid syntheses, and glucose metabolism (Liu and Brent 2010). Evidence for crosstalk between the TR and steroid hormone receptors is increasing, suggesting that it plays a role in gonad differentiation and reproductive function. Thyroid hormone may modulate the transcriptional levels of genes for the enzymes that synthesize estrogens and androgens; thyroid hormone can also modulate the activity of these enzymes (Duarte-Guterman et al. 2014). The actions of nuclear receptors, like the TR, may be affected by the rapid actions of membrane receptors that have interacted with endocrine disruptors (Zhang and Trudeau 2006). The TR has been reported to be involved in the negative regulation of fatty acid metabolism by PPARs, such as when thyroid hormone inhibits the PPAR-regulated expression of the rat peroxisomal enoyl-CoA hydratase/3-hydroxiacyl-CoA dehydrogenase gene (Hihi et al. 2002).

PATHWAYS MEDIATING RECEPTOR CROSSTALK

Cell signaling pathways mediating receptor crosstalk

Recent technological advances have enabled detailed analyses of the pathways mediating receptor crosstalk. Findings on receptor crosstalk involving ER, AR and TR signaling are summarized in Table 2, where they are categorized by chemicals (such as ligands/modulators/inhibitors/stimulators), pathways/crosstalk, types of crosstalk, and functions/subjects. Recent studies are highlighted here because of the development of biotechnological tools and methods that have enabled us to examine the pathways in detail.

In the ER-associated pathways, ER ligands induce signals after binding to nuclear (ERs) or membrane (GPER) receptors. These ligands include natural and synthetic estrogens/ER antagonists (E_2, G-1, fulvestrant, and tamoxifen) and synthetic estrogenic chemicals (bisphenol A, nonylphenol, phthalates, and zearalenone). Crosstalk has been reported between the ER signaling pathway and other pathways involving specific receptors like the AhR, chemokine receptors (CCRs and CXCR1), EGFR, HER2 (ErbB2), insulin-like growth factor 1 receptor (IGF-1R), interleukin 6 receptor (IL-6R), Nur77, leptin receptor (ObR), PPARα, and TGF-βR, and between the ER signaling pathway and other signaling pathways involving unspecified receptors, such as the c-Fos/c-Jun/AP-1, MAPK, PI3K/Akt/mTOR, and Wnt/β-catenin pathways (Table 2). These pathways have been implicated mainly in breast, endometrial, and ovarian cancers, although they are associated with other types of cancers (lung and prostate cancers) and with physiological functions, such as cartilage/adipose maturation, female reproduction, protein degradation, and sugar/lipid metabolism.

In AR-associated pathways, AR ligands, such as natural and synthetic androgens/antiandrogens (bicalutamide, dihydrotestosterone, enzalutamide, flutamide, R1881, SC97, and SC245), induce signals after binding to the AR. Most AR-associated pathways are involved in prostate cancer, and they have also been implicated in other types of cancers, such as fibrosarcoma and bladder and breast cancers, and in physiological functions, such as cholesterol homeostasis, cutaneous wound healing, muscle hypertrophy, and neurite outgrowth.

Table 2. Signaling pathways involving receptor crosstalk (a summary of recent studies).

Chemical[a]	Pathway and crosstalk	Type of Crosstalk[b]	Function or Subject	Reference
ER-associated pathway				
Bisphenol A/E_2	ERα:IGF-1R/IRS-1/Akt	B	Ovarian cancer	Kang et al. 2013
Bisphenol A/E_2/IGF-1	ERα:IGF-1R/IRS-1/Akt	B	Ovarian cancer	Hwang et al. 2013
Bisphenol A/Nonylphenol/TGF-β	ERα:TGF-βR	B	Ovarian cancer	Park and Choi 2014
o,p'-DDT	MAPK/VEGFA:ER	U2	Breast cancer	Bratton et al. 2012
DEHP	PPARα:ERα	U1	Female reproduction	Kawano et al. 2014
Di-*n*-butyl phthalate/TGF-β	ER:TGF-βR	B	Prostate cancer	Lee et al. 2014
E_2	ERα:PI3K/Akt/mTOR	U1	Endometrial cancer	Hou et al. 2014
E_2	pRb:ERα	U2	Breast cancer	Caligiuri et al. 2013
E_2	ER:PI3K/Akt	U1	Glucose uptake	Garrido et al. 2013
E_2	PI3K/Akt/mTOR:ER	U1	Breast cancer	Bostner et al. 2013
E_2	ERα:AhR	U1	Female reproduction	Rataj et al. 2012
E_2	ERβ:c-Fos/c-Jun/AP-1	U1	Breast cancer	Zhao et al. 2010
E_2/EGF	HER2/MAPK:ERα/MMP-1	B	Breast cancer	Jung et al. 2010
E_2/EGF/IGF	ER:EGFR, IGF-1R	B	Breast cancer	Tsonis et al. 2013
E_2/EGF/Lapatinib (HER2 inhibitor)	HER2:ERα/PR	B	Breast cancer	Leary et al. 2010
E_2/EGF/Rapamycin	ER:HER2/PI3K/Akt/mTOR	B	Breast cancer	Yan et al. 2014
E_2/EGF/Trastuzumab	ER:HER2/PI3K/Akt/mTOR	B	Breast cancer	Takada et al. 2013
E_2/EGF/Wnt	ERα:EGFR/WBP2/Wnt/β-catenin	B	Breast cancer	Lim et al. 2011
E_2/Everolimus (mTOR inhibitor)	ER:PI3K/mTOR	U1	Breast cancer	Cottu et al. 2014
E_2/GDNF/Sunitinib (RET inhibitor)	RET/ERK/Akt:ER	B	Breast cancer	Spanheimer et al. 2014
E_2/IGF-1	ERα:IGF-1R	B	Preadipose growth	Dos Santos et al. 2010
E_2/IL-8	GPER/Akt/NF-κB:CXCR1	U1	Breast cancer	Jiang et al. 2013
E_2/Osteopontin/EGF	ER:Integrin/MEK/ERK/EGFR	U1	Lung cancer	Hsu et al. 2015
E_2/TCDD	AhR/AHRR/CYP1A5:ERα	B	Dioxin toxicity	Lee et al. 2011
E_2/TGF-β1	ERα/GRIP1:TGF-βR/MAPK	B	Cartilage metabolism	Kato et al. 2010
E_2/TNF-α	ER:NF-κB	B	Breast cancer	Kastrati et al. 2015
E_2/Wnt3A	Wnt/β-catenin:ERα, ERβ	B	Osteogenic differentiation	Gao et al. 2013
G-1 (selective GPER ligand)/EGF	GPER:EGFR/ERK/c-Fos/AP1	U1	Lipid metabolism	Santolla et al. 2012
Heregulin-β1/E_2	ErbB2/ERK:GPER	U1	Breast cancer	Ruan et al. 2012
IGF-1	IGF-1R/Akt2/FoxO3a:ERα	U2	Breast cancer	Morelli et al. 2010
IGF-1/E_2	IGF-1R/PKCδ/ERK/AP1:GPER	U1	Endometrial cancer	De Marco et al. 2013
IGF-1/E_2	IGF-1R/PI3K/Akt:ER	U1	Breast cancer	Zhang et al. 2012
IGF-1/E_2	IGF-1R/IRS/mTOR/S6K1:ERα	U1	Breast cancer	Becker et al. 2011
IL-6/TAM	IL-6R:ERα/PI3K/Akt, ERK	U1	Ovarian cancer	Wang et al. 2015
Leptin	ObR/ERK:ER	U2	Bone formation	Wang et al. 2012a
Leptin/E_2	ObR/JAK2/STAT3:ER	U1	Breast cancer/Obesity	Valle et al. 2011
MCP-1	CCRs/PI3K/Akt/mTOR:ER	U2	Breast cancer	Riverso et al. 2014
Methyl amoorain/Wnt	ER/Wnt/β-catenin	B	Mammary tumor	Mandal et al. 2013
MG132/Lactacystin/E_2	JAK2/Ubiquitin-proteasome:ERα	U1	Breast cancer	Gupta et al. 2012
Mitogen/E_2	PI3K/mTOR/HDAC1:ERα	U1	Breast cancer	Citro et al. 2015
Nimotuzumab/E_2	EGFR/COX-2:ER	U1	Breast cancer	Wang et al. 2012b
TAM/EGF	ERα/HOXB7:EGFR	B	Breast cancer	Jin et al. 2012
TAM/EGF	ERα:HER2	B	Breast cancer	Giordano et al. 2010
TAM/Fulvestrant/EGF	ERα:HER2	B	Breast cancer	Ito et al. 2012
TAM/Gefitinib (EGFR inhibitor)	ER:EGFR	B	Lung cancer	Shen et al. 2010
TAM/Rescovitine/EGF	ERα:HER2/CDK2	B	Breast cancer	Nair et al. 2011
TGF-β	ERα:TGF-βR/PAI-1	U2	Breast cancer	Stope et al. 2010
TNF-α/E_2	TNF-αR/ERK:ERα	U1	Gynecological disease	Gori et al. 2011
TNF-α/E_2	PI3K/Akt:ERα/Bcl-2	U1	Breast cancer	Bratton et al. 2010
Zearalenone/hCG	ERα:Nur77	U1	Testosterone biosynthesis	Liu et al. 2014a
AR-associated pathway				
Androgen	AR/U19/EAF2:Ras/Raf/ERK	U1	Prostate cancer	Su et al. 2013
Androgen	PTEN/PI3K:AR/FKBP5	U1	Prostate cancer	Mulholland et al. 2011
Bicalutamide (AR inhibitor)	AR:PI3K/Akt	U1	Prostate cancer	Dahlman et al. 2012
Bicalutamide/Everolimus	AR:mTOR	U1	Prostate cancer	Schayowitz et al. 2010

Bicalutamide/Rapamycin	AR:mTOR	U1	Prostate cancer	Wu et al. 2010
Bicalutamide/Ridaforolimus	AR:PI3K/Akt/mTOR	U1	Prostate cancer	Meulenbeld et al. 2013
Bicalutamide/Ridaforolimus	AR:EGFR/Akt/mTOR	U1	Prostate cancer	Squillace et al. 2012
Bicalutamide/Nutlin-3	MDM2/p53:AR	U1	Prostate cancer	Tovar et al. 2011
Cyclopamine (Hedgehog inhibitor)	AR:Hedgehog/Gli	U2	Prostate cancer	Chen et al. 2010
Dihydrotestosterone	COUP-TF II:AR	U1	Prostate cancer	Song et al. 2012
Dihydrotestosterone	PTEN/Akt:AR	U1	Breast cancer	Wang et al. 2011
Dihydrotestosterone	PXR:AR	U1	Prostate cancer	Kumar et al. 2010
Dihydrotestosterone/Cholesterol	AR:SREBP-2/LXR	U1	Cholesterol homeostasis	Krycer and Brown 2013
Dihydrotestosterone/Cholesterol	AR:SREBP-2/LXR	U1	Cholesterol homeostasis	Krycer and Brown 2011
Dihydrotestosterone/E_2	AR:ERα	B	Breast cancer	Need et al. 2012
Dihydrotestosterone/EGF	AR:EGFR	B	Bladder cancer	Izumi et al. 2012
Dihydrotestosterone/EGF	AR:EGFR/ErbB2	U1	Prostate cancer	Zheng et al. 2011
Dihydrotestosterone/IFN	AR:IFN receptor/MxA	B	Prostate cancer	Brown et al. 2015
E_2/Dihydrotestosterone	ERβ:AR/PELP1	B	Prostate cancer	Yang et al. 2012
Enzalutamide (AR antagonist)	AR:HIF-1α	U1	Prostate cancer	Fernandez et al. 2015
Flutamide (AR antagonist)/PM-20	AR:ERK/Cdc25A	U1	Breast cancer	Naderi and Liu 2010
Flutamide/TGF-β	AR:TGF-βR	U1	Cutaneous wound healing	Toraldo et al. 2012
Heregulin (ErbB3 ligand)	ErbB3/EBP-1:AR	U1	Prostate cancer	Zhou et al. 2010
IGF-1/R1881 (synthetic androgen)	β_{1A} integrin/IGF-1R:AR	B	Prostate cancer	Sayeed et al. 2012
IL-6	IL-6R/pSTAT3/Fer:AR	U1	Prostate cancer	Rocha et al. 2013
Nodal/R1881	Cripto-1:AR	U1	Prostate cancer	Lawrence et al. 2011
R1881	AR:Filamin A/TrkA/PI3K/Rac	B	Neurite outgrowth	Di Donato et al. 2015
R1881	AR:PTEN/PI3K/Akt	U1	Prostate cancer	Marques et al. 2015
R1881	AR:Wnt/β-catenin	B	Bladder cancer	Li et al. 2013
R1881/E_2/EGF	AR:ER:EGFR	T	Fibrosarcoma	Fiorelli et al. 2011
R1881/EGF	EGFR:AR/Src	B	Fibrosarcoma	Castoria et al. 2013
R1881/IGF-1	AR/SOCS2:IGF-1R	U1	Prostate cancer	Iglesias-Gato et al. 2014
R1881/IGF-1	AR:IGF-1R	U1	Prostate cancer	Itkonen and Mills 2013
R1881/Rapamycin	PI3K/Akt/mTOR:AR	U1	Prostate cancer	Kaarbø et al. 2010
SC97, SC245 (antiandrogen)	AR:NF-κB	U1	Prostate cancer	Liu et al. 2014b
Testosterone	AR:GPCR/PI3K/Akt/mTOR	B	Muscle hypertrophy	Basualto-Alarcón et al. 2013
Testosterone/Vitamin D	AR:Vitamin D receptor	B	Prostate cancer	Mordan-McCombs et al. 2010
TGF-β1	TGF-βR:ERβ:AR	T	Bladder cancer	Xu et al. 2013
Wnt/Dihydrotestosterone	Wnt/β-catenin/ICAT:AR	U1	Bladder cancer	Zhuo et al. 2011
p-XSC (organoselenium)	PI3K/Akt:AR	U1	Prostate cancer	Facompre et al. 2010
TR-associated pathway				
Finasteride (antiandrogen)	AR:TR-β	U1	Endocrine disruption	Langlois et al. 2011
Propiconazole	AhR:TR	U1	Endocrine disruption	Ghisari et al. 2015
T3	TR:CREB/L-type Ca^{2+} channel	U1	Hyperthyroidism	Chen et al. 2011
T3	TR4:TR	U1	Energy homeostasis	Huang et al. 2010
T3	TR:ER/AR	U1	Amphibian metamorphosis	Duarte-Guterman and Trudeau 2010
T3/Retinoic acid	TR:RAR	U1	Brain development	Gil-Ibáñez et al. 2014
T3/Rosiglitazone (PPAR agonist)	TR-β:PPARγ	B	Energy homeostasis	Kouidhi et al. 2010
T3/TO901317 (LXR agonist)	TR-β:LXR-α/Seladin-1	B	Lipid metabolism	Ishida et al. 2013
T3/TO901317	TR-β/ChREBP:LXR	B	Lipid metabolism	Gauthier et al. 2010

Mediators in the same signaling pathways are shown by a slash (/); and crosstalk, by a colon (:). [a]Chemicals include ligands, modulators, inhibitors and/or stimulators, which are sometimes inseparable from each other. [b]Crosstalk is classified as bidirectional (B; including three-way crosstalk, T) or unidirectional, and the latter is further classified according to the presence of both ligands (U1) or the absence of one or both ligands (U2). Note that crosstalk is classified as B, in which the direction is not apparent. Abbreviations; AhR: aryl hydrocarbon receptor; AR: androgen receptor; CCR: C-C chemokine receptor; CREB: cAMP response element-binding protein; CXCR1: chemokine (C-X-C motif) receptor 1; CREB: cyclic AMP response element-binding protein; DDE: dichlorodiphenyldichloroethylene; DDT: dichlorodiphenyltrichloroethane; DEHP: di-(2-ethylhexyl)-phthalate; DMBA: 7,12-dimethylbenz[*a*]anthracene; E_2: 17β-estradiol; EGF: epidermal growth factor; EGFR: epidermal growth factor receptor; ER: estrogen receptor; ERK: extracellular-signal-regulated kinase; GPCR: G protein-coupled receptor; hCG: human chorionic gonadotropin; HDAC1: histone deacetylase 1; IFN: interferon; IGF-1: insulin-like growth factor 1; IGF-1R: insulin-like growth factor 1 receptor; IL-6R: interleukin 6 receptor; LXR: liver X receptor; MAPK: mitogen-activated protein kinase; mTOR: mammalian target of rapamycin; ObR: leptin receptor; PI3K: phosphoinositide 3-kinase; PPARγ: peroxisome proliferator-activated receptor γ; PR: progesterone receptor; pRb: retinoblastoma protein; *p*-XSC: 1,4-phenylenebis(methylene)selenocyanate; PXR: pregnane and xenobiotic receptor; RAR: retinoic acid receptor; T3: 3,5,3'-triiodo-L-thyronine; TAM: tamoxifen; TCDD: 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; TGF-β: transforming growth factor β; TNF-α: tumor necrosis factor-α; TR: thyroid hormone receptor; TR4: testicular orphan receptor 4.

The thyroid hormone T3 is involved in TR-associated pathways, and crosstalk has been observed between the TR signaling pathway and those mediated by other receptors, such as the AhR, AR, ER, LXR, PPARγ, the retinoic acid receptor (RAR), and the testicular orphan receptor 4 (TR4). TR-associated pathways play crucial roles in endocrine disruption and in development/differentiation, energy homeostasis, and lipid metabolism.

Directionality of crosstalk

Crosstalk between the ER, AR, and TR or between these and other signaling pathways has been classified into bidirectional (or reciprocal) or unidirectional crosstalk. Unidirectional crosstalk has been further subdivided into two types according to the presence or absence of both receptors (or their ligands) (Figure 1). Bidirectional crosstalk has been observed between the ER, AR, or TR pathways and the AhR, EGFR/HER2, GPCR, IGF-1R, interferon receptor, LXR, TGF-βR, tumor necrosis factor-α receptor (TNF-αR), TR4, vitamin D receptor, or Wnt/β-catenin signaling pathways (Table 2). Other cases of bidirectional crosstalk, such as that between the AR and ER pathways or three-way crosstalk (among ER, AR, and TGF-βR, or ER, AR, and IGF-1R) have also been described. Apparent unidirectional crosstalk (type U1) has been reported in many signaling pathways (Table 2).

Ligand-independent crosstalk (type-U2) has been identified in cases in which the receptor has lost the ability to bind the ligand, the receptor itself has disappeared, or it is disabled due to mutations or other mechanisms. For example, Riverso et al. (2014) reported that the MCP-1-stimulated promotion of cell division was mediated through phosphorylation of the ER via ligand-independent crosstalk between the ER and PI3K/Akt/mTOR pathways. *o,p'*-DDT is known to modulate ERα-dependent gene expression, and Bratton et al. (2012) found that *o,p'*-DDT affected the expression of the vascular endothelial growth factor gene (*VEGFA*) and other genes through ER-independent crosstalk between the MAPK pathway and the CBP-mediated transcriptional coactivator pathway. The responsiveness of chondrocytes to estrogen is regulated by ligand-independent crosstalk between the leptin-induced ERK pathway and the ER pathway during bone formation (Wang et al. 2012a).

In breast cancer, responsiveness to estrogen is a key factor in adopting hormonal therapy, and the loss of this responsiveness is critical in tumor progression. Estrogen-independent tumor growth may be promoted by various mechanisms, which are important when selecting therapeutic strategies. For example, crosstalk between the pRb and ER pathways regulates the number of ERs by controlling their degradation through the proteasome pathway, and the loss of pRb decreases estrogen responsiveness, thereby leading to the acquisition of resistance to hormonal therapy (Caligiuri et al. 2013). The expression and function of ERs in breast cancer are regulated by crosstalk between the ER pathway and the IGF-1 (Morelli et al. 2010) or TGF-β (Stope et al. 2010) signaling pathways in a ligand-independent manner. Ligand-independent progression of prostate cancer has also been observed in which crosstalk between the Hedgehog (Hh) and AR signaling pathways is a key factor supporting the growth of androgen-deprived and androgen-independent prostate cancer cells (Chen et al. 2010).

Endocrine-disrupting chemicals in receptor crosstalk

Endocrine-disrupting chemicals induce signals through receptor crosstalk. For example, bisphenol A mediates signals for the progression of ovarian cancer by binding to ERs and by crosstalk with other signaling pathways, such as those of IGF-1 and TGF-β (Hwang et al. 2013; Kang et al. 2013; Park and Choi 2014). Other endocrine-disrupting chemicals affect various functions (such as endocrine disruption and cancer progression) through crosstalk between the ER, AR, TR, and other signaling pathways (Table 2). These endocrine disruptors include *o,p'*-DDT, DEHP (a plasticizer), di-*n*-butyl phthalate (a plasticizer), finasteride (an antiandrogen), propiconazole (a pesticide), *p*-XSC (an organoselenium), TCDD, and zearalenone (a mycotoxin).

The AhR plays an important role in various pathways that mediate the signals of endocrine disruptors. It is a ligand-activated transcription factor involved in the regulation of biological responses to planar aromatic hydrocarbons, such as TCDD (Denison et al. 2002). Crosstalk involving the AhR plays important roles in the actions of endocrine-disrupting chemicals. For example, the inhibitory effects of the AhR against ER functions have been attributed to crosstalk in uterine and other reproductive organs (Safe and Wormke 2003). The suppression of AhR signaling in response to TCDD is partly mediated by the AhR repressor, AHRR, through the interference of AhR-ERα crosstalk (Lee et al. 2011). Rataj et al. (2012) recently found that, in response to E_2, crosstalk between the AhR and ER signaling pathways for the regulation of AhR-target genes was predominantly mediated by ERα. The triazole pesticide propiconazole activates the AhR, but inhibits TR functions through crosstalk (Ghisari et al. 2015). Similarly, the TR is involved in the mechanisms underlying the actions of endocrine disruptors. For example, the anti-androgen finasteride affects the expression of TR-β and thyroid hormone-responsive genes in the brains of intersex frogs (Langlois et al. 2011).

PATHWAY-BASED RISK ASSESSMENT

A variety of assays have been developed to replace or reduce animal tests. A key issue is how to refine these assays by improving their accuracy, sensitivity, reliability, and applicability (speed and cost) (see Kiyama et al. 2014; Kiyama and Wada-Kiyama 2015). To achieve this goal, toxicity testing based on toxicity pathways and targeted testing was recommended as a model for future toxicity testing by the National Research Council (2007) of the USA. Adverse Outcome Pathways (AOPs) provide a conceptual

framework for this task, by connecting molecular initiating events, via toxicity pathways, to outcomes that are relevant to risk assessment (Ankley et al. 2010; Knapen et al. 2015). This conceptual framework has been applied to chemicals that have estrogenic activity or that are related to the metabolism of estrogen (such as bisphenol A; FitzGerald and Wilks 2014), the metabolism of androgens (such as fadrozole; Muth-Köhne et al. 2016), and that of thyroid hormone (such as triclosan; Paul et al. 2013). AOPs that share common elements can be combined into AOP networks (Knapen et al. 2015). The complexity and number of these AOP networks continues to increase. For example, Ankley et al. (2010) proposed an AOP including ER activation in hepatocytes by ER agonists. To this AOP, the responses of granulosa cells and oocytes have been added (Edwards et al. 2016). Knapen et al. (2015) listed multiple AOPs that share molecular initiating events like AhR activation, PPARα/γ activation and cyclooxygenase inhibition.

Much work remains to be done to develop model cases, and more data is needed about pathways, outcomes and effects for each chemical. New technologies, such as next-generation-sequencing based genome-wide association studies (Manolio 2010) and genome editing techniques (Tan et al. 2012), hold promise for assisting with these tasks.

CONCLUSIONS

While the actions of endocrine disruptors may be induced by directly stimulating/modulating the endocrine system, they may also be mediated by signaling through non-endocrine receptors; however, this signaling requires crosstalk with pathways involving endocrine receptors, such as the ER, AR, and TR. We herein summarized crosstalk between these receptors or between them and non-endocrine receptors in order to elucidate the mechanisms underlying the actions of endocrine disruptors. Various signaling pathways are involved in this crosstalk, and are characterized by their types of signaling pathways, tissue/cell types, ligands/modulators/inhibitors/stimulators, and the directionality of their signaling. However, it is still difficult to assess chemicals by using only *in vitro* or *in silico* assays without animal tests; therefore, further characterization of signaling pathways involving crosstalk is warranted.

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