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Endocrine-disrupting chemicals as prostate carcinogens

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Competing interests

The authors declare no competing interests.

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Abstract | Endocrine disrupting-chemicals (EDCs) are natural or synthetic compounds that are ubiquitous in the environment and in daily-usage products, which interfere with the normal function of the endocrine system leading to adverse health effects in humans. Exposure to these chemicals might elevate the risk of metabolic disorders, developmental and reproductive defects, and endocrine-related cancers. Prostate cancer is the most common hormone-dependent cancer in men, and the fifth leading cause of cancer-related mortality, partly owing to a lack of knowledge about the mechanisms that lead to aggressive castrate-resistant forms. In addition to early-stage prostate cancer's dependence on androgen actions, the prostate is a target of oestrogenic regulation. This hormone dependence, along with the fact that exogenous influences are major risk factors for prostate cancer, make the prostate a likely target of harmful actions from endocrine-disrupting chemicals (EDCs). Various sources of EDCs and their different modes of action might explain their role in prostate carcinogenesis.

[H1]Introduction

Endocrine disrupting-chemicals (EDCs) are natural or synthetic compounds found in the environment, everyday objects, food, and cosmetics, which interfere with the normal function of the endocrine system, leading to adverse health effects [1,2]. These chemicals can affect

hormone synthesis, metabolism, release, and transport, as well as altering the interaction of endogenous hormones with their receptors and related signalling cascades [3]. Common sources of EDCs include plasticizers, pesticides, heavy metals, UV-filters, and flame retardants, amongst others [1]. The broad action of EDCs, the diversity of mechanisms that they can reach, their widespread distribution, and the capacity of some of them to bioaccumulate — particularly in adipose tissue (AT) — means that EDCs could substantially affect human health, being crucial components of the exposome (that is, all the environmental exposures an individual experiences throughout their lifetime)

Over the past 20 years , several governmental agencies, including The European Society of Endocrinology (ESE) and the World Health Organisation, have expressed concern about the harmful effects of EDCs on human health and wellbeing. In line with this, the Endocrine Society has highlighted that EDCs can be found as complex mixtures, have significant and/or long-term biological impact even with low exposure levels and produce effects affecting individuals across several generations

Several studies have shown that EDCs exposure might elevate the risk of metabolic disorders, developmental and reproductive defects, and endocrine-related cancers [3,8]. Prostate cancer is a hormone-dependent cancer and the second most common cancer in men, which accounts for a substantial number of deaths, and is the fifth leading cause of cancer-related mortality according to the 2022 global cancer statistics (published 2024)[9]. This scenario is partly attributable to the unknown aetiology of the disease and a lack of understanding of the mechanisms that accelerate the progression of prostate cancer to aggressive castrate-resistant forms. Initially, prostate cancer growth depends on the action of androgens mediated by the androgen receptor (AR), which sustain cell survival by stimulating proliferation and inhibiting apoptosis[10,11]. The intraprostatic activity of 5α-reductase, which converts ~90% of testosterone into 5α-dihydrotestosterone (5α-DHT), a potent metabolite with a 5-fold higher affinity for the AR than testosterone, has also been linked to disease progression [11]**.** By contrast, advanced

stages of prostate cancer are characterized by the acquisition of androgen-resistant phenotypes with tumours growing and metastasizing independently of circulating androgen levels [12].

The prostate is also subject to oestrogenic regulation that directly and indirectly affects its growth and differentiation [13-16], with distinct effects triggered by the nuclear oestrogen receptors (ERs) isoforms, ERα and ERβ, and the membrane G protein-coupled ER (GPER) [17-19]. ERα-signalling has been shown to promote proliferation, inflammation, and migration, whereas ERβ is considered antiproliferative and tumour-suppressive, with its loss being associated with the progression to castration-resistant prostate cancer [13,20]. The role of GPER in prostate cancer is less clear, but a tumour suppressive function has been suggested, as its expression is inversely correlated to the degree of neoplastic cell differentiation [20].

Importantly, AR, ERs and GPER have been shown to be activated (or inhibited) by different classes of EDCs, which can also interfere with other signalling pathways that control cell fate and tissue homeostasis [21-28]. Thus, this hormone dependence suggests the possibility of the prostate as a target of EDCs, which are driving prostate carcinogenesis. This premise is further supported by data indicating that extrinsic factors contribute up to ~70-90% of the risk for prostate cancer [29-31], which also supports the potential that prostate cancer is linked to environmental influences such as EDCs. Indeed, over the past decade, the concept that EDCs might promote prostate cancer development has gained the attention of the scientific community, resulting in the publication of several reviews; however, these do not exclusively focus on prostate cancer, deal only with specific classes of compounds, or limit the discussion of different mechanisms of action to the analysis of the AR and ERs signalling pathways only[32-34]. Thus, this Review provides a holistic overview of EDC classification, sources, and modes of action, discussing the diverse mechanisms that might explain their potential as prostate carcinogens, with a focus on EDCs-induced epigenetic alterations, immune dysregulation and disturbed cell survival and death in the prostate.

[H1]Classification, sources and general mechanisms of EDCs

EDCs can be classified into different categories according to their chemical origin, source, or physiological mode of action (Table 1). By chemical origin, EDCs can be divided into two groups: those that occur naturally, for example, mycooestrogens and phytoestrogens (for example zearalenone and genistein, respectively), and synthetic compounds, such as bisphenol A (BPA), vinclozolin or dioxins[1]. Alternatively, EDCs can be classified based on their source into natural and artificial hormones (for example, phytoestrogens and contraceptive pills, respectively), as drugs with hormonal side effects (such as naproxen and metoprolol), as industrial and household chemicals (for example, polycyclic aromatic hydrocarbons (PAHs), phthalates, fire retardants and plasticizers), as constituents of personal care products (such as ultraviolet absorbers in sunscreens, or phthalates and parabens in lotions and creams) and substances used in agricultural or gardening activities (insecticides and fungicides) [1,3,7]. In the agricultural sector, persistent organic pollutants (POPs) such as organochlorine pesticides (OCPs) are the most concerning, owing to their resistance to degradation and metabolization[35]. Finally the mode of action and physiological responses of EDCs means that they can act as 'hormone mimickers' or blockers (classified as xenohormones or antihormones, respectively)[8]. Notably, some of the substances that have been identified as EDCs can exhibit both xenobiotic and anti-hormone activity (Table 1).

[H2] Xenoestrogens and xenoadrogens

Xenoestrogens are chemicals that interfere with endocrine processes by mimicking the actions of endogenous oestrogen with downstream estrogenic effects via agonistic binding to the oestrogen receptors (ERs)[36]. Substances demonstrated to have estrogenic effects include phytoestrogens, industrial chemicals, polychlorinated biphenyls (PCBs), polybrominated biphenyl ethers (PBDEs), diethylstilboestrol (DES), BPA, UV filters, preservatives, pesticides,

and heavy metals such as cadmium [37-41]. Humans are also constantly exposed to complex mixtures of airborne pollutants with estrogenic activity, such as diesel exhaust particles[42]. Accordingly, xenoandrogens are the group of chemicals capable of disrupting endocrine homeostasis by mimicking androgen actions via agonistic interaction with the AR. This group includes mixtures of PCB congeners, UV filters, tributyltin (TBT) and triphenyltin (TPT) [43-47]. EDCs with xenoandrogenic activity are less common than those with estrogenic activity [48].

As the name indicates, antioestrogens and antiandrogens act as hormone antagonists, blocking the activation of ERs and AR, respectively. By inhibiting ERs and AR activity, these compounds disrupt hormone action, affecting physiological responses across a broad range of human tissues.

Substances with antiestrogenic activity) include both natural and synthetic compounds (Table 1)[49-54]. Products formed during chlorination of wastewater, extracts from soils collected near highways, extracts of motorcycle exhaust particulate and extracts from sedimentation dust from subway stations are also examples of complex mixtures of pollutants with potential antiestrogenic activity, to which humans are exposed in the environment [55-58]. EDCs acting as antiandrogens include PCB 138, organochlorine pesticides, UV filters, dichlorodiphenyltrichloroethane (DDT) metabolite and insecticides (Table 1) [23,52,59,60]. Complex mixtures of pollutants present in soils near highways, gaseous and particulate fractions of ambient air and diesel exhaust particles have also been shown to display antiandrogen activity[42,57,61].

[H1]Relationship between EDCs and prostate cancer

Epidemiological studies are scarce and sometimes difficult to interpret, but they remain a crucial tool in monitoring human exposure to EDCs and establishing their relationship with disease.

The great majority of the existing published studies that focused on the effect of EDC exposure on prostate cancer have addressed the influence of persistent pesticides on the development and aggressiveness of disease [62-67]. High lipid adjusted serum concentrations of the OCPs beta-hexachlorocyclohexane (HCH, 53.9 ng/g lipids, $p = 0.02$), trans-nonachlor (56.4 ng/g lipids, $p = 0.002$), and dieldrin (14.7 ng/g lipids, $p = 0.04$) have been shown to be significantly associated with the risk of prevalent prostate [62]. Data was obtained from the NHANES survey cycles conducted between 1999 and 2004 when blood samples from participants were collected. Adjusted odds ratios (ORs, 95% confidence interval, 95% CI) for the third tertile of detectable values were 3.36 (1.24–9.10) for HCH; 14.1 (2.55–77.9) for trans-nonachlor; and 2.74 (1.01–7.49) for dieldrin compared with concentrations in the lowest tertile or below the limit of detection [62]. A nested case-control study conducted between 1988 and 1999 within a large cohort (222 prostate cancer cases and 1110 age-matched controls) of predominantly Hispanic farmers in California demonstrated that workers with relatively high levels of exposure to OCPs (lindane, adjusted OR = 2.37; 95% CI: 1.22-4.61, and heptachlor, adjusted OR = 2.01; 95% CI: 1.12-3.60), OPs (dichlorvos, adjusted OR = 1.64; 95% CI: 0.97-2.78), fumigants (methyl bromide, adjusted OR = 1.59; 95% CI: 0.77-3.30), or triazine herbicides (simazine, adjusted OR = 1.81; 95% CI: 0.93-3.53) had an elevated risk of prostate cancer than those with lower exposure [63]. Simazine (OR = 1.89; 95% CI: 1.08–3.33) and lindane (OR = 2.02; 95% CI: 1.15–3.55) exposure were also associated with an increased risk of prostate cancer development in farmers from British Columbia (1,516 patients with prostate cancer and 4,994 age-matched internal control patients, covering the period between 1950 and 1998), with significant association observed between prostate cancer and dichlone (OR = 1.79; 95% CI: 1.13–2.85), malathion (OR = 1.34; 95% CI: 1.01–1.78) and endosulfan (OR = 1.52; 95% CI: 1.00–2.29) [64]. In a study performed in Guadeloupe (France), involving 576 men with newly diagnosed prostate cancer (before treatment) and 655 control patients, higher plasma concentrations of DDE were associated with the development of prostate cancer (adjusted OR = 1.53; 95% CI: 1.02-2.30, *p*

= 0.01)[65]. Interestingly, PCB-153 was more strongly associated with low-grade prostate cancer ($p < 0.001$) than with high-grade disease ($p = 0.10$), suggesting that this compound's actions might be more impactful for onset of the disease than for its progression[65]. Higher serum levels of PCBs were also observed in Korean individuals with prostate cancer compared with the control group (median values ranged from 1.13-30.12 in cancer cases vs. 0.50-10.63 ng/lipids in control individuals, hazard ratio, HR: 4.29; 95% CI: 1.52–12.08)[66].

An extensive study in The Netherlands investigated the influence of occupational exposure to a variety of compounds on the development of prostate cancer[67]. Investigation of occupational exposure to pesticides, PAHs, diesel exhaust, metal dust, metal fumes, and mineral oil in a cohort of 58,279 men identified a significant association with prostate cancer only for exposure to pesticides [67]. However, the authors highlighted the need for more specific research and detailed information on exposure or potential confounders[67].

Occupational exposure to PAHs generally occurs from burning of wood, petroleum and coal, via respiratory and cutaneous routes[68]. A study conducted in Detroit (Michigan, USA), between 2001 and 2004, assessed prostate cancer and PAH exposure in 637 men with prostate cancer and 244 control patients of white and African-American ethnicity [68], groups with reported distinct prostate cancer incidence and mortality rates (64% higher incidence and 2.3 times higher mortality in African-American men compared with Caucasian populations [69,70]). Other defined subsets were based on age (<60, 60-69 or >70), family history of prostate cancer (positive or negative), type of disease (aggressive or not) and selected non-occupational sources of PAH exposures (smoking or diet). To maximize statistical power, gene–environment interaction was assessed by the presence or absence of the glutathione S-transferase (GSTP1) Val(105) variant allele [68]. In the multivariate models adjusted for age and PSA, OR for the GSTP1 codon 105 Val genotypes were slightly elevated in African-Americans, but <1 in Caucasians [68]. In cases with an earlier age of disease onset (60 years) or who were smokers or

had a family history of prostate cancer, the association between the GSTP1 Val105 variant and respiratory occupational PAH exposure from petroleum was increased [68]. Overall, the study concluded that the carriage of this variant allele was associated with the exacerbation of respiratory exposure to PAH from any source, which was concomitant with an increased risk of prostate cancer (OR = 1.85; 95% CI: 1.19–2.89; p = 0.006) [68]. A subsequent study from Canada collected detailed work histories from 1,929 patients with prostate cancer (436 with aggressive disease) and 1,994 control patients between 2005 and 2012 [71]. In all analyses, the reference category included men who had never been occupationally exposed to any PAHs, compared to those who had probably or definitely been exposed to PAHs only within the 5 years preceding the diagnosis/interview [71]. After application of a 5-year development period from exposure, no clear association emerged for any of the PAHs. However, a slight increase in the risk of developing prostate cancer was apparent in the case of wood smoke exposure (OR = 1.06; 95% CI: 0.95-1.18) [71]., frequently occurring among firefighters. An accentuated risk for the development of high-grade prostate cancer (OR = 1.37; 95% CI: 0.65-2.89) was reported [71].

EDCs are also present in other daily products, such as food packaging, waterproof clothing, non-stick cookware, carpets, cosmetics and plastics [72-77]. A study analysed the relationship between exposure to the EDC perfluorooctanoic acid (PFOA) and cancer among residents living near the DuPont Teflon manufacturing plant in Parkersburg, West Virginia (USA) [72] and reported that increased PFOA serum levels were associated with several cancers, including prostate cancer (adjusted OR = 1.5; 95% CI: 0.9-2.5; 110–655 µg/L) [72]. A large prospective study, comprising 76,685 men aged 55–74 years across ten US centres[73], evaluated a variety of polyfluoroalkyl substances (PFAS) and showed an inverse association between PFOA and aggressive prostate cancer (OR = 0.79; 95% CI = 0.63-0.99). However, this association was limited to cases diagnosed ≤3 years after blood collection and became weaker or null in cases diagnosed at a later follow-up point[73]. Contrastingly, a significantly higher risk of prostate cancer was also observed in employees of an ammonium perfluorooctanoate manufacturing

facility in Minnesota, compared with an internal reference population of non-exposed workers (USA, HR = 3.0; 0.9–9.7 and HR = 6.6; 1.1–37.7, for moderate or high exposures, respectively, between 1997-2002) [74]. Worryingly, standardized mortality ratios (95% CI) for prostate cancer with no, probable and definite exposure were 0.4 (0.1– 0.9), 0.9 (0.4 –1.8), and 2.1 (0.4 – 6.1), respectively [74]. Residents of Merrimack (USA), a community with documented PFAS contamination of drinking water in public and private water sources, in a study performed between 2015 and 2019, also displayed a significantly higher risk of prostate cancer (risk ratio = 1.36; 95% CI 1.15-1.60) [75].

A nested cohort study from Spain (n=1838 sub-cohort and n=467 non-sub-cohort, between 1992-1996) demonstrated a relationship of parabens with prostate cancer risk. Significantly increased serum levels of methyl- and propyl-paraben were found in prostate cancer patients (1.03 *vs.* 0.93 ng/mL in control, $p = 0.041$; 0.24 *vs.* 0.22 ng/mL in control, $p < 0.001$), respectively). Methyl- and butyl-paraben as well as total were positively correlated with the development of prostate cancer (HR = 1.60, 95% CI = 1.16–2.20; HR = 1.19, 95% CI = 1.14–1.23 and HR = 1.62; 95% CI = 1.10–2.40; respectively) [76]. An increased risk of prostate cancer was also identified in Spanish men with increased serum BPA levels [77]. When categorizing BPA into tertiles, a 40% increase in the risk of prostate cancer was found for tertile 1 ($p = 0.022$), versus 37% for tertile 2 ($p = 0.034$) and 31% for tertile 3 ($p = 0.072$) [77]. Moreover, mean serum values of BPA in prostate cancer cases were higher than the ones from the non-sub-cohort (1.33 vs 1.29 ng/mL, respectively) [77].

A cohort study in Guadeloupe (French West Indies) was prospectively conducted on patients with incident prostate cancer who initially participated in a population-based case–control study between 2004 and 2007 and subsequently underwent radical prostatectomy in one single centre (Urology Department of the University Hospital of Guadeloupe) [78]. Plasma samples were obtained 1–3 months before surgery to determine POPs concentrations [78]. The xenoestrogen

chlordecone, measured in 326 plasma samples (0.16-19.1 µg/L), was associated with increased biochemical recurrence of prostate cancer after prostatectomy (median follow-up of 6.1 years, adjusted HR = 2.51; 95% CI: 1.39-4.56, p = 0.002) [78].

[H1] Mechanism of action of EDCs

EDCs exert their actions by highly complex mechanisms including nuclear receptor binding, interaction with membrane receptors, epigenetic modifications, altered expression of microRNAs and disruption of hormone synthesis and metabolism (Fig. 1). Noteworthy, the consequences of EDCs actions are strongly dependent on the timing of exposure during individuals' developmental stages, as well as on its duration, frequency and concentration [79].

[H2]Nuclear receptor binding

The most well-understood mechanism of EDCs action is the interaction with nuclear receptors (NR) (Fig. 1), which is a consequence of the general high liposolubility of these compounds. NRs act as transcription factors, with crucial roles in regulating gene expression in target cells and tissues [80,81]. After ligand binding, NRs dimerize, translocate to the nucleus and bind to the respective hormone-responsive elements, which are consensus DNA sequences in the promoter region of target genes[81]. The interaction of the ligand–NR complex with DNA and its activity regulating gene transcription is modulated by a set of co-activators and co-repressor proteins [27,82,83]. Both the ERs and AR are classical NRs belonging to the steroid receptor superfamily [84]. In addition to the classical steroid NRs, EDCs can also bind other members of the NR superfamily, including the oestrogen-related receptors (ERRs), constitutive androstane receptor (CAR), pregnane X receptor (PXR), peroxisome-proliferator activated receptor (PPAR), retinoic acid (RA) receptor (RAR) and thyroid receptor (TR) [84,85].

[H3] Oestrogen receptors

The two ER subtypes, ERα and ERβ, which are encoded by distinct genes on separate chromosomes (*ESR1* in chromosome 6 and *ESR2* in chromosome 14, respectively) and exhibit tissue-specific expression patterns and functions [86], are targets of EDCs, which disrupt their transcriptional activity. Notably, EDCs display different binding capacities depending on the ER subtype, and some only bind ERα or ERβ[87]. For example, 2,2-bis(p-hydroxyphenyl)-1,1,1-trichloroethane (HPTE) is selective for ERα both *in vitro* and *in vivo*[88,89]. ERα selective agonism was also observed for similar chemicals with bis-hydroxyphenyl core structures, such as BPA[89]. An increase in ERα expression and translocation from the cytoplasm to the nucleus was also observed in prostate neoplastic cells (LNCaP) upon exposure to 4-nonylphenol (NP)[90]. By contrast, phytoestrogens – such as coumestrol, genistein, zeralenone and equol – showed a higher affinity for ERβ than for ERα [91]. The anti-estrogenic activity of the organophosphate esters 4-hydroxyphenyl diphenyl phosphate (*para*-OH-TPHP) and resorcinol bis(diphenyl phosphate) (RDP) was demonstrated by their ability to inhibit ERα, with 20 % relative inhibitory concentration (RIC_{20}) values of 5.1×10^{-7} M and 5.6×10^{-7} M, respectively [92]. Besides differential selectivity and affinity, the agonistic or antagonistic properties of an EDC might also depend on which ER subtype it binds, as proved by the capability of chlordecone and methoxychlor to display ERα agonistic activity though being ERβ antagonists [93].

Estrogenic EDCs, including phthalates, PCBs, pesticides, BPA, alkylphenols and phytoestrogens, can bind also bind the AR, mainly antagonizing its activity [94-96]. Androgen-mimicking EDCs, benzo[a]pyrene (BaP), dichlorvos, genistein and endosulfan, have been also identified[26].

Despite having high levels of similarity and identity with ERs in the DNA-binding and ligand-binding domains, the distinct ERRs — ERRα, ERRβ and ERRγ — do not interact with 17β-oestradiol (E_2) [97]. However, these receptors can bind to the functional oestrogen-response elements, and their transcriptional activity is repressed by some EDCs such as DES and BPA [97,98]. ERRγ was shown to bind *p*-hydroxybenzoic acid esters, NP, 4-tert-octylphenol, 2-tert-butylphenol, pentachlorophenol, hexachlorobenzene, TBT, Di-(2-ethylhexyl) phthalate (DEHP),

hydroxylated benzophenones and some phytoestrogens [35,99-104]. Two other compounds, toxaphene and chlordane, have been identified as ERRα antagonists[105].

[H3] CAR and PXR

CAR and PXR have been associated with the metabolism and transport of xenobiotics by regulating the expression of cytochrome P450 enzymes [106-108]. Moreover, these receptors can establish crosstalk with other NRs, disrupting cell and tissue homeostasis by interfering with the control of intracellular signalling pathways[109,110]. Unlike other NRs, CAR is constitutively active under most circumstances, although some steroids can repress its activity [109]. Many environmental chemicals can alter CAR activity, including *trans*-nonachlor, methoxychlor, alachlor, arsenite, BPA, butylate, chloropropham, chlorpyriphos, cypermethrin, cyproconazole, phthalates, dieldrin, endosulfan, fenitrothion, imazalil, kepone, metolachlor, NP, parathion, PCBs, pentachlorophenol, PFAS, propachlor, and triclopyr[106,109,111-120].

An extensive list of EDCs trigger the activity of PXR, including some phthalates, phenolic compounds and derivates, pesticides, plasticizers, UV-screens, mycoestrogens and phytoestrogens, brominated flame retardants, NP, PBDEs, DDT, *trans*-nonachlor and phthalic acid [115,121-146].

[H3] PPAR

The PPAR family of NRs includes three receptor subtypes, PPARα, PPARβ and PPARγ, which have crucial roles in the control of cellular differentiation, adipogenesis, and energy homeostasis by regulating lipid and carbohydrate metabolism [147,148]. PPARα is essentially expressed in cardiac and skeletal muscles, adipose tissue, liver, kidney and intestine, and is important in fatty acid catabolism[149-154]. PPARγ has been shown to have a crucial function in adipocyte differentiation and lipid storage[155-157], whereas PPARβ has a broader tissue expression and function, with a role in cell differentiation and survival and in both systemic and tissue-specific fatty acid metabolism[157]. Beyond the activation by natural ligands, such as polyunsaturated fatty acids and eicosanoids, PPARs' activity is influenced by a panoply of

environmental pollutants. Phthalates, and organotins have been shown to activate these receptors [158-167]. The obesogens TBT and bis(triphenyltin) oxide induce adipocyte differentiation by promoting PPARγ transcriptional effects on target genes [168]. Furthermore, perinatal exposure to BPA or BPA analogues has been shown to alter PPARγ-mediated early adipogenesis in the rat[169,170].

[H3]Retinoid receptors

The retinoid-responsive NRs include the RAR and the retinoid X receptors (RXRs), which include α, β and γ subtypes and distinct isoforms [171]. Specific regulation of gene expression is achieved by 48 possible RAR–RXR heterodimer complexes [171,172]. Moreover, the responsiveness of RXR to its ligand was shown to depend on RAR agonist binding; thus, RXR is considered a silent or subordinate partner[173-175]. At low levels, retinoids have been proposed to exert anticarcinogenic effects in various tissues by suppressing cell proliferation, differentiation and apoptosis[176-187]. However, high retinoid levels are associated with an increased risk of cancer, particularly prostate cancer [188-190]. Accordingly, the organochlorine pesticide toxaphene was shown to inhibit the binding of the endogenous ligand 3H-All trans retinoic acid to RAR in the human prostate [191] and the pesticide methoprene can also interact with RXR activating transcription through RXR response elements[192]. Although environmental concentrations of methoprene are not enough to cause RA-like effects, ultraviolet and/or microbial degradation products of methoprene could affect morphogenesis via teratogenic effects through the retinol signalling pathway [192]. Furthermore, the methoprene metabolite methoxy-methoprene acid can bind and activate RXR[193]. TBT and TPT were also demonstrated to activate mammalian RXR in the F9 murine embryonic carcinoma cell line at the same concentrations of RXR's physiological ligand 9-cis RA[161].

Alterations in retinoid circulatory levels caused by exposure to PCBs raise the question of whether is pertinent to consider retinoids as biomarkers of exposure to organochlorides[194]. In line with the previous hypothesis, PCBs were dose-dependently associated with levels of

retinoids in fish, birds and mammals[195-200], suggesting important effects of these compounds in retinoid-dependent signalling pathways in birds and mammals[201-209]. PAHs are another group of widespread pollutants that affect the retinoid system and have been shown to have carcinogenic potential, mainly owing. to their mutagenic ability (DNA adducts) and highly reactive metabolites, such as epoxides[210-212].

[H3]Thyroid receptors

Five isoforms of TR exist: TRα1, TRα2, TRβ1, TRβ2 and TRβ3; TRα1 seems to act as a repressor of TR action[213]. TRα is expressed in all tissues, but TRβ is only found in the kidney, liver, central nervous system and pituitary gland[214]. Through the mediated response of TRs, thyroid hormones (THs) regulate metabolism, cardiac function, mental status and bone remodelling[215-225], controlling cell differentiation and growth in various organs[226-233]. PCBs can dysregulate thyroid action, decreasing hormone levels, blocking binding to TR and affecting the expression of TH-responsive genes [234-238]. Both *para*-OH-TPHP, and another organophosphate ester, the tris (2-biphenylyl) phosphate demonstrated to have antagonistic activity on TRβ, whereas *para*-OH-TPHP presented significantly higher affinity for TRβ (RIC_{20} of 7.5×10^{-7} M vs. 5.4×10^{-6} M, respectively) [92]. Other classes of compounds that affect THs actions by reducing their levels include flame retardants (for example tetrabromobisphenol A, PBDEs and polybrominated biphenyls), pesticides (such as DDT and hexachlorobenzene), UV filters (such as octyl-methoxycinnamate), phthalates (including di-n-octyl phthalate) and PFAS (such as perfluorooctane sulfonate) [215,239-261].

[H2]Aryl hydrocarbon receptor

Although not classified as an NR, the aryl hydrocarbon receptor (AhR) is a ligand-activated transcription factor, displaying functional similarities with the members of the NR superfamily[262]. After interacting with the nuclear protein Arnt, AhR specifically binds to dioxin-responsive elements in the upstream regulatory regions of target genes [262]. AhR transcriptional

activity induces the expression of cytochrome P450 enzymes (*CYPs*), for example *CYP1B1*, one of the major enzymes involved in the hydroxylation of androgens and oestrogens, which is a key reaction in hormone-dependent carcinogenesis [263,264]. Studies have demonstrated that AhR can be activated by several EDCs including dibutyl phthalate, diisodecyl phthalate, DEHP, some phenols, perfluorooctanoic acid, perfluoroalkyl acids, methoxychlor, PCBs, BaP, TBT, phytoestrogens and UV filters [262,265-271].

[H2Interaction with membrane receptors

Rapid nongenomic actions of EDCs via their interaction with plasma membrane receptors, not dependent on the regulation of gene transcription, have been reported. These mechanisms of rapid responses involve second messenger-triggered signalling cascades and include the membrane-bound ERs *m*ERα and *m*ERβ and the GPER [272]. The *m*ERα and *m*ERβ are the classical nuclear ERs, which are translocated to the plasma membrane via mechanisms that remain unelucidated[273].

The *m*ERα and *m*ERβ also mediate a nongenomic pathway via the rise of intracellular calcium (Ca^{2+}) levels driven by a rapid increase in Ca^{2+} influx, which can promote changes in intracellular and extracellular processes, cell motility and hormone secretion [274]. Some xenoestrogens such as dieldrin, endosulfan, NP and BPA can affect Ca^{2+} influx and prolactin release in pituitary tumour cells via *m*ERα activation, with consequences on hormonal regulation, cell proliferation and immune response[274]. GPER is expressed the brain, ovary, breast, testis, heart, pancreas and prostate[275-282]. Thus, GPER activation is an alternative oestrogen-signalling pathway that might used by EDCs, leading to deregulated hormonal balance and downstream effects in a broad range of tissues. Xenoestrogens, such as BPA, genistein, DDT derivates, atrazine, PCBs, kepone, methoxychlor, cadmium, arsenite and NP bind with high affinity to GPER[283-286].

[H2]Epigenetic modifications

Besides directly interfering with the mode of action of NRs and, therefore, gene expression, EDCs can also induce epigenetic modifications(FIG. 1) [287]. Moreover, epigenetic alterations capable of altering the DNA landscape and gene transcription rate can be heritable through successive generations [288].

The main epigenetic changes induced by EDCs are DNA methylation and histone modifications[16,289-292]. The DNA methylation pattern, determined by the activity of a family of DNA methyltransferases (DNMTs), establishes the chromatin structure. An open chromatin structure (active) is associated with hypomethylated DNA sequences, whereas hypermethylated DNA is packaged in a more compact structure (inactive) [293]. DNA hypermethylation can block the access of transcription factors to gene promoter binding sites, suppressing gene expression [293]. Thus, aberrant hypermethylation can have a profound effect on cell fate by suppressing, for example, the expression of tumour suppression genes [294-300].

Chromatin conformation can also be altered by post-translational modifications of charged amino acids of histone tails, such as acetylation, methylation, phosphorylation, ubiquitination or ADP-ribosylation, which protrude histones from the nucleosome, inducing a DNA relaxation and regulating gene expression [301]. Thus, alterations at this level can dramatically affect gene expression. For example, changes in the global levels of individual histone modifications have been reported to predict the clinical outcome of prostate cancer, more specifically involving H3 K18Ac and K4diMe staining, which distinguished between two groups of patients with a distinct risk of tumour recurrence (4% and 31%, respectively)[302].

Perinatal and early-life exposure to BPA, cadmium, 17β-estradiol-3-benzoate (EB), PCBs, DES, phthalates, methoxychlor or vinclozolin have all been shown to alter the DNA methylation pattern in prostate cells [16,303-308]. PCBs might also reduce the expression and activity of DNMTs, which has been shown in the liver of offspring whose progenitors were exposed to these EDCs

during gestation [306,307,309]. In addition, differential histone methylation was observed in rat testes after *in utero* exposure to vinclozolin or dibutyl-phthalate [289], with BPA, DES and phthalates also inducing histone conformational alterations [310,311]. The physiological consequences in the prostate triggered upon EDCs exposure via epigenetic mechanisms are systematized and further explored in the corresponding section.

[H2]Altered expression of microRNAs

MicroRNAs (miRNAs) are conserved small noncoding RNA molecules that mainly bind to the 3' untranslated regions of target messenger RNAs (mRNAs), altering their translation and stability[312]. An estimated 30% of protein-coding genes are regulated by miRNAs [313], which have a crucial role in the regulation of fundamental cellular processes, such as cell proliferation, migration and programmed cell death, and hormone metabolism and intracellular signalling [314-316]. Thus, mechanistic disruption of the miRNAs landscape can have profound physiological consequences. Deregulation of miRNA homeostasis has been correlated with diseases such as obesity, diabetes and cancer [316-318] and EDCs are candidates molecules to interfere with small noncoding RNA signalling (FIG. 1) as they have been shown to affect the biogenesis, editing and stability of miRNAs, altering their tissue expression levels[319]. Treatment of the oestrogen-responsive human breast cancer cell line MCF-7 and placental cell lines with BPA, NP or DDT, led to atypical miRNA expression[320-322] and NP has also been shown to affect the expression profile of several miRNAs, such as miR-16, miR-195, miR-200b and miR-205, which are related to metabolism, immune response, apoptosis and cell differentiation [322]. Notably, the levels of miR-200b and mi205 are inversely associated with prostate cancer aggressiveness[323,324]. Other classes of compounds capable of deregulating miRNAs expression are phthalates, phenols and alkylphenols, with effects demonstrated in human placenta and in mouse embryos [319,325]. PCBs, 2, 3, 7, 8-tetrachlorodibenzo-p-dioxin (TCDD) and DES also disrupt the miRNAs population,

altering their expression and/or functionality, leading to disruption of hormone homeostasis, metabolic disorders and cancer[326-331] .

Studies showing a link between EDCs-dysregulated miRNA populations and prostate cancer begin to emerge. The oral administration of 2 µg/kg BPA every day for 8 weeks reduced the expression of cfa-miR-204 in the prostate of beagle dogs, concomitantly with *KRAS* oncogene upregulation, which triggered the malignant transformation of prostatic hyperplasia via this axis [332]. Decreased miRNA expression (miR-134, miR-373, miR-155, miR-138, miR-205, miR-181d, miR-181c) targeting KRAS superfamily members was also observed during the malignant transformation of human prostate epithelial and stem cells by arsenic [333]. Downregulation of miRNAs in rat dorsolateral prostate (rno-miR-329-3p, and rno-miR-126a-3p) and plasma (rno-miR-329-3p) was found after postnatal administration (days 1, 3, and 5) of 2.5 mg/kg EB, which was accompanied by increased prostate weight and dorsolateral prostate inflammation. This study also found downregulated expression of miR-329-3p's target genes (*Esrrg*, *Tp53inp2* and *Bmp2r)*, which can result in activation of malignancy and cell proliferation/tumour growth [334].

[H2]Disruption of hormone synthesis and metabolism

EDCs can also interfere with hormone synthesis and metabolism (FIG. 1).

The activity of steroidogenic enzymes such as hydroxysteroid dehydrogenases, aromatase, sulfatase and sulfotransferases and the steroidogenic pathway (FIG. 2) can be affected by xenoestrogens. Some phthalates have been shown to inhibit 3β-hydroxysteroid dehydrogenase and 17β-hydroxysteroid dehydrogenase isozyme 3 in both rat and human testis in a dose-dependent manner [335,336]. For example, BPA inhibited the activity of 11β-hydroxysteroid dehydrogenase isoform 1 isolated from human liver, rat Leydig cells and testis microsomes and 11β-hydroxysteroid dehydrogenase isoform 12 (FIG. 2) from human and rat kidney microsomes [337]. The flavonoids genistein, daidzein, formononetin, and biochanin A

significantly inhibit the 3β-hydroxysteroid dehydrogenase isozyme 2 [338,339]. Moreover, genistein has been shown to reduce 17β-hydroxysteroid dehydrogenase isozyme 3 activity in human and rat testicular microsomes, as well as in rat Leydig cells [336]. The UV-filter benzophenone-1 has also been reported to inhibit 17β-hydroxysteroid dehydrogenase isozyme 3 (FIG. 2)[340].

Oestrogen sulfotransferase (FIG. 2) is necessary for the excretion of oestrogens and inhibition of this enzyme by EDCs can, therefore, increase bioavailability of oestrogens to target organs [341,342]. Estrone sulfatase activity was shown to be reduced by the flavonoids quercetin, kaempferol, naringenin, and the sterol sulfatase enzyme is inhibited by daidzein [343,344].

Aromatase activity (FIG. 2) can be disrupted by several classes of environmental pollutant compounds, which can induce or inhibit its activity, altering the normal physiological ratio of androgens:oestrogens. Pesticides — atrazine, simazine, terbuthylazine, propazine, methomyl, pirimicarb, propamocarb, iprodione, prothioconazole, benomyl and carbendazim — and other compounds such as dichlorodiphenyldichloroethylene (DDE), NP, BPA and arsenic are known inducers of aromatase activity in several neoplastic and non-neoplastic human cell lines (including those of breast, ovary, adrenal cortex, and placenta), and in rat hepatocytes, Leydig cells and prostate [345-356]. On the other hand, disruptive actions of environmental pollutants such as prochloraz, fenarimol, endosulfan, chlorothalonil, propiconazole, TBT, imazalil, triadimenol, triadimefon, dicofol, DES, chlordecone, PBDES, parabens, dibutyltin and TPT lead to the opposite effect, inhibiting aromatase activity [349,350,357-364]. Exposure to BPA was also shown to reduce the levels of the 5α-reductase isozymes R1 and R2 in rat prostate, increasing the levels of isoform R3, which has been proposed as a biomarker of malignancy [356].

EDCs can also inhibit other p450 enzymes that are involved in the metabolism of testosterone and estrone[365,366]. The p450 enzyme families most affected by EDCs are *CYP1*, *CYP2*, *CYP3* and *CYP4*. Chemicals that can affect the *CYP1* family, for example *CYP1A* isoforms, are TCDD, BPA and alachlor [367-369], whereas in the *CYP2* family, DDE, DDT, methoxychlor, BPA, benzophenone,

alachlor, some flame retardant, trans-nonachlor, endosulfan, chlordane, dieldrin, aldrin and pentachlorophenol disrupt activity of the *CYP2A*, *CYP2B* and *CYP2C* isoforms[111,115,131,134,368-374]. The *CYP3A* isoform was shown to be affected by environmental pollutants, such as TBT, DDE, DDT, methoxychlor, BPA, benzophenone, alachlor, trifluralin, vinclozolin, lindane, chlordane, dieldrin, endosulfan and trans-nonachlor [111,131,134,370-372,375] and EDCs such as hepatochlor, BPA, NP and some phthalates disrupt the activity of *CYP4* family members[115,376,377].

Although altered expression of *CYPs* has not been directly associated with prostate cancer, significant correlative relationships between the expression of *CYPs* (*CYP7B1, CYP27A1, CYP39A1, CYP51, CYP1B1, CYP3A5, CYP4F8, CYP5A1, CYP4F2, CYP2J2, CYP2E1, CYP2R1, CYP27B1, CYP24A1)* and some prostate-cancer-related genes (*CDH2, MMP9, SCHLAP1, GCR, CYP17A1, ACTA2, CXCL14, FAP, CCL17, MSMB, IRF1, VDR*) was observed [378]. The relationship between *CYPs* and genes associated with cancer indicates the existence of common regulatory pathways that might have a synergistic effect to ensure the survival of cancer cells and tumour growth.

Reduced 5α-reductase activity, thereby limiting the conversion of testosterone to 5α-DHT, could be another route for an unbalanced androgen:oestrogen ratio to predispose to prostate malignant transformation. These data highlight the complexity of the action of EDCs in steroid biosynthesis and metabolism.

[H1]Physiological effects of EDCs driven by epigenetic alterations

Epigenetic alterations are common events seen in cancer cells, which contribute to the establishment of malignant phenotypes as the global changes in chromatin state disrupt the expression of oncogenes and tumour suppressor genes, triggering tumour progression, aggressiveness and resistance to therapy[379]. Aberrant hypermethylation has been shown to have a substantial effect on the progression of prostate cancer by affecting hormone signalling [294-297], DNA repair [298], tumour suppression [299,300,380-383], cell adhesion [384-387], cell cycle and the

expression of proapoptotic genes [388-390]. This wide range of actions justifies the concern about EDCs and their role in deregulating the epigenetic pattern towards a cancer-promoting state.

Prenatal and early life exposure to EDCs can alter the methylation level of several genes, with harmful outcomes later in life. Activity of phosphodiesterase type 4 variant 4 (PDE4D4), an enzyme responsible for cyclic AMP breakdown and directly associated with preneoplastic prostate lesions, is augmented in rats exposed to environmental doses of BPA during the neonatal period[391]. In human healthy prostates, the specific methylation cluster for PDE4D4 is gradually hypermethylated with ageing [391]. However, in this work, early and prolonged hypomethylation at this site was seen after exposure, culminating in continued and elevated expression of PDE4D4[391]. Another study demonstrated that exposure to EB and BPA during neonatal development stage increased susceptibility to prostate cancer in rodent models [305]. This experiment identified 111 EB-associated genes and 86 BPA-associated genes with significantly different methylated regions, 20 of them in common [305]. The majority of these genes were related to cell-to-cell signalling and interaction, cell-mediated immune response, and cellular growth and proliferation. The oncogenic signalling molecules protein kinase B (AKT) and extracellular signal-regulated kinases 1/2 (ERK1/2), which support stem and cancer cell proliferation, migration and tumorigenesis, were specific targets[305]. In rats, DEHP exposure altered methylation of the prostate carcinogenesis-related genes *PSCA, GSTP1* and *PTGS2*, plausibly contributing to the increasing susceptibility to prostate cancer in later life [305]. EDCs also can alter the catalytic activity or the expression levels of histone-modifying enzymes, which interact with steroid receptors facilitating the transcription of their target genes [306]. Jarid1b is a histone demethylase upregulated in prostate cancer cells that catalyses the removal of trimethylation of lysine 4 on histone H3 (H3K4me3) [392]. This histone demethylase interacts with AR, promoting its transactivation [306]. A study of the effect of PCBs on the interaction between AR and Jarid1b interaction demonstrated that PCBs promoted AR transcriptional activity in a dose-dependent manner[306]. Notably, the effects of PCBs were

dependent on the presence of Jarid1b and at least 2 DNA-binding sites for the Jarid1b enzyme[306]. BPA was shown to downregulate nucleolar RNAs with a C/D motif via altered recruitment of H3K9me3, H3K4me3, and H3K27me3 to 5'-regulatory exonic sequences [393]. Expression of 4 of these 5 nucleolar RNAs (SNORD59A, SNORD82, SNORD116, and SNORD117) was shown to be reduced in prostate cancer samples compared with adjacent normal tissue[393]. Another study demonstrated that BPA increased the activity of the histone methyltransferase MLL1 via activation of nongenomic signalling (PI3K) in the neonatal developing prostate[394]. Whole-genome transcriptome sequencing determined the differentially expressed genes targeted by BPA, exhibiting a persistent elevation of H3K4me3[394]. Moreover, BPA administration exaggerated the response to carcinogenesis-promoting hormone treatment (testosterone + E_2 implantation)[394]. Indeed, both DNA methylation and histone modifications (H3K9ac, H3K9me3, H3K27me3, and H4K20me3) could be proposed as molecular biomarkers of BPA-induced prostate cancer progression[395,396]. *In silico* studies and molecular docking analysis demonstrated that androgenic EDCs (BaP, dichlorvos, genistein and endosulfan) can bind the epigenetic regulatory enzymes DNA methyltransferase 1 (DNMT1) and histone deacetylase 1 (HDAC1) [26]. Furthermore, exposure to these EDCs enhanced the expression of DNMT1 and HDAC1 in the human prostate neoplastic androgen-sensitive cell line LNCaP[26].

EDCs have demonstrated transgenerational effects — altered gene expression induced by EDCs via epigenetic mechanisms, especially when exposure occurs early in life, can be heritable through successive generations[304,397]. For example, male rats exposed to vinclozolin during foetal development, as well as non-exposed F2-F4 generations, developed tumours (12-22%, breast adenomas, malignant breast carcinoma, lung sarcoma, and melanoma), whereas their control counterparts were tumour-free [398]. F1-F4 vinclozolin generation males also presented accentuated higher frequencies of prostatic lesions (45-55%), with abnormal prostate histology that ranged from primary ductal atrophy to cystic hyperplasia and focal prostatitis[398]. Vinclozolin also able to transgenerationally altered the prostate transcriptome

(259 genes with significantly changed expression), including genes associated with prostate cancer (for example, beta-microseminoprotein and tumor necrosis factor receptor superfamily 6) [399].

Overall, the promotion of epigenetic alterations seems to be a common mechanism underlying the action of EDCs in tumorigenesis.

[H1]Immune system alterations

A panoply of immune and inflammatory cells (for example, tumour-associated macrophages (TAMs), lymphocytes, dendritic cells, neutrophils and myeloid-derived suppressor cells) and several cytokines (such as IL-1β, IL-6, IL-10, IL-17, TGF-β, TNF-α) are present in the tumour microenvironment [400]. Lack of balance in these biochemical and cellular components results in a chronic inflammatory state, which is associated with cancer development [400-402]. The inflammatory environment ranges from high immunological reactivity by cytotoxic innate and adaptive immune cells during the early stages of tumorigenesis to peripheral tolerance and immunosuppressive tumour environment in advanced stages of the disease, which are linked with poor prognosis [400,402]. Cancer-associated inflammation contributes to genomic instability, epigenetic modification, induction of cancer cell proliferation, enhancement of anti-apoptotic pathways, stimulation of angiogenesis, and cancer dissemination [401]. Approximately 20% of cancers, including prostate cancer, are attributable to chronic inflammatory conditions, with environmental factors being strong drivers of immune response impairment [403,404].

Two major properties make the immune system susceptible to chemical deregulation: first, the fact that the immune system develops later in life and bone marrow-derived immune components are continuously being renewed and second, immune surveillance, which requires a delicate control of the balance between activation, silencing and regulation of immune reactivity[405]. In a risk assessment study involving 27 compounds, the relationship between

immunotoxicity and carcinogenicity was reported at 81%, suggesting that if a compound is immunotoxic, it is highly likely to also be carcinogenic [406]. EDCs that affect the activity of immune cells or alter cytokine production might also compromise cancer immune surveillance[406], which is associated with several cancer types including haemopoietic, prostate, liver and pancreas [407-409]. Reports assessing the direct relationship between EDC-induced immune dysfunction and prostate cancer are almost non-existent; however, the dysregulation of the immune component is correlated with procarcinogenic features, and some studies have explored this idea [410,411]. Although some EDCs exert immunosuppressive actions and others have been shown to exacerbate immunological responses, paradoxically, both responses are able to promote tumorigenesis[412-415].

Immunosuppression – specifically impairment of neutrophil chemotaxis and adhesion — was observed in industrial workers exposed to several pesticides, such as trichlorfon, malathion, DDT, hexachlorocyclohexane and fenitrothion[412,413]. NP and 4-octylphenol have also been shown to reduce macrophage-derived chemokine expression when macrophages were LPS-activated, via ER-dependent mechanisms [416]. However, duality was observed in the case of NP, as this EDC was shown to upregulate key target genes — the pro-inflammatory cytokines IL-8 and IL-1β — involved in the inflammation process of prostate cell lines PNT1A and LNCaP[90,417]. Some pesticides, the fungicide ziram, organotins (TBT and dibutyltin), and PCBs have been shown to decrease natural killer (NK) cells' activity, which might be relevant for immune surveillance and destruction of abnormal cells such as tumour cells)[418-420].

EDCs also affect adaptive immunity. Exposure to cadmium, PCBs, dioxins, dibenzofurans, hexachlorobenzene, dieldrin and DDT have been shown to disrupt the proliferation of thymocytes and thymic maturation of T cells, inhibiting T cell proliferation and interfering with metabolic pathways[421-425]. TCDD has been shown to cause thymic atrophy, suppressing cell-mediated immunity, and inhibiting the complement system and myelotoxicity, which might

increase the predisposition to carcinogenicity[410,411]. Besides TCDD, PCBs can also induce atrophy of the thymus in numerous species, including rats, rabbits, pigs, monkeys and humans [420,426-429].

EDCs can stimulate inflammation and immune response. The organotins TBT and TPT have been shown to promote CCR9 chemokine receptor expression to levels above that seen with anti-CD3/-CD28-induced activation, increasing T cell recruitment in the gut[414]. Immune dysregulation propitiating chronic gut inflammation is relevant in the context of prostate cancer, as it can lead to increased levels of pro-inflammatory cytokines and immune cell infiltration in the prostate [430,431], creating a pro-tumorigenic environment. This relationship is corroborated by studies that demonstrate the association of inflammatory bowel disease with prostate inflammation and prostate cancer[430,431]. Notably, neonatal administration of the xenoestrogens DES and EB resulted in marked inflammation of prostate lobes later in life (180 and 90 post-natal days, respectively)[415,432]. BPA exposure has also been associated with exacerbated prostate inflammation [391,433-435]. Prepubertal BPA exposure induced inflammation in the adult rat prostate, whereas adult BPA exposure aggravated pre-existing benign prostate hyperplasia[436,437]. Moreover, chronic BPA exposure promoted the infiltration of both $CD4^+$ and $CD8^+$ T cells in the rat dysplastic epithelium of prostatic intraepithelial neoplasia (PIN) lesions [438]. Accumulation of $CD4^+$ T cells is linked to a worse prognostic, as the infiltration of these cells in prostate tumours correlates with an increased risk of lethal prostate cancer in humans[439]. Altogether, these findings suggest that BPA exposure alters T cell homeostasis, possibly predisposing to prostate tumorigenesis [438]. This hypothesis is also supported by the literature regarding other cancers. For example, BPA can alter and disturb the antigen-specific immune response, leading to moderate Th1-type immunoreaction [440]. Furthermore, exposure to aldicarb-contaminated groundwater was associated with increased $CD8^+$ T cell number and decreased $CD4^+$:$CD8^+$ T cell ratio [441].

Independently of stimulating immune reactivity or immunosuppressors, EDCs affect important immune system components and, in some cases, immune function, which might be related to the development of prostate cancer and/or progression to more aggressive forms.

[H1]The effect of EDCs on the fate of prostate cells

Deregulated cell proliferation and resistance to death are among the most widely studied hallmarks of cancer [442]. In non-neoplastic tissues, cell growth and division are tightly controlled by various signals and cell cycle regulators, which contribute to maintaining tissue homeostasis [443]. By contrast, cancer cells display enhanced cell cycle activity [444] and acquire the capacity to sustain high proliferation rates, for example, by dividing even in the absence of mitogens or growth-stimulating factors [442]. In addition, cancer cells become resistant to damage and capable of evading programmed cell death [442,445].

Apoptosis is the most common mechanism of programmed cell death, and has a crucial role in removing injured or unnecessary cells. Apoptosis is regulated in part by several Bcl-2 family, which control mitochondrial integrity and the activity of pro-apoptotic molecules [446]. Overall, the balance between pro-apoptotic and anti-apoptotic signals and regulators determines the fate of the cell[447]. The deregulation of these control mechanisms enables cancer to circumvent apoptosis. Such mechanisms include the loss of function of the tumour suppressor protein p53, which usually induces the expression of anti-apoptotic proteins or survival factors and the apoptosis of cells that display critical DNA damage[442]. An efficient apoptotic programme protects against carcinogenesis and, therefore, several apoptosis regulators have been exploited as therapeutic targets[442]. Some of the evidence supporting a role of EDCs as carcinogens includes their actions as deregulators of cell proliferation and apoptosis, most likely by interfering with oestrogen and/or androgen signalling pathways. [448]

Oestrogens are well-known mitogens and potent apoptosis regulators [449]. Several reports indicate that the ERα pathway is responsible for the E_2-induced cancer-promoting response, whereas ERβ is associated with a protective role against carcinogenesis [450,451]. ERs are key players in regulating cell proliferation in prostate cancer after exposure to xenoestrogenic EDCs [15,391,452]. In this context, perinatal exposure to environmentally relevant doses of BPA (10 µg/kg body weight) have been shown to alter rodent prostate growth and differentiation, resulting in precancerous lesions[15,391,452]. This effect occurred either via altering the expression of genes encoding cell cycle and/or apoptosis regulators, or by nongenomic modulation [391]. NP also can stimulate the proliferation of both non-neoplastic (PNT1A, 10^{-6} M) and neoplastic (LNCaP, 10^{-10} M) human prostate cells, upregulating Cyclin D, Cyclin E and Ki67 gene expression via interaction with ERα, and not affecting p53 expression [90,417]. Cyclin E and Cyclin D promote G1/S phase transition of the cell cycle and are often used as markers to evaluate the carcinogenic potential of EDCs [417,453]. Evidence suggests that, besides ER-mediated pathways, AR signalling is also involved in NP-induced prostate cancer cell proliferation. NP (10^{-6} M), as well as hexabromocyclododecane (HBCD, 10^{-8} M), were shown to increase the viability and growth of LNCaP cells through AR activation, leading to the downregulation of the cell-cycle inhibitors p21 and p27 and upregulation of Cyclin D or Cyclin E [454]. HBCD and NP exposure also affected the expression of the pro-apoptotic gene *BAX*, reducing apoptosis of LNCaP cells by decreasing BAX protein levels[454]. Higher expression levels of cathepsin D, a protease that regulates cancer progression and metastasis, were also observed after treatment of LNCaP cells with NP [454]. Other compounds with androgenic activity, including the xenoandrogens TBT and TPT, have been shown to increase the proliferation of LNCaP and related cell lines (LA16)[455]. Moreover, the increased proliferative activity, along with activation of AR-dependent transcription, in TBT/TPT treated-LNCaP cells further sustains the hypothesis that these chemicals could promote prostate tumour aggressiveness, as the AR mutation observed in LNCaP is frequently found in advanced human prostate cancer, rendering it susceptible to this type of dysregulation [455-457].

Remarkably, EDCs with androgenic activity can also affect prostate cells through AR-independent mechanisms, which is demonstrated by their effects on the fate of AR-negative prostate cells, such as PC3. BaP exposure significantly increased the proliferation of the neoplastic human prostate cell line PC3, with a reduction in the G0-G1 phase population and elevation in S phase[458]. The migratory capacity of PC3 cells was also significantly increased, owing to the modulation of MMP-9, *CYP1A1*, *CYP1B1*, Cyclin D1, and E-cadherin levels [458]. Alterations in epithelial-mesenchymal transition (EMT) markers were also observed in DU145 and PC3 cells after endosulfan exposure, reflecting repression of E-cadherin expression and induction of fibronectin, SNAIL2, ZEB2, TWIST1 and Vimentin [459]. Similarly, despite being a xenoestrogen, low doses of BPA have been shown to activate AR and mitogenesis in prostate adenocarcinoma cells (LNCaP) [24]. The xenoestrogen EB, which is related to tumour growth or abnormal proliferation, induced substantial changes in expression levels of several miRNAs (rno-miR-146-5p, rno-miR-329-3p, and rno-miR-126a-3p) in the dorsolateral prostate of exposed rats[334].

In prostate epithelial cells, the expression of the tumour suppressor protein p27 is modulated by androgens, with reduced expression levels after malignant transformation being associated with the acquisition of androgen-independent growth [460]. In the RWPE-1 prostate epithelial cell line, cadmium was shown to potentiate androgen-independent malignant transformation along with increased ER and 5α-aromatase expression, suggesting that oestrogen signalling might be critical to this process [461]. Indeed, cadmium enhanced cell growth and reduced expression levels of tumour suppressor protein p27 and p21 [461,462], increasing other cell cycle-associated proteins such as cyclin D1 and B1 [462].

EDCs can also affect cell fate independently of ER-mediated and AR-mediated mechanisms. Indeed, arsenic-malignant-transformed prostatic epithelial and stem cells demonstrated impairments in the Toll-like receptor 3 anti-tumour pathway [448]. In the same cell line, inorganic

arsenic was shown to stimulate cell self-renewal, suppressing the differentiation of prostate stem-progenitor cells by activation of the p-62-KEAP1-NRF2 pathway [463]. Another worrying factor in arsenic-associated cancer stem cell overabundance is the ability of arsenic-transformed malignant epithelial cells (MECs) to influence the nearby non-neoplastic stem cells [464]. A noncontact co-culture model demonstrated that arsenic-transformed prostate MECs caused the hypersecretion of MMPs with increased invasiveness, clonogenicity and suppression of the tumour suppressor gene *PTEN* in normal stem cells, consistent with the acquisition of a cancer phenotype [464]. Moreover, dysregulated miRNA expression has been implicated as an important mechanism in the modulation of prostate cell fate by EDCs. Aberrant miRNA expression was observed during the malignant transformation of human prostate epithelial and stem cells by arsenic, linked with RAS activation[333]. Increased expression of activated ERK was shown in both transformants, concomitantly with altered components of the PI3K/PTEN/AKT pathway including decreased PTEN and increased BCL2, BCL-X_L, and VEGF [333]. In LNCaP and PC3 cells treated with butyl benzyl phthalate, miR-34a expression was downregulated, with the resulting promotion of cell proliferation [465].

In summary, EDCs could plausibly drive prostate carcinogenesis either via ER-dependent and AR-dependent mechanisms or by directly or indirectly affecting other components of key survival pathways, resulting in the enhancement of cell cycle progression, inhibition of apoptosis and stimulation of metastatic capacity.

[H1]The role of adipose tissue

Adipose tissue has major roles in mediating the toxicological effects of EDCs [466-470], as many (although not all) EDCs are lipophilic molecules that are stored and tend to accumulate in the adipose tissue. Thus, adipocytes act as an internal source of chronic low-level systemic exposure to EDCs [467,471], which could be more important in obesity conditions. Moreover,

awareness of the contribution of the adipose tissue to the consequences of exposure to EDCs is increasingly relevant owing to the escalation of obesity in the 21st century. Around 18% of the adult population is estimated to be obese in 2030, and 30% of children also are estimated to have obesity[472,473].

The dynamics of body fat-stored EDCs have been described. EDCs undergo lipolysis in the adipose tissue, which progressively releases large quantities of EDCs into the circulation in a continuous cycle of post-exposure storage and subsequent release [467,470,471]. Approaches to study these dynamics include a murine cell model mimicking lipolysis for testing PCBs mobilisation [467], which demonstrated the mobilisation of PCBs from adipocytes during lipolysis and showed that the structure of PCBs congeners defines their release rate [467]. These findings were pivotal in highlighting the importance of the specific chemical properties of EDCs on their mobilisation from adipose tissue [467]. Another study using a xenografted fat model of TCDD exposure [470] demonstrated that TCDD stored in the adipose tissue can be released and distributed to the organs of the recipient mice. Moreover, the authors confirmed that the released compound led to altered gene expression in the liver and adipose tissue, stimulating inflammation, gluconeogenesis and fibrosis [470].

Epidemiological studies have shown that adipose tissue can be used as a biological sample to monitor EDCs levels and their effects on the human body [474]. In this context, a study analysed OCP levels in the periprostatic adipose tissue (PPAT) of patients with prostate cancer from Mainland France and the French West Indies to investigate correlation with tumour aggressiveness [474]. Most OCPs (8 out of 13) were found at elevated concentration in the PPAT of Caucasian patients, but DDE content was twice as high in PPAT from African-Caribbean patients and chlordecone was only detected in the PPAT from African-Caribbean patients [474]. Among the pesticides assessed, the organophosphate mirex (which was banned in the USA in the 1970s) was associated with aggressive features of prostate cancer in Caucasian men[474].

Altogether, these findings highlight an ethnogeographical variation in adipose tissue accumulation and response to OCPs [474]. In this context, it is important to emphasise that besides this ethno-geographic variation in adipose tissue accumulation, exposure to EDCs may vary according to sociodemographic factors, lifestyle characteristics, and inter-individual susceptibility.

Adipose tissue is, unquestionably, an endocrine organ and a target of EDC-induced dysregulation [471], with implications for to other tissues. In the case of prostate cancer, the 'threat' of adipose tissue is particularly relevant as it has been shown that PPAT dysregulation is a driver for aggressiveness, invasiveness, and metastasis development [473,474]. Furthermore, adipocyte-secreted factors in obesity such as chemokines, cytokines and metabolites increase the proliferation and invasion of prostate cancer cells, fuelling cancer progression [475,476].

Overall, data regarding the relationship between EDCs, adipose tissue and prostate cancer are scarce. However, the available evidence should stimulate research to address whether EDCs can induce adipocyte dysfunction, contributing to prostate malignant transformation and cancer progression. Furthermore, improved understanding of the role of adipose tissue in shaping the toxicological profile of EDCs is paramount, particularly regarding whether adipose release and, therefore, EDC exposure is dependent on, for example, an individual's ethnicity, genetics, or other physiological conditions.

[H1]Future directions

Research is needed to comprehensively characterize the individual and combined exposure and effects of EDCs, which requires collection of large amounts of data regarding exposure. Large-scale, well-designed longitudinal prospective studies are needed to gather information from diverse populations worldwide and more accurately determine the consequences of a specific exposome. Robust epidemiological studies are needed to confirm the underlying mechanisms of action and identify the critical exposure windows. Research efforts should also

be directed towards identifying specific pathways and downstream molecular targets activated by EDCs, which will be critical for the development of preventive approaches.

The actions of EDCs as prostate carcinogens require improved understanding of how EDCs can affect the components of the tumour microenvironment, particularly the adipose tissue, as adipocytes are a source of prolonged exposure to EDCs, dysregulation of which can contribute to carcinogenesis.

Future studies should also focus on implementing primary and secondary preventive measures to substantially reduce exposure to EDCs. Primary prevention measures would involve stricter regulations and monitoring of their compliance, including enforcing bans or restrictions on products that contain chemicals with endocrine-disrupting potential, such as pesticides, plastics, cosmetics, and household goods. Secondary prevention would include public health initiatives aimed at reducing exposure in at-risk populations and public awareness campaigns about the impact that minimal changes in life habits could have on this matter, such as reducing the consumption of processed foods. Additionally, improving occupational safety measures in industries where workers are exposed to hazardous chemicals could further reduce EDCs' exposure risks.

[H1]Conclusions

These data support a role for EDCs as potential prostate carcinogens. Several classes of compounds, via several different exposure routes, can promote prostate dysfunction by inducing epigenetic changes, immune dysregulation, and cell fate disturbance (FIG. 3). Identification of the molecular mechanisms underlying the carcinogenic potential of EDCs is in progress and epidemiological studies have illustrated that specific compounds are associated with an increased risk and aggressiveness of prostate cancer. However, the specific targets and effects of EDCs still need to be fully identified. Furthermore, thresholds of exposure related to

the carcinogenic potential of EDCs must be established, in order to limit exposure to harmful compounds and provide awareness of their potential effects.

Research in this area has several limitations, particularly the lack of comprehensive analyses of the exposome, which reflects real-life environmental exposure conditions. Studies combining two or more EDCs with different modes of action are challenging to perform, which makes correctly interpolating the results complicated. Furthermore, carrying out case-control studies of the impact of EDCs in humans is difficult, due to the variability in environmental concentrations, time of exposure, and the lipophilic nature of EDCs that means they accumulate in the adipose tissue. Finally, the complexity of the tumour microenvironment makes studies difficult to plan, as this panoply of cellular and molecular components able to tightly influence cancer cell fate and which are sensitive to exogenous stimuli, as is the case of EDCs.

Nonetheless, research to explore the relationship between EDCs and prostate cancer is crucial for the future. The overall goal of this work — to obtain responses that are as translatable as possible to the real context — is needed to provide to implement effective prevention policies to mitigate EDCs' effects and drive public awareness.

Figure legends

FIG. 1. Comprehensive overview of endocrine-disrupting chemicals (EDCs)' mechanisms of action. **(a)** Interaction with nuclear receptors (NRs). After the agonistic interaction of EDCs with NR, the receptor dimerizes, translocates to the nucleus, and binds to the respective hormone-responsive elements. The interaction of the EDC-NR complex with DNA enhances or suppresses gene transcription, disrupting the network of synthesized proteins. Antagonistic EDCs can block the interaction of NR with its natural ligands. **(b)** Interaction with membrane receptors. Rapid nongenomic actions of EDCs can occur through their interaction with membrane hormone receptors, seven helix G-protein coupled receptors or NRs that can be translocated to the cell

membrane and act as membrane receptors, as is the case of oestrogen receptors (ERs). This mechanism encompasses second messenger-triggered signal cascades through successive phosphorylation of the substrates. Calcium (Ca^{2+}) release is also observed, as well as the stimulation of the activity of transcription factors (TF), indirectly regulating the transcription rate. **(c)** Epigenetic changes. The main epigenetic changes induced by EDCs are DNA methylation and histone modifications. The DNA methylation pattern is determined by the activity of a family of DNA methyltransferases (DNMTs). Some EDCs can interact with these enzymes, either increasing (activator EDC) or decreasing (repressor EDC) their activity. DNA hypermethylation can block the access of the transcriptional machinery to gene promoter binding sites, suppressing gene expression, whereas hypomethylation has the reverse effect. Chromatin conformation can also be altered by EDCs-induced post-translational modifications of charged amino acids of histone tails (e.g. acetylation, phosphorylation and ubiquitination), which protrude histones from the nucleosome, playing a regulatory role in gene expression. **(d)** Altered expression of micro RNAs (miRNAs). EDCs can affect the biogenesis, edition and stability of miRNAs, altering their tissue expression levels and, consequently, their interaction with target mRNAs, altering mRNA translation and stability. **(e)** Disruption of hormone synthesis and metabolism. The function of steroidogenic enzymes is affected by EDCs' ability to activate or inhibit their activity or regulate the expression of enzyme-coding genes.

FIG. 2. Endocrine-disrupting chemicals affecting the mineralocorticoid, glucocorticoid, and androgen biosynthetic pathways. Compounds with inhibitory (red)/stimulatory (green) effects on the activity of steroidogenic enzymes involved in the mineralocorticoid, glucocorticoid, and androgen biosynthesis are identified in groups 1 to 4. Legend: BBOP: bis(2-butoxyethyl); BPA: bisphenol A; *CYP11A1*: cholesterol side-chain cleavage enzyme-coding gene; *CYP17A1*: 17α-hydroxylase-coding gene; *CYP19A1*: gene codifying aromatase-coding gene; *CYP21A2*: gene codifying 21-hydroxylase-coding gene; DBT: dibutyltin; DCHP: dicyclohexyl; DDE:

Dichlorodiphenyldichloroethylene; DES: diethylstilbestrol; NP: 4-nonylphenol; PBDES: polybrominated biphenyl ethers; *SRD5A2*: 5α-reductase type 2 enzyme-coding gene; TBT: tributyltin; TPT: triphenyltin; 3β-HSD: 3β-hydroxysteroid dehydrogenase; 11β-HSD: 11β-hydroxysteroid dehydrogenase; 17β-HSD: 17β-hydroxysteroid dehydrogenase.

FIG. 3. Endocrine-disrupting chemicals (EDCs) as prostate carcinogens. EDCs affect the development of prostate cancer (PCa) and aggressiveness of disease by a panoply of mechanisms that disrupt prostate cell fate. These compounds induce **(a)** epigenetic and **(b)** immune system alterations and interfere with **(c)** nuclear receptor (NR)-dependent/-independent pathways, increasing cell proliferation, migratory capacity and invasiveness). **(d)** Moreover, due to their lipophilic nature, some EDCs can bioaccumulate in the periprostatic adipose tissue (PPAT), being gradually and long-term released, dysregulating PPAT function and their secreted factors. Legend: AKT: protein kinase B; AR: androgen receptor; BaP: benzo[a]pyrene; BPA: bisphenol A; *CYP1A1*: cytochrome P450 family 1 subfamily A; *CYP1B1* cytochrome P450 family 1 subfamily B; DBT: dibutyltin; DDT: dichlorodiphenyltrichloroethane; DEHP: Di-(2-ethylhexyl)phthalate; DES: diethylstilbestrol; DNMT1: DNA methyltransferase 1; EB: 17β-estradiol-3-benzoate; ER: estrogen receptor; ERK1/2: extracellular signal-regulated kinase 1/2; HBCD: hexabromocyclododecane; HCB: hexachlorobenzene; HCH: hexachlorocyclohexane; HDAC1: histone deacetylase 1; H3K9ac: acetylation of lysine 9 on histone H3; H3K4me3: trimethylation of lysine 4 on histone H3; H3K9me3: trimethylation of lysine 9 on histone H3; H3K27me3: trimethylation of lysine 27 on histone H3; H4K20me3: trimethylation of lysine 20 on histone H4; IL: interleukin; microRNA 34a: miR-34a; MMP-9: matrix metalloproteinase-9; NK: natural killer; NP: nonylphenol; PCBs: polychlorinated Biphenyls; PDE4D4: phosphodiesterase type 4 variant 4; PSCA: prostate stem cell antigen; TBT: tributyltin; TCDD: tetrachlorodibenzo-p-dioxin; TPT: triphenyltin.

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Author contributions

M.F. and T.M.A.C researched data for the article. M.F., T.M.A.C, S.C. and S.S. wrote the article. All authors contributed substantially to discussion of the content. All authors reviewed and/or edited the manuscript before submission. M.F. and T.M.A.C. contributed equally. S.C. and S.S. contributed equally as senior authors.

Competing interests

The authors declare no competing interests.

Table 1| Classes of EDCs categorized by their chemical origin and mode of action.

Class	Origin	Mode of Action (examples)	References
Phytoestrogens	Naturally occurring	Xenoestrogens	91,136,269,338,477,478

		(isoflavones, coumestans, lignans)	
Plasticizers	Synthesized	Xenoestrogens, Antiandrogens (BPA, phthalates)	16,25,97,101,115,117,124,144,169,254, 290,292,305,311,320,337,352,356,368,3 77,479-485
Drugs (*e.g.* contraceptive pills)	Synthesized	Xenoestrogens (DES, naproxen, ethinylestradiol, progestin)	41,81,290,310,486-488
Dioxins and dioxin-like substances (PCBs)	Synthesized	Xenoestrogens, Xenoandrogens, Antiestrogens, Antiandrogens	43,51,56,130,198,209,235,260,342,367, 489-491
Fire Retardants	Synthesized	Xenoestrogens (PBDEs) Antiestrogens (*para*-OH-TPHP, RDP)	92,258,260,261,492-494
Heavy metals	Naturally occurring	Xenoestrogens (Cadmium)	284,303,495
Pesticides	Synthesized	Xenoestrogens (lindane, atrazine, MXC), Xenoandrogens (TBT, TPT) Antiestrogens, Antiandrogens (DDT, VNZ)	21,45-47,100,106,146,239,245,262,267,304,37 1,397,398,496-498
Preservatives	Synthesized	Xenoestrogens (parabens)	364
Anti-corrosives	Synthesized	Antiestrogens (Benzotriazole)	54,270
UV filters	Synthesized	Xenoestrogens (BP1, BP2), Xenoandrogens (BP2, HMS), Antiestrogens (BP3, BP4), Antiandrogens (PS)	44
Cleaning products	Synthesized	Xenoestrogens (NP)	28,118,351

BP: Benzophenone; BPA: Bisphenol A; DDT: Dichlorodiphenyltrichloroethane; DES: Diethylstilbestrol; HMS: Homosalate; MXC: Methoxychlor; NP: Nonylphenol; PBDEs: Polybrominated Diphenyl Ethers; *para*-OH-TPHP: 4-hydroxyphenyl diphenyl phosphate; PCBs: Polychlorinated biphenyls; PS: Phenyl salicylate; RDP: resorcinol bis(diphenyl phosphate; TBT: Tributyltin; TPT: Triphenyltin; VNZ: vinclozolin

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fellowships].

Key points

- Endocrine disrupting chemicals of various sources, classifications, and mechanisms of actions, might promote prostate cancer development.
- Epigenetic alterations, specifically aberrant methylation patterns and histone modifications are common mechanisms that underlie the tumorigenic actions of EDCs.
- Some EDCs exert immunosuppressive actions, while others have been shown to exacerbate immunological responses; paradoxically both are able to promote tumorigenesis.
- EDCs could plausibly drive prostate carcinogenesis by directly or indirectly affecting components of key survival pathways, resulting in the enhancement of cell cycle progression, inhibition of apoptosis and stimulation of metastatic capacity.
- Adipose tissue is an endocrine organ (and a target of EDC-induced dysregulation) having the ability to shape the toxicological effects of EDCs and their impact on adjacent tissues, as is the case of the prostate.

Toc blurb

Endocrine disrupting-chemicals (EDCs) can interfere with the normal function of the endocrine system leading to adverse health effects in humans. In this Review, the authors discuss how exposure to these chemicals might be major risk factors for prostate cancer, and consider the various sources of EDCs and their different modes of action.

Figure 1

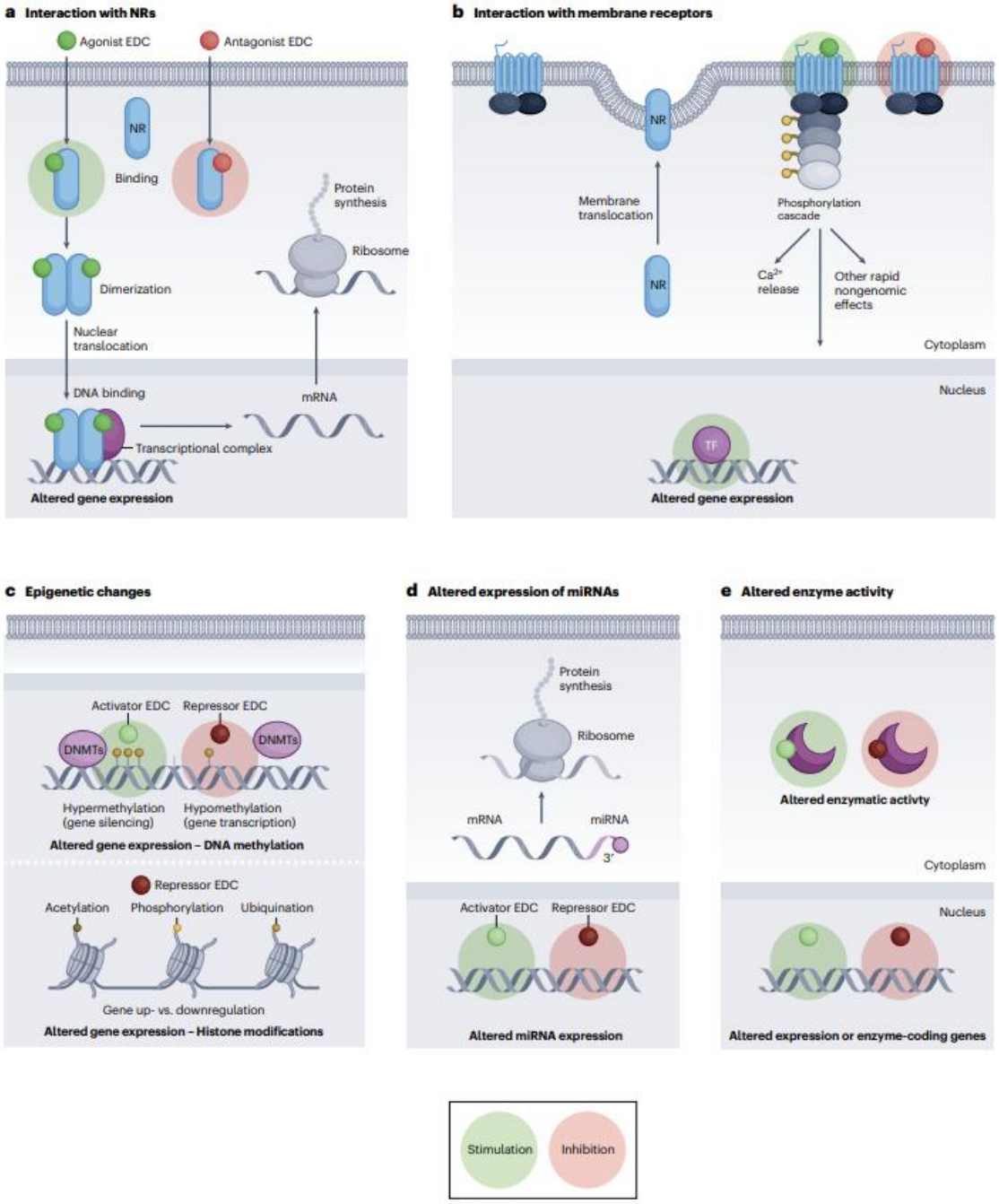

a Interaction with NRs
Agonist EDC
Antagonist EDC
NR
Binding
Protein synthesis
Ribosome
Dimerization
Nuclear translocation
DNA binding
mRNA
Transcriptional complex
Altered gene expression
b Interaction with membrane receptors
NR
Membrane translocation
NR
Phosphorylation cascade
Ca2+ release
Other rapid nongenomic effects
Cytoplasm
Nucleus
TF
Altered gene expression
c Epigenetic changes
Activator EDC
Repressor EDC
DNMTs
DNMTs
Hypermethylation (gene silencing)
Hypomethylation (gene transcription)
Altered gene expression – DNA methylation
Repressor EDC
Acetylation
Phosphorylation
Ubiquination
Gene up- vs. downregulation
Altered gene expression – Histone modifications
d Altered expression of miRNAs
Protein synthesis
Ribosome
mRNA
miRNA
3'
Activator EDC
Repressor EDC
Altered miRNA expression
e Altered enzyme activity
Altered enzymatic activty
Cytoplasm
Nucleus
Altered expression or enzyme-coding genes
Stimulation
Inhibition

Figure 2

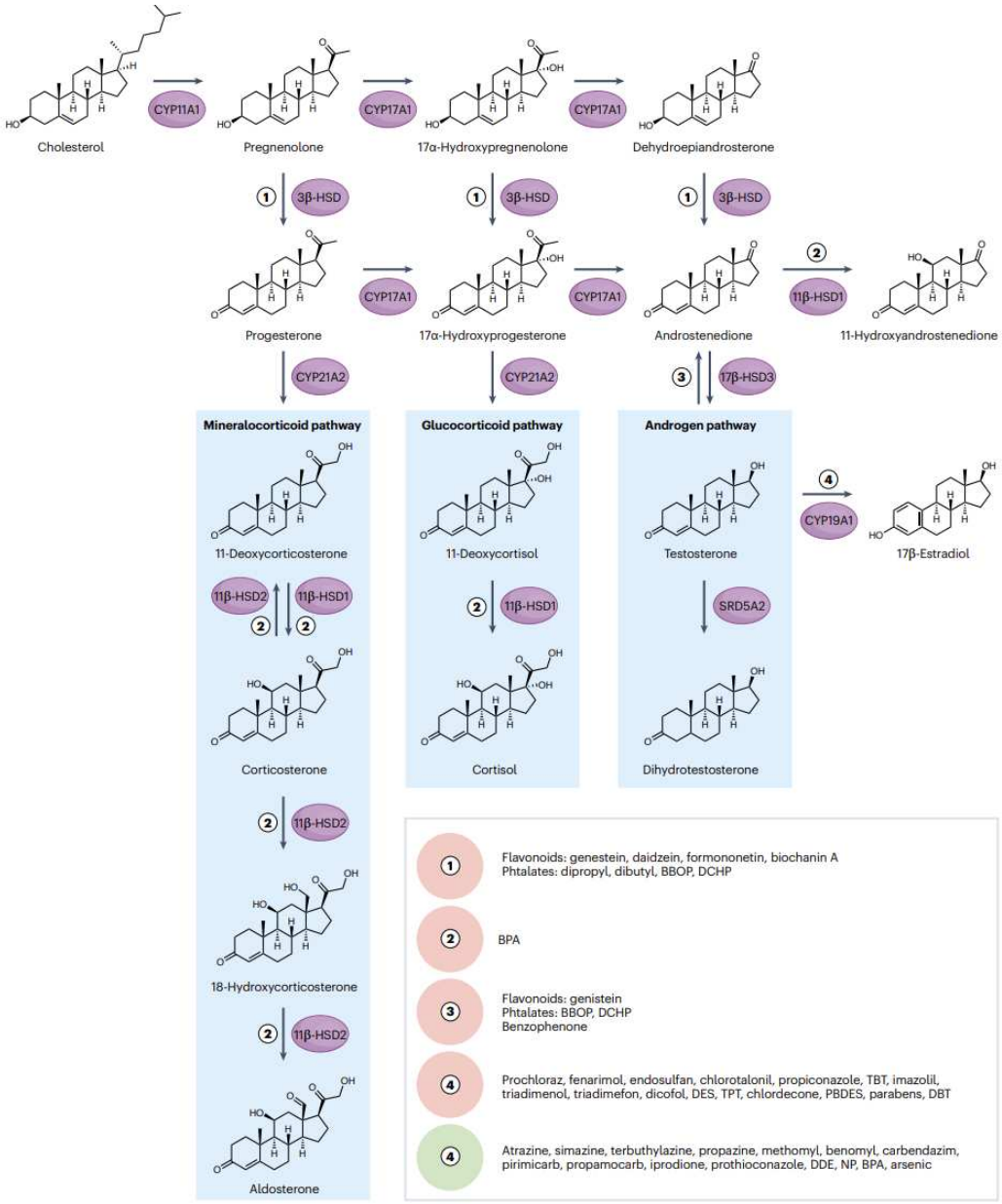
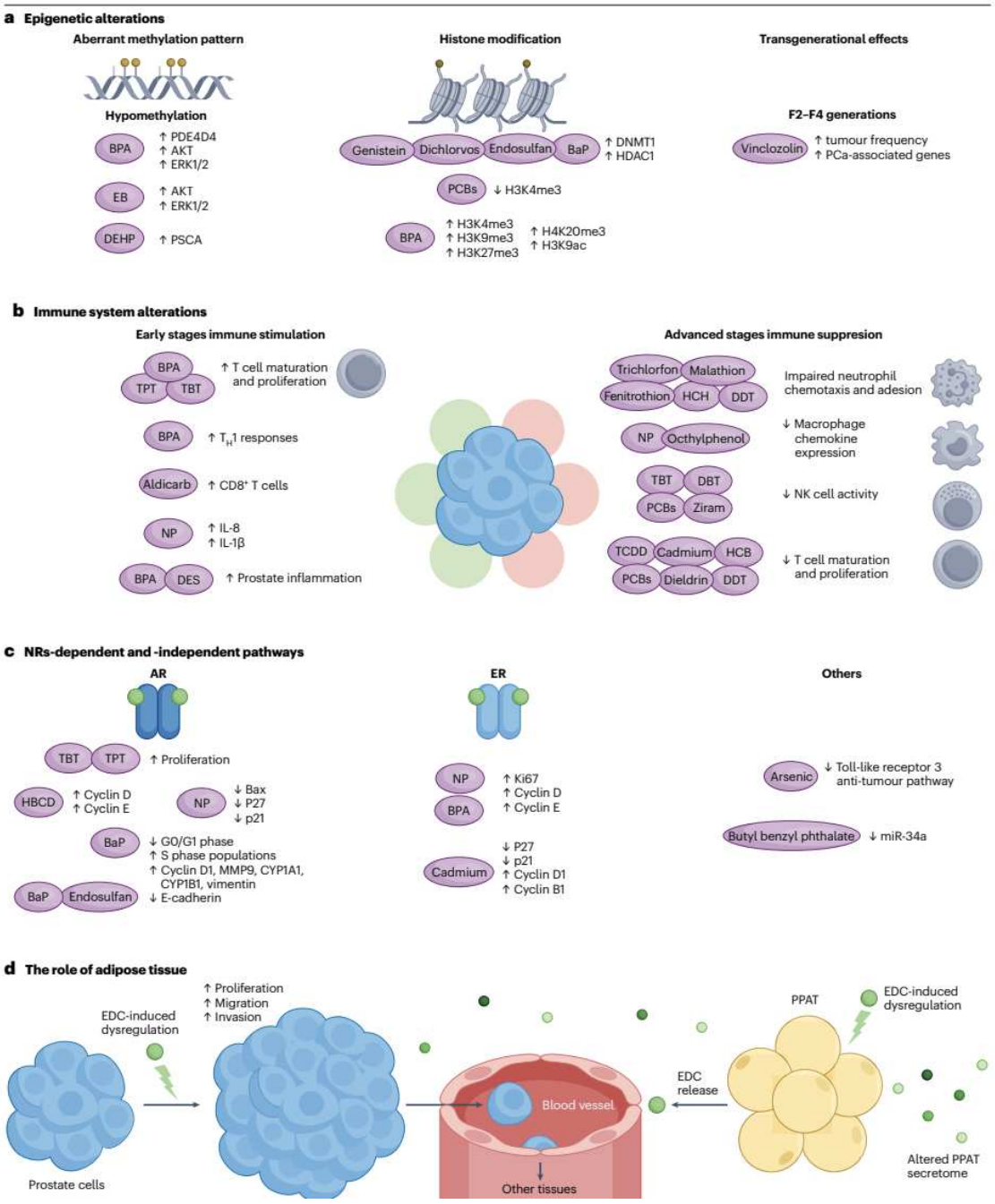

Cholesterol
CYP11A1
Pregnenolone
CYP17A1
17α-Hydroxypregnenolone
CYP17A1
Dehydroepiandrosterone
1 3β-HSD
1 3β-HSD
1 3β-HSD
Progesterone
CYP17A1
17α-Hydroxyprogesterone
CYP17A1
Androstenedione
2 11β-HSD1
11-Hydroxyandrostenedione
CYP21A2
CYP21A2
3 17β-HSD3
Mineralocorticoid pathway
Glucocorticoid pathway
Androgen pathway
11-Deoxycorticosterone
11-Deoxycortisol
Testosterone
4 CYP19A1
17β-Estradiol
2 11β-HSD2
2 11β-HSD1
2 11β-HSD1
SRD5A2
Corticosterone
Cortisol
Dihydrotestosterone
2 11β-HSD2
18-Hydroxycorticosterone
2 11β-HSD2
Aldosterone
1 Flavonoids: genestein, daidzein, formononetin, biochanin A
Phtalates: dipropyl, dibutyl, BBOP, DCHP
2 BPA
3 Flavonoids: genistein
Phtalates: BBOP, DCHP
Benzophenone
4 Prochloraz, fenarimol, endosulfan, chlorotalonil, propiconazole, TBT, imazolil, triadimenol, triadimefon, dicofol, DES, TPT, chlordecone, PBDES, parabens, DBT
4 Atrazine, simazine, terbuthylazine, propazine, methomyl, benomyl, carbendazim, pirimicarb, propamocarb, iprodione, prothioconazole, DDE, NP, BPA, arsenic

Figure 3


a Epigenetic alterations
Aberrant methylation pattern
Hypomethylation
BPA
↑ PDE4D4
↑ AKT
↑ ERK1/2
EB
↑ AKT
↑ ERK1/2
DEHP
↑ PSCA
Histone modification
Genistein
Dichlorvos
Endosulfan
BaP
↑ DNMT1
↑ HDAC1
PCBs
↓ H3K4me3
BPA
↑ H3K4me3
↑ H3K9me3
↑ H3K27me3
↑ H4K20me3
↑ H3K9ac
Transgenerational effects
F2–F4 generations
Vinclozolin
↑ tumour frequency
↑ PCa-associated genes
b Immune system alterations
Early stages immune stimulation
BPA
TPT
TBT
↑ T cell maturation and proliferation
BPA
↑ T$_H$1 responses
Aldicarb
↑ CD8$^+$ T cells
NP
↑ IL-8
↑ IL-1β
BPA
DES
↑ Prostate inflammation
Advanced stages immune suppresion
Trichlorfon
Malathion
Fenitrothion
HCH
DDT
Impaired neutrophil chemotaxis and adesion
NP
Octhylphenol
↓ Macrophage chemokine expression
TBT
DBT
PCBs
Ziram
↓ NK cell activity
TCDD
Cadmium
HCB
PCBs
Dieldrin
DDT
↓ T cell maturation and proliferation
c NRs-dependent and -independent pathways
AR
TBT
TPT
↑ Proliferation
HBCD
↑ Cyclin D
↑ Cyclin E
NP
↓ Bax
↓ P27
↓ p21
BaP
↓ G0/G1 phase
↑ S phase populations
↑ Cyclin D1, MMP9, CYP1A1, CYP1B1, vimentin
BaP
Endosulfan
↓ E-cadherin
ER
NP
BPA
↑ Ki67
↑ Cyclin D
↑ Cyclin E
Cadmium
↓ P27
↓ p21
↑ Cyclin D1
↑ Cyclin B1
Others
Arsenic
↓ Toll-like receptor 3 anti-tumour pathway
Butyl benzyl phthalate
↓ miR-34a
d The role of adipose tissue
EDC-induced dysregulation
↑ Proliferation
↑ Migration
↑ Invasion
Prostate cells
Blood vessel
Other tissues
EDC release
PPAT
EDC-induced dysregulation
Altered PPAT secretome