CHAPTER 14.

Receptor-mediated mechanisms

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Introduction

Carcinogenic agents can cause cancer by inducing DNA damage through various genotoxic mechanisms that result in mutations. Many of the agents classified as *carcinogenic to humans* (Group 1) by the *IARC Monographs* are not directly or indirectly genotoxic but cause cancer via mechanisms that, by themselves, do not generate or involve DNA damage. One non-genotoxic mechanism involves receptor mediation (Pitot, 1995).

Hormonally active agents that are associated with carcinogenic effects typically act as ligands for nuclear receptors and, in some cases, for receptors located at the cell surface. There are also agents that are considered to be carcinogenic through receptor mediation but in addition have genotoxic effects; polycyclic aromatic hydrocarbons (PAHs), such as benzo[*a*]pyrene, are examples of this group. Yet other agents have cancer-enhancing or tumour-promoting effects through pathways involving receptors but also cause formation of reactive oxygen species or enhance the bioactivation of pro-carcinogens to ultimate carcinogens, both of which can potentially damage DNA and result in mutations; 2,3,7,8-tetrachlorodibenzo-*para*-dioxin (TCDD) is an example of this group.

Thus, the distinction between genotoxic carcinogens and carcinogens that act through receptor-mediated mechanisms is often not black and white. Insight continues to evolve about the mechanisms by which some carcinogens act through receptors. For example, there is now evidence that certain polychlorinated biphenyls (PCBs) can be metabolized to reactive, DNA-damaging intermediates that may contribute to their receptor-mediated carcinogenicity (Ludewig and Robertson, 2012; Lauby-Secretan et al., 2013; IARC, 2016).

The purpose of this chapter is to provide an overview of receptor-mediated mechanisms thought to be involved in carcinogenesis, followed by a discussion reflecting on the complexity of these mechanisms and how such mechanistic information can be used for rational hazard identification of carcinogenic agents. Receptor-mediated carcinogenesis was often discussed in the 1990s as a major mechanism of cancer induction by non-genotoxic carcinogens (Pitot, 1995). However, carcinogenesis research has since moved beyond these receptors to the

downstream mechanisms involved in their action or has often focused on just one agent's effects. Indeed, a recent PubMed search for articles with "receptor-mediated carcinogenesis" in the title yielded only eight hits, four of which are reviews, all published between 1992 and 1999, and one journal issue devoted to this topic (volume 333 of *Mutation Research*, in 1995). Despite a very large number of relevant primary publications, there have been no major general reviews on this subject since the mid-1990s. Other reviews identified by the keywords "receptor-mediated" and "carcinogenesis" or "toxicity" are devoted to specific carcinogens, tumour types, or target tissues, such as the liver (Andersen et al., 2014). Yet, several of the IARC Group 1 carcinogens act entirely or in part via receptor-mediated mechanisms, including benzo[*a*]pyrene, TCDD, 3,3′,4,4′,5-pentachlorobiphenyl (PCB 126), 2,3,4,7,8-pentachlorodibenzofuran (PeCDF), and the hormonal agents that are used in combined oral contraceptives and in treatment for menopausal symptoms (IARC, 2012a, b).

General comments

Biological mechanisms involving receptor activation fall into two broad categories: (i) those that involve intracellular receptors that translocate into the nucleus and act as transcription factors regulating gene expression (genomic action), and (ii) those that involve cell surface receptors and some intracellular receptors that activate signal transduction pathways, resulting in biological responses, including gene transcription (non-genomic action). The effects on gene transcription of the first group of receptors typically have a slow onset and a long duration, whereas the effects of the second group of receptors are typically rapid and transient. Both classes of receptors can be involved in mechanisms of carcinogenesis.

Although some exogenous ligands act as agonists by competing for binding with an endogenous ligand, others may bind but lack the intrinsic activity to activate the receptor they bind to and thus have an antagonist effect. There are also receptors for which no endogenous ligand has been identified with certainty, such as the aryl hydrocarbon receptor (AhR); these receptors are conceivably activated only by exogenous agents, because they are often involved in detoxification processes that have evolved as protective mechanisms. Exogenous agents may also indirectly affect receptor-mediated mechanisms by modulating the amount of endogenous ligand available for receptor binding and activation, through effects on the biosynthesis, bioavailability, bioactivation, and degradation of the bioactive ligand. In addition, exogenous agents may influence the abundance of receptors by modifying receptor biosynthesis and degradation. Finally, exogenous agents may indirectly affect receptor-mediated mechanisms by having effects on or acting as co-activators and co-repressors of nuclear receptors.

The effects of agents that act via receptor mediation depend in many cases on the dose, duration and route of exposure, and timing of exposure during the life of an organism. For example, the effects in animals of exposure to diethylstilbestrol in utero or neonatally are known to differ from those after exposure in adult life (IARC, 2012b) (see also Chapter 20, by Rice and Herceg). The duration of internal exposure depends in part on the half-life of the agent in vivo and on its bioaccumulation. Notorious in this regard are compounds such as TCDD and PCBs, which are stored in fat tissue and have a long half-life (6–10 years); consequently, even a short-term exposure can result in a sustained internal dose (IARC, 1997).

Importantly, many agents that act by receptor mediation display non-linear dose–response relationships for end-points such as cell proliferation, similar to the dose–response of steroid hormones (Reddel and Sutherland, 1987; Pitot, 1995; Sewall and Lucier, 1995; Gaido et al., 1997; Toyoshiba et al., 2004; Walker et al., 2005); androgenic and estrogenic steroid hormones typically stimulate in vitro proliferation of receptor-positive cells at low, physiological concentrations but are inhibitory at supraphysiological and pharmacological concentrations (Lee et al., 1995; Almstrup et al., 2002; Simons, 2008). This phenomenon has important implications for quantitative risk assessment. However, this is outside the scope of this chapter, which, like the *IARC Monographs*, focuses on hazard identification.

Oral exposure can result in a first-pass effect if elimination of the agent by the liver is efficient, thereby reducing the dose to organs beyond the liver. When hepatic elimination is slow, the systemic dose of a carcinogen may be high and may lead to cancer induction. This was demonstrated in mouse strains that differed in inducibility of CYP1A1/2 enzymes – members of the cytochrome P450 (CYP450) family of enzymes – by the AhR mechanism when treated with benzo[*a*]pyrene (Nebert et al., 1979).

The downstream biological effect of receptor binding is really what determines the potential for

carcinogenicity of an agent that acts via a direct receptor-mediated mechanism. Effects that are generally considered to be associated with carcinogenic activity of such agents include, but are not limited to, the following: enhancement of carcinogen bioactivation; reduction of DNA repair; induction of oxidative stress; stimulation of cell proliferation, angiogenesis, and invasive or migratory cell properties (including epithelial–mesenchymal transition); inhibition of cellular apoptosis, senescence, and/or differentiation; evasion of immune surveillance; and epigenetic effects (Hanahan and Weinberg, 2011) (see Chapter 10, by Smith).

Finding any one such effect, or even a combination of several of these effects, as a result of exposure to an agent that binds to cellular receptors is not by itself sufficient evidence that the agent is a carcinogen, but such findings do generate suspicion that the agent might cause cancer. If such receptor binding is associated with the mechanism by which a recognized human carcinogen operates, the evidence for carcinogenicity in humans may be sufficient. An example of this is the recent upgrading by IARC of PCB 126 and PeCDF to Group 1 carcinogens, based on the similarity of their binding to AhR (IARC, 2012a, 2016).

Proof that a receptor-mediated mechanism is involved in carcinogenesis in mammals would require evidence that blocking the activation of a specific receptor, or genetic removal of the receptor or reduction of its expression in mouse models, interferes with tumour induction by the carcinogen in question. The latter approach was used to demonstrate that several of the toxic effects of TCDD are indeed mediated by AhR in vivo (Poland and Glover, 1980; Birnbaum et al., 1990; Fernandez-Salguero et al., 1995). Although some of these studies evaluated the involvement of AhR in effects of TCDD that are mechanistically associated with carcinogenesis, this approach has not been applied to determine whether AhR is necessary for TCDD-induced tumour formation. Studies with mice that overexpress or lack estrogen receptor alpha (ER-α) have demonstrated that this receptor is involved in many of the developmental and carcinogenic effects of neonatal treatment with diethylstilbestrol in female animals (see below) (Couse et al., 1997, 2001; Couse and Korach, 2004).

Non-genomic receptor-mediated mechanisms and carcinogenesis

Non-genomic regulation of gene expression and cellular function involves signal transduction pathways that are activated by a wide range of receptor molecules located at the plasma membrane. These receptor modules are activated by an equally large number of ligands, ranging from locally produced autocrine and paracrine growth factors to circulating cytokines and hormones. The major groups of these receptors include tyrosine kinase receptors such as the epidermal growth factor (EGF) receptor, serine/threonine kinase receptors such as the protein kinase C receptor, G protein-coupled receptors, and receptors for cytokines, chemokines, and other ligands. They all catalyse phosphorylation of downstream signalling molecules upon ligand binding, some via activation of G protein signalling, ultimately resulting in regulation of expression of specific genes or sets of genes that control cellular function and behaviour and potentially influence carcinogenic processes (Pitot, 1995; Shawver et al., 1995).

12-*O*-tetradecanoylphorbol-13-acetate (TPA) may act as a tumour promoter through activation of membrane-located protein kinase C receptors, activating downstream signalling pathways that contribute to the enhancing effects of TPA on formation of skin tumours (Niedel et al., 1983; Nishizuka, 1984). However, conclusive evidence for this mechanism is still lacking (Gschwendt et al., 1995; Marks and Gschwendt, 1995). Moreover, TPA is a complete carcinogen for the skin in mice when given at sufficiently high doses with a sufficiently long period of observation (Iversen and Iversen, 1979). The involvement of protein kinase C in TPA-induced tumour promotion is highly complex and is only partially understood (Griner and Kazanietz, 2007), and more recent research is focused on downstream signalling effects (Hsu et al., 2000; Lu et al., 2007). TPA has also been shown to act through other receptor mechanisms (Marks and Gschwendt, 1995) and, when applied to the skin in mice, to induce inflammation, which in itself can stimulate cell proliferation and generate reactive oxygen species (Aldaz et al., 1985; Wei and Frenkel, 1993).

Receptors for several steroid hormones are not only intracellular nuclear receptors (see below) but may also be present at the plasma membrane, where their activation by agonists causes rapid non-genomic signal transduction-mediated effects. These non-classical receptor-mediated effects have been shown to occur for the androgen receptor (AR) (Bennett et al., 2010; Lang et al., 2013), the glucocorticoid receptor (Matthews et al., 2008; Samarasinghe et al., 2012), the progesterone receptor (PR)

(Wheeler et al., 2000; Peluso, 2011), and the estrogen receptor (ER) (Acconcia and Kumar, 2006; Song and Santen, 2006).

Activation of rapid membrane-initiated estrogen signalling by estrogenic agonists causes non-genomic signal transduction-mediated effects (Acconcia and Kumar, 2006; Song and Santen, 2006). The biological significance and contribution of these effects to carcinogenesis are uncertain at present. One of the two rapidly acting non-genomic membrane-located forms of PR, PR membrane component 1 (PGRMC1), is expressed in human ovarian cells and tumours (Wendler et al., 2012). PGRMC1 expression is associated with cell proliferation in ovarian cancers and may have anti-apoptotic effects (Wheeler et al., 2000; Peluso et al., 2008). PGRMC1 also interacts with and changes the function of some CYP450 enzymes and may affect carcinogen metabolism (Rohe et al., 2009; Szczesna-Skorupa and Kemper, 2011). There are no published studies to date indicating a contribution of these non-genomic ER- and PR-mediated effects to cancers associated with exposure to estrogens and progestins.

None of the IARC Group 1 carcinogens are known to be carcinogenic by acting via non-genomic receptor mechanisms, but this cannot be ruled out, for several reasons. Both estrogens and progestins can act via transmembrane receptors, and TCDD can affect signalling pathways via mechanisms that do not involve AhR (Tijet et al., 2006; Biswas et al., 2008; Boutros et al., 2009; Kim et al., 2009; Denison et al., 2011). Thus, it is conceivable that carcinogenicity associated with exposure to estrogens, progestins, or dioxins may involve mediation by non-genomic action of these agents. In addition, indirect non-genomic activity of carcinogenic agents could conceivably affect receptor abundance or stimulate signal transduction pathways that lead to pro-carcinogenic effects.

Nuclear receptor-mediated mechanisms and carcinogenesis

Nuclear receptor-mediated mechanisms involve intracellular receptors, most of which belong to the so-called nuclear receptor superfamily (Evans, 1988; Mangelsdorf et al., 1995). There are a large number and a wide variety of nuclear receptors that act via genomic mechanisms involving direct binding to specific DNA sequences (response elements) or indirect binding to AP1 or Sp1 sites in the promoter regions of the specific genes they regulate (Kushner et al., 2000; Aranda and Pascual, 2001; Safe and Kim, 2008). Once the nuclear receptor is bound to a response element, various co-regulator molecules are recruited that are critical for regulation of the initiation of gene transcription in a cell type-specific manner (Edwards, 2000; Lonard and O'Malley, 2012). Many members of the nuclear receptor superfamily are involved in physiological functions that mediate the effects of steroid hormones and other endogenous ligands (Evans, 1988; Tsai and O'Malley, 1994; Whitfield et al., 1999; Jacobsen and Horwitz, 2012).

ER, PR, and AR are examples of receptors that bind to and are activated by steroid hormones, whereas the retinoic acid receptors and the retinoid X receptors bind to vitamin A metabolites (Rochette-Egly and Germain, 2009; Duong and Rochette-Egly, 2011; Dawson and Xia, 2012). There are also nuclear receptors for which no endogenous ligands have been identified, but they do bind to exogenous ligands. These receptors are thought to mediate protection against harmful xenobiotics, predominantly by inducing expression of specific drug-metabolizing CYP450 enzymes (Boutros et al., 2009). Examples of the latter category are the pregnane X receptor and the constitutive androstane receptor (Nebert and Dalton, 2006; Tompkins and Wallace, 2007; Elcombe et al., 2014), both of which frequently engage in cross-talk with various other nuclear receptors and transcription factors (Lim and Huang, 2008).

Several other nuclear receptors with endogenous ligands are involved in physiological functions, but they are also activated by xenobiotics. An example of this category is the group of peroxisome proliferator-activated receptors (PPARs), which are involved in lipid metabolism but are also activated by xenobiotics with peroxisome proliferating activity; the PPARα subtype has been implicated in the hepatocarcinogenicity in rats of some of these xenobiotics (Green, 1995; Cattley, 2004; Corton et al., 2014), which are probably not human hepatocarcinogens (IARC, 1994, 1996). Many nuclear receptors need to homodimerize before they can bind to response elements, and several others heterodimerize with the retinoid X receptor before binding (Dawson and Xia, 2012).

AhR, which binds to TCDD and ligands that are structurally similar to TCDD, does not belong to the nuclear receptor superfamily and is in a class by itself. There are no established physiological endogenous ligands for AhR, even though this receptor has physiological functions, because mice that lack AhR expression show developmental abnormalities (Gonzalez and

Fernandez-Salguero, 1998; Carlson and Perdew, 2002). However, some endogenous compounds that bind to and activate AhR have been identified, such as certain tryptophan derivatives, but their physiological role has not yet been firmly established (Denison and Nagy, 2003; Henry et al., 2006). The tryptophan metabolite kynurenine has been identified as an endogenous ligand of human AhR. After receptor binding, downstream effects are the suppression of anticancer immune mechanisms and the promotion of cancer cell survival and motility in human brain tumours (Opitz et al., 2011), but the role of kynurenine in carcinogenesis has not been established. To exert its effects, AhR heterodimerizes with a unique molecule, the AhR nuclear translocator (ARNT).

AhR, ER, and PR mediate effects of several agents that are classified as IARC Group 1 human carcinogens (IARC, 2012a, b) and are discussed in more detail below. Although AR has been implicated in the causation of prostate cancer in humans, this has not been firmly established, and there is only *limited evidence* of the carcinogenicity of androgenic steroids in humans; they are classified by IARC as *probably carcinogenic to humans* (Group 2A), because there is *sufficient evidence* of their carcinogenicity in experimental animals (IARC, 1979, 1987). In rats, testosterone is a weak complete carcinogen and a strong tumour promoter in the prostate (Bosland, 2014).

Estrogen receptor (ER) and progesterone receptor (PR)

ER was discovered by Jensen (Jensen et al., 1968; Jensen and DeSombre, 1973), and its gene was cloned in 1986 (Greene et al., 1986). A second form of ER was discovered in 1996 and was named ER-β to distinguish it from the receptor previously cloned, ER-α (Kuiper et al., 1996).

Genomic activity of ER, also termed nuclear-initiated steroid signalling, is achieved through two main mechanisms. The first involves the direct binding of ER to its target gene. Estrogen binding to its receptor in the cytosol triggers a series of events, starting with loss of chaperone molecules such as heat shock protein 90 (Hsp90), and followed by migration of the receptor from the cytosol into the nucleus. Dimerization of the receptor then induces a conformational change that allows subsequent binding of the receptor dimer to specific sequences of DNA known as estrogen response elements. The DNA–receptor complex recruits other proteins such as co-activators, which are responsible for the initiation of transcription of downstream DNA into mRNA, resulting in translation to proteins to produce changes in cellular function (Dickson and Stancel, 2000; Aranda and Pascual, 2001). The second mechanism of transcriptional regulation does not involve estrogen response elements but is based on interaction of ER with the transcription factors Fos and Jun to bind to AP1 sites, or with Sp1 to bind to Sp1 sites (Nilsson et al., 2001).

The two basic forms of ER, ER-α and ER-β, show some sequence homology and are widely distributed in tissues of the body, including target tissues of estrogen carcinogenicity, but they differ greatly in cell type-specific abundance. In addition, although their basic molecular mechanism of action is similar, they differ in specificity and binding affinity for ligands (Matthews and Gustafsson, 2003; Thomas and Gustafsson, 2011) and often have opposite activity in breast, prostate, and colon cancer cells (Bardin et al., 2004; Roger et al., 2008; Chen and Iverson, 2012; Nelson et al., 2014).

There are several isoforms of ER-α and ER-β that result from alternative mRNA splicing (Moore et al., 1998; Flouriot et al., 2000; Wang et al., 2005). Of these variants, ER-α36 and ER-α46 are predominantly localized to the plasma membrane and cytoplasm, mediating membrane-initiated rapid non-genomic signalling (Flouriot et al., 2000; Wang et al., 2005). Of note, the so-called estrogen-related receptors show a high degree of sequence homology with the ERs, but they are orphan receptors for which no ligand has been identified (Deblois and Giguère, 2011, 2013). Although activation of the α-isoform of estrogen-related receptors resulted in suppression of growth of xenografted human breast cancer cells in nude mice (Chisamore et al., 2009), there is no evidence that these nuclear receptors are involved in estrogen-induced carcinogenesis.

Two isoforms of PR have been identified, PR-A and PR-B, which are encoded by the same gene but controlled by different estrogen-regulated promoter regions and different translation initiation events (Conneely et al., 1989; Kastner et al., 1990; Kraus et al., 1993). These two receptor forms play different roles in various tissues and cell types and may have opposite molecular effects (Jacobsen and Horwitz, 2012). Although PRs are in many respects similar to ERs in the way they initiate transcription, dimerization may not always be necessary, and PR monomers can bind to progesterone response element half-sites (Jacobsen et al.,

2009; Jacobsen and Horwitz, 2012). The gene expression and other biological responses mediated by receptor isoforms are often progestin- and PR subtype-specific (Graham and Clarke, 2002; Jacobsen and Horwitz, 2012; Moore et al., 2012). The expression of both isoforms is induced by estrogens, but progestins downregulate PRs (Jacobsen and Horwitz, 2012).

Breast cancer induced by hormonal therapies

Combined estrogen–progestin treatments, as therapy for menopausal symptoms or as oral contraceptives, are carcinogenic to the female breast, but only the menopausal therapy is carcinogenic to the endometrium, whereas only the contraceptive treatment is carcinogenic to the uterine cervix and liver (IARC, 2012b). The mechanisms by which these hormonal regimens cause these cancers in women are not clear.

The outcome of the estrogen-alone arm of the Women's Health Initiative randomized clinical trial was remarkable in that breast cancer incidence was reduced (Anderson et al., 2012), whereas breast cancer incidence was increased in women treated with combined estrogen–progestin (Chlebowski et al., 2010). These findings clearly indicate that the addition of progestins (in the form of continuous medroxyprogesterone) to treatment with estrogens (conjugated equine estrogens) is a determining factor in breast carcinogenesis induced by these hormones.

In the prospective Million Women Study, estrogen-only treatment increased risk of breast cancer, and combined estrogen–progestin treatment was associated with a greater increase in breast cancer risk than that observed with estrogen alone (Beral, 2003). The stimulating effect of adding progestin treatment to estrogen exposure in the induction of breast cancer has also been demonstrated in a rat model (Blank et al., 2008). Furthermore, the pure anti-estrogen ICI 182780 inhibited growth stimulation of transplanted ER-positive mouse mammary tumours by medroxyprogesterone in intact mice (Giulianelli et al., 2012).

However, precisely how these two hormones and their respective receptors interact in increasing breast cancer risk is far from understood. Both ER-α and ER-β can mediate the growth stimulatory and, at higher doses, inhibitory effects of estrogen, and the ratio of abundance of the two ER isoforms and the cellular context in which they operate appear to be critical determinants of the eventual effect (Sotoca et al., 2008; Soldati et al., 2010). In addition, these ERs may cross-talk with signalling pathways and interact with PR (Giulianelli et al., 2012; Cotrim et al., 2013).

Initially, ER- and PR-mediated induction of cell proliferation had been postulated to be responsible for the carcinogenic effects of estrogens and progestins (Anderson et al., 1989; King, 1991; Yager et al., 1991; Pike et al., 1993; Feigelson and Henderson, 1996). However, this may be too simple a proposition, because these hormonal factors also have a wide range of other biological effects. Although cell proliferation is no doubt a necessary component of the carcinogenic process, is it probably not sufficient, and additional factors, some of which may also be receptor-mediated, are likely to be required to induce malignant cell transformation (Dickson and Stancel, 2000) (see also below). Enhanced cell proliferation has been found in some substructures of the breast of women treated with estrogen–progestin menopausal therapy (Hofseth et al., 1999), and similar effects have been observed in mice (Raafat et al., 2001; Haslam et al., 2002). However, there are partially conflicting data in humans (Harvey et al., 2008), and progesterone has been found to inhibit estrogen-stimulated proliferation of breast cancer cells in vitro, depending on dose and timing (Groshong et al., 1997; Lippert et al., 2000).

There are convincing data indicating that the hormonal changes during the normal menstrual cycle are associated with cyclic changes in the rate of proliferation of epithelial cells in the breast, which reaches a maximum during the luteal phase, when circulating levels of both estradiol and progesterone are high (Anderson et al., 1989; Pike et al., 1993). The cell proliferation rate of the breast epithelium is increased during both the follicular phase and the late luteal phase (Anderson et al., 1989). These findings suggest that cyclicity in circulating hormone levels may be a driving force in stimulating cell proliferation in the normal breast, resulting in a higher risk of breast cancer with a higher number of years during which a woman menstruates (Henderson et al., 1982). If this notion were correct, one would expect that continuous exposure to estrogen plus progestin would not increase breast cancer risk, but the Women's Health Initiative randomized clinical trial with continuous exposure to both agents demonstrated that this is clearly not the case (Chlebowski et al., 2010). Furthermore, similar effects in increasing breast cancer risk were found for both sequential and continuous combined estrogen–progestin treatment in the prospective Million Women Study (Beral, 2003).

The breast cells that proliferate are not the cells that strongly express ER or PR, suggesting that paracrine mechanisms, possibly involving breast stromal cells, play a major role. Breast density (i.e. the relative proportion of the stromal component of the breast) has been found to be associated with the rate of cell proliferation (Clarke et al., 1997; Russo et al., 1999; Harvey et al., 2008). Thus, in vitro studies with benign or malignant breast epithelial cells exposed to the sex hormones contained in estrogen–progestin treatments have limited significance, because they do not involve a stromal component, although once they are malignantly transformed, breast cancer cells may become independent of paracrine mediation and regulate their growth by autocrine mechanisms (Obr and Edwards, 2012).

Also, cell culture-based studies have yielded a somewhat confusing overall picture of how estrogen and progestin treatments interact in affecting cell proliferation. Progestins can inhibit estrogen-stimulated proliferation of breast cells (Seeger et al., 2003a, b), but they also increase the ratio of apoptosis to proliferation (Krämer et al., 2005; Seeger et al., 2005). Dose and type of progestin appear to be critical in determining the eventual effect (Seeger et al., 2003b, 2005). Despite their limitations, these in vitro studies have shown that ER- and PR-mediated apoptosis must be considered as an important effect of combined estrogen–progestin treatment, and they have provided evidence that growth factors can be determinants of these effects (Krämer et al., 2006).

More recent observations in normal human breast tissue have provided evidence that ER-α is predominantly expressed in luminal cells, whereas PR expression is enriched in the basal cell compartment, which may contain progenitors of luminal cells and possibly cancer progenitor cells (Hilton et al., 2012). This observation may have a bearing on the notion that there are four basic breast cancer types (and possibly subtypes of these) (Sorlie et al., 2001; Guiu et al., 2012; Elsawaf et al., 2013). Although it is currently not known which of these four breast cancer types are associated with estrogen–progestin treatment, breast cancer risk associated with hormonal menopausal therapy varied among different histological types of invasive and in situ breast cancer in the Million Women Study (Reeves et al., 2006). Of interest in this respect is the observation that there may be cross-talk between PR subtypes and human epidermal growth factor receptor (HER)/ErbB receptors in HER-positive breast cancers (Lindet et al., 2012).

Genotoxicity of estrogen metabolites potentially plays a role in the carcinogenicity of estrogen and estrogen–progestin treatments (Yager and Liehr, 1996; Cavalieri et al., 2000; Yager and Davidson, 2006). In addition, some estrogen metabolites (the 4- and 16α-hydroxylated but not the 2-hydroxylated metabolites) can also have cell proliferative effects through poorly defined mechanisms that may involve ER mediation (Seeger et al., 2006).

Overall, there is little doubt that ER- and PR-mediated mechanisms, including stimulation of breast cell proliferation, are involved in the carcinogenicity of estrogen–progestin treatments (Sutherland et al., 1998; Anderson and Clarke, 2004). However, other mechanisms are clearly also operational and are probably critically important as well; the interplay of these molecularly diverse mechanisms is likely to be highly complex and is still poorly understood (Yager and Davidson, 2006). In addition, the understanding of how these receptors function is still evolving in many ways. For example, it has become apparent that microRNAs regulate ER and PR expression and in turn are regulated by these receptors as well (Adams et al., 2007; Maillot et al., 2009; Pandey and Picard, 2010; Cochrane et al., 2012), but it is not known whether or how these mechanisms are involved in breast carcinogenesis.

Cancer of the endometrium and ovary

The reduction of risk of cancer of the endometrium and ovary by use of combined oral contraceptives is well established, whereas menopausal estrogen therapy unopposed by progestins causes cancer of the endometrium (IARC, 2012b). In the normal premenopausal endometrium, cell proliferation rates are high during the follicular phase, when estradiol levels peak, but they decline as progesterone levels rise in the luteal phase (Whitehead et al., 1981; Key and Pike, 1988).

It is well established that the longer a woman menstruates, the higher the risk of cancer of the endometrium (Key and Pike, 1988; Karageorgi et al., 2010). This relationship is similar for cancers that differ in the degree of genomic instability (Amankwah et al., 2013) and for both the common endometrioid form of endometrial cancer (type I) and the less common type II endometrial cancers (including serous, clear cell, and mixed Müllerian tumours) (Setiawan et al., 2013).

Estrogen therapy during menopause also increases endometrial cell proliferation, and this effect

is counteracted by progesterone (Whitehead et al., 1981), whereas progestin-only contraceptives suppress cell proliferation in the endometrium (Landgren et al., 1990; Moyer and Felix, 1998). It is not clear whether changes in cell proliferation are the only explanation for the induction of endometrial cancer by estrogens and for the preventive effects of combined oral contraceptives on endometrial and ovarian cancer and the preventive effects of progestins on endometrial cancer induced by estrogens. Even less is known about hormonal effects on the ovary that may be involved in ovarian carcinogenesis.

Diethylstilbestrol

The human transplacental carcinogen diethylstilbestrol is not only genotoxic but is also probably the strongest known estrogen. Its genotoxic effects in human and rodent tissues and cells are unlikely to be receptor-mediated. Non-genotoxic effects of diethylstilbestrol mediated by ERs are hormonal in nature and involve estrogenic stimulation of cell proliferation, which has a biphasic dose–response relationship in breast cancer cells in vitro (Reddel and Sutherland, 1987).

Diethylstilbestrol induces epigenetic changes in DNA methylation in target tissues in rodents (Li et al., 2003; Newbold et al., 2007; Tang et al., 2008). These changes may be heritable (Anway and Skinner, 2006) and conceivably underlie the mechanism responsible for the developmental and carcinogenic effects observed in the second, and possibly the third, generation of rodents after in utero exposure to diethylstilbestrol (Newbold et al., 1998, 2000); these effects have also been reported in female and male offspring of women exposed to this synthetic estrogen during pregnancy (Titus-Ernstoff et al., 2008; Kalfa et al., 2011). Whether these epigenetic effects are ER-mediated is unknown (Newbold et al., 2006). It is also unclear whether the immunosuppressive effects of diethylstilbestrol are ER-mediated (Brown et al., 2006). Overall, the contribution of ER-mediated mechanisms in the carcinogenic effects of in utero exposure to diethylstilbestrol is not clear. It seems likely that any ER-mediated effect of prenatal exposure to diethylstilbestrol facilitates its genotoxic effects by stimulating cell proliferation in target cells, or otherwise by increasing the induction of the DNA alterations that underlie the carcinogenicity of diethylstilbestrol (IARC, 2012b).

Studies with mice that overexpress or lack ER-α suggest that endogenous estrogen in the adult animal acts as a tumour promoter via ER mediation, after induction of permanent genotoxic and epigenetic effects by exposure to diethylstilbestrol early in life (Couse et al., 1997, 2001; Couse and Korach, 2004). This notion would be consistent with the observation that malignancies induced by diethylstilbestrol in women exposed in utero do not appear until after menarche (Couse and Korach, 2004). The role of ER in the increased risk of breast cancer observed in women exposed to diethylstilbestrol during pregnancy is not clear, but a combination of genotoxic effects and stimulation of cell proliferation is likely (IARC, 2012b).

In conclusion, cell proliferation appears to be involved in how hormones used in menopausal therapy cause cancer of the breast and endometrium and possibly cancer of the ovary, and how combined oral contraceptives cause malignancies of the liver, uterine cervix, and breast, but the precise mechanisms by which these tumours are caused and how exactly these hormonal treatments are involved mechanistically is far from clear. Most recent research has focused on molecular alterations in cancers at these sites and the mechanisms by which they can develop, but how hormonal factors intersect with these processes remains unknown (Merritt and Cramer, 2010).

Even more nebulous is how combined oral contraceptives provide lasting protection against cancer of the endometrium and ovary, and how precisely progestins protect the endometrium against estrogens used in menopausal therapy. Downregulation of PR may in part explain these protective effects, because it may result in reduction of cell proliferation, but other mechanisms are also likely to be involved. Similarly, just evoking stimulation of cell proliferation as the mechanism by which unopposed estrogen causes endometrial cancer is probably an oversimplification as well. Involvement of ER in the mechanism by which diethylstilbestrol causes cancer in women after prenatal exposure may be limited to the effects of endogenous estrogens acting as tumour promoters.

Aryl hydrocarbon receptor (AhR)

AhR is a member of the PER-ARNT-SIM family of basic helix–loop–helix transcription factors (Burbach et al., 1992). This receptor is induced by and binds to a very large number of exogenous ligands, including PAHs such as benzo[*a*]pyrene, planar PCBs, polychlorinated dibenzofurans, and its most potent

ligand, TCDD (Denison et al., 2002; Tsuchiya et al., 2003; Flaveny et al., 2009).

Endogenous ligands for AhR have not been identified with certainty, but it is likely that these exist and that AhR has a physiological role (Gonzalez and Fernandez-Salguero, 1998; Carlson and Perdew, 2002; Bock and Köhle, 2009). Certain endogenously formed tryptophan derivatives that bind to and activate AhR have been identified, but their physiological role has not yet been firmly established (Denison and Nagy, 2003; Henry et al., 2006; Perdew et al., 2015). Factors that can activate AhR in cultured liver cells have been found in the serum of knockout mice that lack AhR (McMillan and Bradfield, 2007), but whether these are the elusive endogenous ligands is uncertain.

This cytosolic receptor, once bound to a ligand, translocates to the nucleus, loses various chaperone molecules, such as Hsp90, and heterodimerizes with ARNT. The AhR–ARNT complex then binds to xenobiotic response elements, also termed dioxin response elements, in the promoter regions of the genes it regulates, including those encoding CYP1A1, CYP1A2, CYP1B1, glutathione-*S*-transferase M, and nicotinamide adenine dinucleotide phosphate NAD(P)H:quinone oxidoreductase, all of which are involved in metabolism of xenobiotics (Beischlag et al., 2008; Denison et al., 2011). Involvement of AhR in immune regulation, the cell cycle, the function of mucosal barriers, and development has recently been identified (Hubbard et al., 2015).

In addition, AhR can interact with molecules other than ARNT and can engage extensively in cross-talk with various signalling pathways. It can interact directly with phosphorylated retinoblastoma protein, leading to cell-cycle arrest, and with ER-α and ER-β in various ways, resulting in repression of ER-mediated signalling and anti-estrogenic effects (Safe et al., 1998; Safe and Wormke, 2003; Dietrich and Kaina, 2010; Denison et al., 2011). Interestingly, ARNT by itself can activate ER-α, and particularly ER-β (Rüegg et al., 2008). AhR may activate cyclin A via JunD and ATF2, thereby inhibiting contact inhibition in vitro, which would be a pro-carcinogenic effect (Weiss et al., 2008; Dietrich and Kaina, 2010).

The great diversity of genes regulated by AhR and the many mechanisms involved are remarkable and illustrate the considerable complexity in how AhR functions (Denison et al., 2011). This complexity is exacerbated because (i) ligand-dependent differences have been observed in co-activator recruitment and in binding specificity of AhR towards sequence variants in xenobiotic response elements, (ii) cell type-specific co-activators and co-repressors can modulate DNA binding specificity of the AhR–ARNT complex, (iii) AhR and the AhR–ARNT complex may themselves act as co-activators for other transcription factors, and (iv) extensive cross-talk exists with important signalling pathways (Beischlag et al., 2008; Denison et al., 2011).

It is not surprising that activation of AhR results in distinct species- and tissue-specific changes in gene expression profiles and that these may be subject to temporal changes and can be dependent on, as well as independent of, TCDD and dioxin-like compounds such as PCBs and dibenzofurans (Vezina et al., 2004; Tijet et al., 2006; Kopec et al., 2008, 2013; N'Jai et al., 2008; Dere et al., 2011a, b). In this regard, it is relevant that there are interspecies and rat and mouse strain-specific differences in AhR binding affinity for TCDD, as well as in functional AhR polymorphisms, AhR abundance, and cofactors required for AhR activity, which may all be critical to the carcinogenic process (Barrett, 1995; De Souza et al., 2009; Flaveny et al., 2009).

The binding affinity of human AhR for dioxin is much weaker than that found for AhR in some rodent species (Ema et al., 1994; Ramadoss and Perdew, 2004). Rodents have a high degree of AhR sequence homology (Korkalainen et al., 2001), but there is less homology with human AhR (Ema et al., 1994; Flaveny et al., 2008). There are also differences between humans and rodents in the response of hepatic gene expression to TCDD, but little difference in inducibility of CYP450 enzymes (Mandal, 2005).

Mice that carry AhR variants with different dioxin-binding affinities vary in their response towards TCDD toxicity and PAH-induced carcinogenesis (Garte and Sogawa, 1999; De Souza et al., 2009; Flaveny et al., 2010). Thus, there are differences between humans and rodents in AhR binding affinity that may account for interspecies variation in AhR-mediated carcinogenicity. Toxicogenomic comparisons of human, rat, and mouse cells or tissues exposed to TCDD indicate considerable interspecies differences in the response to dioxin (Boverhof et al., 2006; Black et al., 2012). Of note, there are AhR polymorphisms in humans, some of which could conceivably be associated with differences in toxic effects and cancer risk in response to exposure to TCDD (Garte and Sogawa, 1999; Hung et al., 2013; Luo et al., 2013).

AhR-mediated carcinogenesis

TCDD and dioxin-like PCBs are considered to be AhR-mediated carcinogens. PCBs as a group have recently been designated by IARC as Group 1 carcinogens (Lauby-Secretan et al., 2013; IARC, 2016). TCDD is a multisite human carcinogen (Warner et al., 2011; IARC, 2012a, 2016). There is *sufficient evidence* from epidemiological studies that exposure to PCBs causes melanoma (Loomis et al., 1997; Gallagher et al., 2011; IARC, 2012a, 2016). For non-Hodgkin lymphoma, there are mixed data, suggesting that risk may be elevated in men but not in women (Bertrand et al., 2010; Laden et al., 2010; Maifredi et al., 2011; Bräuner et al., 2012; Kramer et al., 2012; IARC, 2016). The most recent update of the follow-up study on people affected by the poisoning incident in 1968 in Japan, where rice oil was contaminated with PCBs and polychlorinated dibenzofurans, indicated small but statistically significant associations with risk of all cancers and risk of cancer of the liver and lung (Onozuka et al., 2009). The epidemiology for PeCDF is very sparse (IARC, 2012a).

TCDD has an extremely wide range of biological and toxic effects, many, but not all, of which are mediated by AhR (Poland and Glover, 1980; Birnbaum et al., 1990; Fernandez-Salguero et al., 1995). AhR is critical to the carcinogenicity of TCDD and at least some dioxin-like compounds, such as certain PCBs and polychlorinated dibenzofurans, as summarized in Volume 69 (IARC, 1997), Volume 100F (IARC, 2012a), and Volume 107 (IARC, 2016) of the *IARC Monographs*. In Volume 69, it was stated that "even though Ah receptor activation is likely to be required for the carcinogenicity of 2,3,7,8-TCDD, its precise role in this process remains unclear." Ten years later, Walker (2007) concluded that "despite … decades of research, we still do not have a clear mechanism of action leading from ligand binding of TCDD or a related ligand to the AhR and the ultimate development of toxicities [including carcinogenesis]". Research from the past several years does not change this conclusion (Budinsky et al., 2014).

TCDD, PCB 126, and PeCDF are complete carcinogens as well as tumour promoters in rodents, and some other PCBs and polychlorinated dibenzofurans have tumour-promoting activity as well (Hébert et al., 1990; Anderson et al., 1991; Waern et al., 1991; Hemming et al., 1995; IARC, 1997). Induction of xenobiotic-metabolizing CYP450 enzymes has been recognized as one of the major effects of activation of AhR relevant to its contribution to the carcinogenic effects of planar PAHs, TCDD, and dioxin-like compounds (IARC, 1997, 2012a). However, many other major effects of AhR activation can conceivably also contribute to the carcinogenicity of these AhR ligands, including induction of cell proliferation, oxidative stress, cross-talk with signalling pathways involved in carcinogenic mechanisms, induction of cell proliferation, and alteration of cell–cell interactions (Schwarz and Appel, 2005; Dere et al., 2006; Dietrich and Kaina, 2010). Sustained activation of AhR has been postulated to be necessary for its carcinogenic activity in the liver in rodents (Budinsky et al., 2014). Carcinogenicity of PCBs is likely to involve not only AhR activation but also other such mechanisms (IARC, 2016).

Many of these effects and mechanisms may be ligand-specific, as indicated by comparative toxicogenomic studies of the liver of mice in vivo and of primary rat hepatocytes in vitro after short-term exposure to dioxin-like compounds (Kopec et al., 2008, 2010; N'Jai et al., 2008; Rowlands et al., 2011). In toxicogenomic studies, longer-term in vivo exposure (13 or 52 weeks) of rats to the AhR ligands TCDD, PeCDF, and PCB 126, as well as the non-AhR ligand 2,2′,4,4′,5,5′-hexachlorobiphenyl (PCB 153), revealed considerable ligand specificity (Vezina et al., 2004; Ovando et al., 2010).

Nevertheless, these gene expression profiling studies did show partial overlap of genes regulated by TCDD, PCB 126, and PeCDF (Vezina et al., 2004; Kopec et al., 2008; Ovando et al., 2010). PeCDF and PCB 126 appeared to share more gene responses than either compound shared with TCDD (Vezina et al., 2004). These studies used equipotent doses on the basis of so-called toxic equivalency factors, and showed AhR-mediated gene expression responses that were shared among TCDD, PCB 126, and PeCDF or 2,3,7,8-tetrachlorodibenzofuran. However, the non-coplanar PCB 153, which does not activate AhR but may antagonize it (Suh et al., 2003), also shared some gene responses with TCDD and PCB 126 (Kopec et al., 2010; Ovando et al., 2010).

Exposure to TCDD, and possibly to 2,2′,3,3′,4,4′-hexachlorobiphenyl (PCB 128) and PeCDF, affects various metabolic genes and cell regulatory pathways known to be involved in cancer, such as genes of the G protein-coupled receptor protein signalling pathway and genes of the polyamine and glutathione pathways (Jennen et al., 2011). Exposures to

combinations of PCBs have not been studied but would be of interest, given that, for example, PCB 153 significantly increased the carcinogenic potency of PCB 126 (NTP, 2006c). Overall, the mechanism of action of TCDD and dioxin-like compounds appears to be highly complex and to be dependent on ligand, dose, duration of exposure, and sex, and it is only partly understood (Silkworth et al., 2008; Budinsky et al., 2014).

Oxidative stress and oxidative DNA damage have long been recognized as important factors in carcinogenesis (Klaunig et al., 2011) (see Chapter 15, by Bucher). Oxidative stress has been demonstrated to occur after in vivo and in vitro exposure to AhR ligands including TCDD, PCB 126, and PeCDF (Yoshida and Ogawa, 2000; Hennig et al., 2002). Upregulation of CYP1A1 and CYP1B1 by activated AhR increases the chance of production of reactive oxygen species upon uncoupling of the catalytic cycle of these enzymes, as has been shown for exposure to dioxin-like coplanar PCBs (Schlezinger et al., 2006; Green et al., 2008). In addition, in experiments with mice, AhR activation has been associated with mitochondrial production of reactive oxygen species in a process that does not appear to involve CYP450 enzymes (Senft et al., 2002).

Many signalling pathways are mechanistically involved in carcinogenesis, including those involved in regulation of cell proliferation, apoptosis, senescence, and angiogenesis (Hanahan and Weinberg, 2011) (see Chapter 10, by Smith). There is considerable evidence of extensive cross-talk of AhR with several of these and other pathways, including various nuclear transcription factors (Haarmann-Stemmann et al., 2009; Puga et al., 2009) and the transforming growth factor beta (TGF-β) (Gomez-Duran et al., 2009) and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathways (Tian et al., 1999; Vogel and Matsumura, 2009). There is also evidence for cross-talk with the constitutive androstane receptor and one of its target genes in mice, *Cyp2b10* (Patel et al., 2007), and with cyclin G2 (Ahmed et al., 2012).

The extensive cross-talk with ER signalling mentioned above explains the anti-estrogenic properties of TCDD (Safe and Wormke, 2003; Denison et al., 2011). There is evidence that this AhR–ER cross-talk can occur at different levels of AhR involvement in the regulation or dysregulation of gene expression, including non-classical modes with AhR–ARNT or just AhR acting as co-repressor (Ohtake et al., 2003; Labrecque et al., 2012).

Mediated by AhR, TCDD downregulates the EGF receptor and inhibits binding of EGF to its receptor in several tissue types (Madhukar et al., 1984; Kitamura et al., 2006; Haarmann-Stemmann et al., 2009). This reduces EGF signalling, which may be an anti-carcinogenic rather than a pro-carcinogenic effect. Conversely, EGF receptor signalling appears to inhibit AhR action at the DNA level (Sutter et al., 2009), indicating significant cross-talk with EGF pathways.

Induction of cell proliferation has long been considered to be a causal factor in carcinogenesis in humans and experimental animals (Preston-Martin et al., 1990; Schwarz et al., 1995), with receptor mediation and an imbalance between proliferation and apoptosis in favour of cell growth as major mechanisms (Roberts et al., 1997; Oliver and Roberts, 2002). TCDD has been found to induce hepatocellular replicative DNA synthesis in vivo in some studies (Lucier et al., 1991) but not in others (Fox et al., 1993; Bauman et al., 1995), and it inhibits growth of primary hepatocytes in vitro (Hushka and Greenlee, 1995). Lack of AhR in knockout mice resulted in increased hepatocellular apoptosis (Zaher et al., 1998), but TCDD treatment of rats that express AhR also resulted in increased apoptosis in the liver during hepatocarcinogenesis (Stinchcombe et al., 1995). In human skin cells in vitro, TCDD caused inhibition of cellular senescence, presumably via AhR, which may explain in part the tumour-promoting activity of TCDD in initiated skin in mice (Ray and Swanson, 2009). However, whether this mechanism occurs in vivo and in the liver is not known. PCBs can also stimulate hepatic cell proliferation, but this is not consistently found and may or may not be AhR-dependent.

The coplanar PCB 126 and the non-coplanar PCB 153 both induced proliferation, but only after a tumour-initiating dose of diethylnitrosamine, and both had liver tumour-promoting activity (Rignall et al., 2013). However, in other studies, PCB 153 stimulated hepatocellular proliferation in rats but not when preceded by treatment with diethylnitrosamine, whereas the coplanar 3,3′,4,4′-tetrachlorobiphenyl (PCB 77) inhibited or stimulated hepatocellular proliferation (Tharappel et al., 2002; Lu et al., 2003, 2004). PCB 126, but not PCB 153, stimulated proliferation of cultured liver cells (Vondrácek et al., 2005). In studies with exposures of up to 2 years, PCB 153 did not stimulate hepatic cell proliferation and

had equivocal carcinogenic activity, whereas PCB 126 did stimulate proliferation after exposure for 1 year and was carcinogenic (NTP, 2006a, b). In similar studies, PeCDF and the coplanar 2,3′,4,4′,5-pentachlorobiphenyl (PCB 118) also stimulated hepatic cell proliferation and had carcinogenic activity (NTP, 2006c, 2010). Overall, the involvement of AhR-mediated changes in cell proliferation and apoptosis in TCDD carcinogenesis is not clear and may depend on context (in vivo or in vitro), tumour induction protocol (initiation–promotion or continuous treatment), tissue, dose and duration of TCDD treatment, and species (Budinsky et al., 2014). This may also be the case for dioxin-like PCBs and dibenzofurans.

AhR appears also to be critical to the carcinogenicity of PAHs that are preferentially metabolized by CYP1A1 and CYP1A2, such as benzo[*a*]pyrene and dibenzo[*a,l*]pyrene (Shimizu et al., 2000; Nakatsuru et al., 2004), but not 7,12-dimethylbenz[*a*]anthracene (DMBA) (Ide et al., 2004). This is presumably because DMBA is metabolically activated by CYP1B1, which does not need induction by AhR but is constitutively expressed in rodent target tissues, and is required for the carcinogenicity of DMBA (Buters et al., 1999; Ide et al., 2004). Diethylnitrosamine, which is not an AhR ligand and is metabolically activated not by CYP1A1 but by CYP2E1, induced liver tumours in mice, and this effect was markedly enhanced in mice that lack AhR (Fan et al., 2010).

TRAMP (transgenic adenocarcinoma mouse prostate) mice, which have disrupted retinoblastoma and p53 function in the prostate, resulting in tumour development in this organ, displayed increased tumour formation when crossed with AhR-null mice (Fritz et al., 2007). These findings suggest that AhR can function as a tumour suppressor, which is supported by the observation of increased cell proliferation and reduced apoptosis in liver tumours induced by diethylnitrosamine in AhR-null mice (Fan et al., 2010).

There is some evidence from studies with human tumour cells in culture to support the idea that AhR has tumour-suppressive potential (Zudaire et al., 2008). This notion may appear to be in conflict with the reduced or absent tumour development in mice that lack AhR in response to treatment with benzo[*a*]pyrene and dibenzo[*a,l*]pyrene (Shimizu et al., 2000; Nakatsuru et al., 2004). However, mice that lack the *Arnt* gene specifically in the skin did not develop skin cancer when treated with benzo[*a*]pyrene plus TPA, whereas they did so when treated with a carcinogen that does not require AhR mediation, such as *N*-methyl-*N*-nitrosourea, followed by TPA (Shi et al., 2009). This finding strongly suggests that CYP1A1 induction by the AhR–ARNT complex in response to benzo[*a*]pyrene treatment is required for benzo[*a*]pyrene to be carcinogenic.

In conclusion, AhR is activated by many chemical agents; some of these are carcinogens, and others are not. Most or all carcinogenic compounds that activate AhR are likely to also act via other mechanisms to cause cancer. Thus, AhR activation is probably best considered as an important mechanistic effect of carcinogens rather than as the sole or predominant carcinogenic mechanism of such compounds.

In view of the complexity of AhR-mediated mechanistic events, it is likely that there are many ways in which this important receptor can be involved in the carcinogenic process. Nonetheless, it is clear that AhR is critical to the carcinogenicity of TCDD and some or many dioxin-like compounds as well as some important PAHs, and it is evident that this receptor can be involved in cancer-initiating as well as tumour-promoting mechanisms.

Summary

How do we evaluate – on the basis of mechanistic data – the carcinogenicity to humans of chemicals that have not been tested in chronic animal bioassays or adequate epidemiological studies? Are all chemicals that bind to and activate AhR, or all agents that activate both ER and PR, human carcinogens?

A case in point is the designation of PCB 126 and PeCDF as *carcinogenic to humans* (Group 1) in Volume 100F of the *IARC Monographs* (IARC, 2012a). This classification was based on the ability of these chemicals to activate AhR, induce CYP1A1, CYP1A2, and other drug-metabolizing enzymes, stimulate cell proliferation, induce oxidative stress, and have carcinogenic and tumour-promoting activities in ways similar to those observed with TCDD. A critical point was the ability of these agents to produce a spectrum of neoplasms that is similar to the tumours found after treatment with TCDD in the same rodent species. This designation would probably not have been justified in the absence of such animal bioassay data.

There may be compounds that activate AhR and induce CYP1A1 and CYP1A2 but are not carcinogenic. β-Naphthoflavone is an example of such a compound that activates AhR and induces CYP1A1 but is not a carcinogen (Denison et al.,

2011), even though it is a liver tumour promoter after treatment with diethylnitrosamine (Hayashi et al., 2012). Omeprazole also activates AhR and induces CYP1A1 but is not carcinogenic (Kleeberg et al., 1999). However, many other agents that activate AhR and induce CYP1A1 and CYP1A2 are carcinogenic. Furthermore, induction of oxidative stress by TCDD and dioxin-like compounds is non-specific and is – like various other pleiotropic effects of these agents – perhaps not required for AhR-mediated carcinogenesis. Such effects can only be considered additional evidence suggesting that a compound that activates AhR and induces CYP1A1 and CYP1A2 is carcinogenic to humans or experimental animals.

Stimulation of cell proliferation is often invoked as an effect that indicates carcinogenic potential of chemicals and as a cause of human cancer (Preston-Martin et al., 1990; Oliver and Roberts, 2002). But one can ask whether receptor-mediated effects resulting in enhancement of cell proliferation and/or reduction of apoptosis are sufficient for carcinogenicity, or whether more is needed.

Induction of cell proliferation by estrogens and progestins or by TCDD and dioxin-like compounds is not a simple effect but is highly complex and dependent on a wide variety of factors, as was pointed out above. Only in certain circumstances will these agents stimulate cell proliferation in target tissues, whereas in other situations they may inhibit proliferation (Hushka and Greenlee, 1995). Furthermore, there is only scant direct evidence that increased cell proliferation by itself causes tumours or malignant transformation. Most likely, genetic damage is required in combination with cell proliferation or reduction of apoptosis; in that concept, receptor-mediated carcinogens are tumour promoters, co-carcinogens, enhancers of susceptibility, or indirect inducers of genotoxicity, for example via induction of oxidative stress. For example, increased cell proliferation has been shown to neoplastically transform rat hepatocytes only after treatment with a genotoxic agent (Lee et al., 1989). NIH 3T3 cells will undergo complete neoplastic transformation under favourable conditions after sustained proliferation, but these cells are already immortalized (Yao et al., 1990; Chow and Rubin, 2000).

Thus, it appears that stimulation of cell proliferation by itself is not sufficient to induce cancer, but that it can be a powerful enhancer of carcinogenesis by facilitating initiating events, for example through fixation of pro-mutagenic DNA lesions, affecting DNA repair, inducing error-prone DNA synthesis (Mimura and Fujii-Kuriyama, 2003), and/or by acting as a driving force during tumour promotion and progression. These notions obviously have implications for the use of cell proliferation as a criterion in hazard identification of suspected carcinogens and in carcinogen risk assessment (Melnick et al., 1996).

Receptor-mediated events are typically dose-dependent, and dose–response relationships between ligands and receptor-mediated effects are often nonlinear. This has led to the concept of a dose threshold for receptor-mediated carcinogens that is used in carcinogen risk assessment. However, non-threshold dose–responses also occur, and there are many factors that can affect the shape of dose–responses of non-genotoxic or receptor-mediated carcinogens (Melnick et al., 1996). Moreover, for steroid hormone-like compounds, such as those used in combined oral contraceptives and hormonal menopausal therapy, the dose–response is typically biphasic (inverted U-shaped), and the effect threshold is observed at very low doses (Reddel and Sutherland, 1987; Groshong et al., 1997).

A further complicating issue is the evidence for a wide range of modifying factors that can affect the receptor-mediated action of suspected carcinogenic agents; not only is the dose critical, but species, sex, age, tissue or cell context, duration and timing of exposure, and route of exposure are all crucially important modifying factors, as pointed out above. Often neglected are co-exposures that may be important in determining the ultimate effect; for example, exposure to cigarette smoke and its constituents may influence the outcome of exposure to TCDD or other dioxin-like compounds (Kitamura and Kasai, 2007).

The diversity of ER-, PR-, and AhR-mediated effects observed across species, sexes, tissues, and cell types and across exposure conditions (dose, duration, timing, and route of exposure) poses considerable obstacles to rational testing for carcinogenic and mechanistic effects that predict human carcinogenicity of agents that act via these receptors. Whole-animal models are essential to sort out these effects, and animal bioassays that are designed to detect relevant carcinogenic effects remain indispensable. However, no good animal models exist for exposures to some of the important receptor-mediated carcinogens. It is not clear how to best test for effects of agents that are used or intended as oral contraceptives, and there are no truly relevant animal models reflecting conditions found

during and after human menopause. Mice or rats ovariectomized at age 1–1.5 years may be useful as a model for menopause, but this approach has not been used much. More research will be needed to develop and validate approaches with appropriate animal models for these important exposure conditions in humans.

As indicated above, there are also no validated models to evaluate the protective effects of combined oral contraceptives and hormonal agents used in menopausal therapy. Although standard animal models for cancer of the colon and breast could be used, there is a paucity of models for cancer of the endometrium, ovary, and cervix. To investigate effects of environmental exposures to receptor-mediated dioxin-like compounds, the Harlan Sprague-Dawley rat has proven to be suitable and sensitive in a large number of studies with these agents. Mice that lack or overexpress AhR have been useful to examine mechanisms underlying the effects of TCDD, but differences related to genetic background and strain hamper the generalization of the results of such research. Studies with diethylstilbestrol have demonstrated that for exposure to hormonal agents in early life, particularly in utero, neonatal treatment of CD-1 mice and Sprague-Dawley rats is informative and relevant for effects observed in humans. However, in vitro models may not be very relevant for studying the effects of most carcinogens that act via receptor mediation, because of the likely importance of paracrine mechanisms involving stromal cells, as shown for ER- and PR-mediated events. However, as a screening tool, approaches based on the use of cell cultures will remain very important for initial investigations and studies that are not feasible in whole animals.

Perhaps the most difficult aspect of evaluating the carcinogenic potential of agents that act via receptors, particularly AhR, ER, and PR, is the sheer complexity of how these receptors are involved in mediating the effects of chemical agents (Pandey and Picard, 2010; Denison et al., 2011; Jennen et al., 2011; Ruiz-Aracama et al., 2011; Thomas and Gustafsson, 2011; Cochrane et al., 2012; Jacobsen and Horwitz, 2012). Signature changes in gene expression induced in target cells or tissues by suspected carcinogens would be a most useful tool for carcinogen identification if they would suggest or predict the carcinogenicity of the agents. However, no consensus alterations in gene expression profiles have yet been identified for groups of agents that are thought to act via similar mechanisms, such as dioxin-like compounds or estrogenic substances. In fact, as pointed out above, even within the group of dioxin-like compounds there is considerable variation in the gene expression changes they induce (Vezina et al., 2004; Kopec et al., 2008, 2010; Ovando et al., 2010; Jennen et al., 2011). In addition, knowledge about the mechanisms by which these chemicals act continues to evolve in major ways. For example, recent data indicate that some PCBs can be genotoxic because they are metabolized to DNA-damaging reactive intermediates, overturning the notion that PCBs are purely receptor-mediated agents (Ludewig and Robertson, 2012; IARC, 2016).

In conclusion, receptor-mediated mechanisms are central to the carcinogenicity of important groups of human carcinogens, but they are often incompletely or poorly understood. Research during the past two decades has revealed a high degree of complexity as to how such carcinogenic agents mechanistically act via receptors, and insight into these mechanisms continues to evolve. Receptor binding and activation by chemical agents or the induction of cell proliferation or oxidative stress are by themselves insufficient as evidence for carcinogenicity in animals or humans.

To make progress in the identification of receptor-mediated carcinogens, it will be important (i) to identify signature changes in gene expression in relevant tissues and cells in validated animal models that are predictive of carcinogenic activity of groups of structurally and functionally related chemical agents, and (ii) to further develop and validate such in vivo models. It also remains critical to continue generating data that allow evaluation of coherence in mechanisms and concordance in exposure-associated tumour types and target sites between animal models and humans.

An improved understanding is still needed of the relationships between carcinogenic activity and timing, dose, and duration of exposure to receptor-mediated carcinogens, and of the cancer-inhibitory activity of exposure to some of these agents for some tissue sites, such as that demonstrated for the reduction of risk of cancer of the endometrium, ovary, and colorectum by combined oral contraceptives and of risk of cancer of the colon by estrogen-only menopausal therapy (IARC, 2012b).

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