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REVIEW ARTICLE

EDC-induced mechanisms of immunotoxicity: a systematic review

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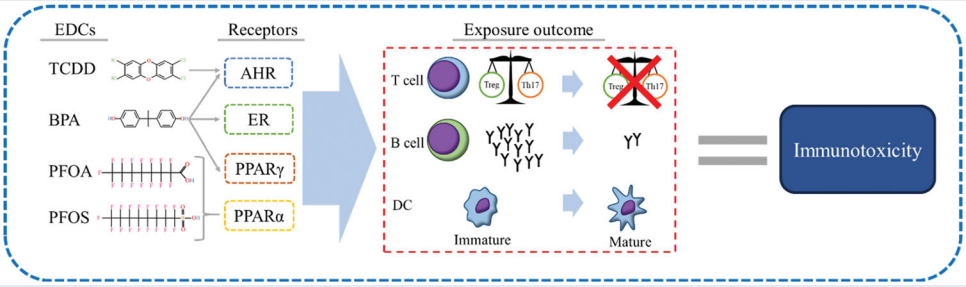
ABSTRACT

Endocrine-disrupting chemicals (EDCs) refer to a group of chemicals that cause adverse effects in human health, impairing hormone production and regulation, resulting in alteration of homeostasis, reproductive, and developmental, and immune system impairments. The immunotoxicity of EDCs involves many mechanisms altering gene expression that depend on the activation of nuclear receptors such as the aryl hydrocarbon receptor (AHR), the estrogen receptor (ER), and the peroxisome proliferator-activated receptor (PPAR), which also results in skin and intestinal disorders, microbiota alterations and inflammatory diseases. This systematic review aims to review different mechanisms of immunotoxicity and immunomodulation of T cells, focusing on T regulatory (Treg) and Th17 subsets, B cells, and dendritic cells (DCs) caused by specific EDCs such as 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), bisphenols (BPs) and polyfluoroalkyl substances (PFASs). To achieve this objective, a systematic study was conducted searching various databases including PubMed and Scopus to find *in-vitro*, *in-vivo*, and biomonitoring studies that examine EDC-dependent mechanisms of immunotoxicity. While doing the systematic review, we found species- and cell-specific outcomes and a translational gap between *in-vitro* and *in-vivo* experiments. Finally, an adverse outcome pathway (AOP) framework is proposed, which explains mechanistically toxicity endpoints emerging from different EDCs having similar key events and can help to improve our understanding of EDCs mechanisms of immunotoxicity. In conclusion, this review provides insights into the mechanisms of immunotoxicity mediated by EDCs and will help to improve human health risk assessment.

GRAPHICAL ABSTRACT



Overview of the mechanisms of immunotoxicity of EDCs for T, B, and Dendritic cells and the main outcomes of exposure that result in immunotoxicity: imbalance of Treg/Th17 lymphocyte populations; a decrease of antibodies production; an increase of DCs maturation.

Abbreviations: 3'IgHRR: 3'immunoglobulin heavy chain regulatory region; AHR: Aryl hydrocarbon receptor; AIP: AHR-interacting protein; AO: Adverse outcome; AOP: Adverse outcome pathway; AP-1: Activator protein 1; APC: antigen-presenting cell; ARNT: AHR nuclear translocator; Bach2: BTB Domain And CNC Homolog 2; BMDL: Benchmark dose lower confidence limit; BCL-6: B-cell lymphoma 6 protein; BCR: B-cell receptor; BFR: Brominated flame retardant; Blimp-1: B lymphocyte-induced maturation protein-1; BMDC: Bone marrow dendritic cells; BP: Bisphenol; BPA: Bisphenol A; BPAF: Bisphenol A-F; BPF: Bisphenol F; BPS: Bisphenol S; CD: Cluster of differentiation; CDKN1A: Cyclin Dependent Kinase Inhibitor 1A; CK1: Casein kinase 1; CYP: Cytochrome P450; DC: Dendritic cell; DDT: Dichlorodiphenyltrichloroethane; Dec602: Dechlorane 602; DNA: Deoxyribonucleic acid; EDC: Endocrine-disrupting chemicals; EFSA: European Food Safety Authority; EPA: Environmental Protection Agency; ES: Estrogen receptor; FICZ: 6-Formylindolo(3,2-b)carbazole; FoxP3: Forkhead box P3; FR: Flame retardant; GvH: Graft vs host; HSP90: 90 KDa heat shock protein; i.p.: Intraperitoneal; IDO: Indoleamine 2,3-Dioxygenase; IFNγ: Interferon gamma; Ig: Immunoglobulin; IgH: Immunoglobulin heavy chain; IgJ: Immunoglobulin J chain; Igκ: Immunoglobulin κ chain; IKK: IκB kinase; IL:

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Supplemental data for this article can be accessed here.

Interleukin; IL-1RA: Interleukin-2 receptor alfa chain; ITE: 2-(1′ H-indole-3′-carbonyl)-thiazole-4-carboxylic acid methyl ester; KE: Key event; LCK: Lymphocyte-specific protein tyrosine kinase; MHCII: Major histocompatibility complex type 2; MIE: Molecular initiating event; miRNA/miR: Micro RNA; MLN: Mesenteric lymph node; moDCs: Monocyte-derived dendritic cells; NEMO: NF-kappa-B essential modulator; NFκB: nuclear factor kappa-light-chain-enhancer of activated B cells; NOD: Non-obese diabetic; NQO-1: NAD(P)N:quinone oxidoreductase-1; NRF-2: Nuclear factor-erythroid 2-related factor-2; o.g.: Oral gavage; OPFR: Organophosphate flame retardant; OVA: ovalbumin; PD: Pharmacodynamic model; PAI2: plasminogen activator inhibitor-2; PBPK: Physiologically-based pharmacokinetic modeling; PFAS: Polyfluoroalkyl substances; PFC: Perfluorinated compound; PFOA: Perfluorooctanoic acid; PFOS: Perfluorooctanesulfonic acid; POD: Point of departure; PP: Peyer patch; PPAR: Peroxisome proliferator-activated receptor; PPRE: peroxisome proliferator response element; PTX: pertussis toxin; QIVIVE: Quantitative *in-vitro* to *in-vivo* extrapolation; QSAR: Quantitative structure-activity relationship; RB1: Retinoblastoma transcriptional corepressor 1; RNA: Ribonucleic acid; RORγδ: RAR-related orphan receptor gamma-delta; ROS: Reactive oxygen species; RXR: Retinoid X receptor; SHP-1: Src homology region 2 domain-containing phosphatase-1; STAT: Signal transducer and activator of transcription; TBBPA: Tetrabromobisphenol A; T-bet: T-box expressed in T cells; TCDD: 2,3,7,8-Tetrachlorodibenzo-p-dioxin; TCR: T-cell receptor; Teff: T effector cell/lymphocyte; TGF-β: Transforming growth factor beta; Th: T helper cell/lymphocyte; TLR: Toll-like receptor; TNF-α: Tumor necrosis factor alfa; TPHP: Triphenylphosphate; Tr1: Type 1 regulatory T cells; Treg: T regulatory cell/lymphocyte; WHO: World Health Organization; XRE: Xenobiotic response element

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1. Introduction

EDCs are defined by the Endocrine Society as exogenous chemicals or mixtures of chemicals that interfere with any aspect of hormone action (Gore et al. 2014). The WHO defines EDCs as chemicals that alter the functions of the endocrine system and cause adverse health effects in an intact organism and its progeny or populations. EDCs can be found in the environment and daily use products, including pesticides (i.e. DDT) children products, food contact materials (i.e. phthalates, BPA), textiles (i.e. PFCs as PFOS and PFOA), construction materials (i.e. FRs), and as a result of industrial processes (i.e. TCDD) (Kuo et al. 2012; Ju and Zouboulis 2016; WHO 2016; Martínez et al. 2018). People are exposed to these chemicals mainly by ingestion, inhalation, and dermal exposure, and they tend to bio-accumulate inside the body. EDCs can also be transferred from mother to child through placenta and lactation (Chalubinski and Kowalski 2006; Fonnum and Mariussen 2009; Schuhmacher et al. 2013, 2019). Specific EDCs have been reported to affect the endocrine, reproductive, neuronal, and immune systems (Kuo et al. 2012; Sharma et al. 2017). Furthermore, it has been reported that EDCs affect the innate and adaptive immunity through different mechanisms resulting, for instance, in the impairment of T cell differentiation process or production of immunoglobulins by B cells (Segura et al. 1999; Kuo et al. 2012; Gostner et al. 2015; Lee et al. 2017; Bansal et al. 2018; Gutiérrez-Vázquez and Quintana 2018; Nowak et al. 2019; Predieri et al. 2020).

A specific mechanism of immunomodulation and immunotoxicity is the activation of AHR by EDCs. (Holsapple et al. 1991; Blaylock et al. 1992; Malaisé et al. 2020; Rosenmai et al. 2021). AHR activation can lead to both an increase and a decrease of oxidative stress in a ligand-specific manner. For instance, the expression of CYP1A1 leading to ROS generation has been reported after AHR activation by TCDD (Durrin et al. 1987; Furman et al. 2009). On the contrary, other AHR ligands such as BPA can activate NRF-2 and antioxidative enzymes as NQO-1 resulting in protection from ROS-induced oxidative damage (Furue et al. 2014; Jang et al. 2020). Thus, EDCs metabolism can result in increased oxidative stress that may lead to DNA damage and cellular death or instead result in protection from ROS-induced oxidative damage (Chiba et al. 2011; Furue et al. 2014; Jang et al. 2020). In addition, AHR ligation has been linked with NFκB pathway activation or inhibition in a ligand- and cell-specific way (Simones and Shepherd 2011; Vogel et al. 2013; Phadnis-Moghe et al. 2015, 2016; Ehrlich et al. 2018; Gao et al. 2020). Furthermore, other nuclear receptors such as the ER and the PPAR have also been linked to immunotoxicity by EDCs

(Wang, Cao, et al. 2014; Qiu et al. 2018). Besides its role in controlling reproductive functions, ER can modulate the immune system by affecting adaptive cells (T and B cells) and innate cells (DCs, monocytes, macrophages, etc.). For instance, ER affects the expression of several key transcription factors controlling immune cell differentiation and function, such as T-bet in Th1 cells and SHP-1 in B cells (Khan and Ansar Ahmed 2015). In addition, PPARα and PPARγ can also affect the immune system mainly by interacting with intracellular factors as NFκB and STATs (Zhang and Young 2002).

Other factors like cytokines, endogenous and microbiota-derived ligands, tissue-specific signals like cell-to-cell interactions, and the dose and duration of AHR activation have been proposed to impact EDCs induced immunotoxicity. For AHR, the experimental model used is also important, and the different AHR affinities between species have to be taken into account (Moriguchi et al. 2003; Gagliani et al. 2015; Dant et al. 2017; Ehrlich et al. 2018). The complex interaction of all these factors makes it a challenging task to translate knowledge from *in-vitro* to *in-vivo* since it is difficult to mimic the natural microenvironment of the immune cells (Duarte et al. 2013; Singh et al. 2020). In order to better understand chemical exposure outcomes, AOP models can be used. AOPs are models that identify the sequence of molecular and cellular events produced after chemical exposure (Vinken 2013; NTP 2021). The OECD has provided a conceptual framework for testing and assessment of EDCs that can be used for immunotoxicity (OECD 2012; Kumar et al. 2020), consisting of different levels that include in-silico predictions, *in-vitro* and *in-vivo* assays for specific endocrine mechanisms and pathways in both mammal and non-mammal models and information about adverse effects.

On the other hand, IVIVE allows the results of *in-vitro* experimentation to be used to predict *in-vivo* dose-response relationships (Sewell et al. 2017). Further, PBPK models use toxicokinetic information to translate chemical exposure into an internal dose (tissues as well blood and urine) and allow extrapolation between different species and routes of exposure (Caldwell et al. 2012; Fairman et al. 2020; Kumar et al. 2020). It is also common to use PBPK/PD models that include pharmacodynamic information, which can explain internal exposure and the mechanism of action of a chemical (Diack and Bois 2005; Mumtaz et al. 2012).

The objective of this review is to decipher the different mechanisms of chemical-induced immunotoxicity by conducting a systematic study for selected EDCs (Dioxins, PFASs, BPs, and FRs). The focus will be the role of AHR, PPAR, and ER causing genetic modifications in a specific group of immune cells (DCs, T, and B cells), resulting in cellular and molecular changes. Finally, an AOP framework for developing AOP networks will be proposed, enhancing our mechanistic understanding of how EDCs affect the immune system, and improving the risk assessment.

2. Methods

2.1. Data search

A systematic approach was used for searching databases Scopus and PubMed with different keywords (Supplementary Table 1). Different search strings were selected to identify all the relevant publications for a specific group of chemicals. Research articles from 2005 to 2020 were included in this review. This timespan was chosen to include the latest findings and limit the number of articles. Review articles and duplicated studies were filtered to further refine our article selection.

2.2. Chemical exposure

Selected chemicals for this systematic review are well-known chemicals like TCDD, PFAS, BPA and its alternatives (i.e. BPS, BPF, BPAF, etc.) and some emerging toxicants like FRs. These compounds are endocrine disruptors with immunotoxic properties, and a wide range of health effects have been found in the last few years (Kuo et al. 2012; Ju and Zouboulis 2016; WHO 2016; Sharma et al. 2017; Martínez et al. 2018).

2.3. Inclusion criteria

We included papers according to the following criteria: biomonitoring data, *in-vitro* or animal models, without restriction based on age or sex. *In-vitro* models: myeloid- and lymphoid-derived cells (e.g. DCs, T and B lymphocytes) and studies performed on immunogenic organs (e.g. bone marrow, thymus). *In-vivo* models: mice, rat, and zebrafish. Biomonitoring: human.

2.4. Exclusion criteria

We did not consider non-original articles like reviews, meta-analyses, meeting abstracts, and duplicated articles. Papers in which no toxics were used or that did not focus on the AHR, ER, or PPAR mechanistic pathways were also discarded. For the "AHR mechanistic pathway related to T Cells," section we only considered those including Tregs or Th17 studies for being the T cells that express the highest levels of AHR (Lamas et al. 2018).

2.5. Publications included

Our search identified a total of 231 articles, of which 56 were included in the systematic study. For AHR, 48 from 56 articles were taken for the review: 23 articles about T cells, 13 of DCs, and 12 of B cells. For ER, 3 from 56 articles were included: 2 articles about T cells (one also about DCs) and 1 about B cells. For PPAR, 5 from 56 papers were used for the study: 3 articles about T cells and 2 about B cells. Figure 1 and Table 1 summarize the systematic search and publication included with the list of the keywords used for the systematic search.

3. Results

3.1. AHR mechanistic pathways

AHR is a nuclear receptor present in the cytosol in complex with the HSP90, the AIP, the co-chaperone p23, and the c-SRC protein kinase, which maintain AHR in an inactive basal

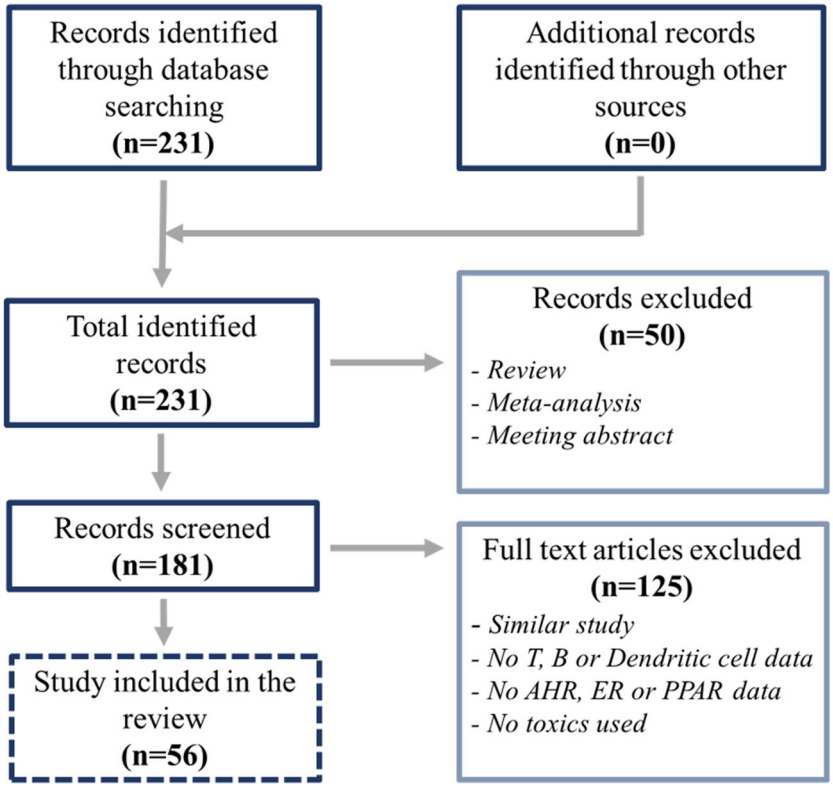

Figure 1. Diagram summarizing the systematic search. It includes the total articles identified, the exclusion criteria and the number of final articles included in the review.

Table 1. list of the keywords used for the systematic search including the number of papers found with each search string.

Search keywords: Scopus and PubMed	Paper count
TCDD + Immune OR Immunity OR Immunotoxicity + AHR	188
Flame-retardant + Immune OR Immunity OR Immunotoxicity + AHR	4
BPA + Treg	9
Flame-retardant + T-regulatory-cells	1
ER + Bisphenol + Immune OR Immunity OR Immunotoxicity	19
PPAR + PFOS + Immune OR Immunity OR Immunotoxicity	10

state (Perdew 1988; Nair et al. 1996; Carver and Bradfield 1997; Dong et al. 2011). After ligand interaction, AIP is released from the complex and conformational changes occur, resulting in AHR translocation to the nucleus (Ikuta et al. 1998; Pollenz and Barbour 2000). Once in the nucleus HSP90 dissociates and the ARNT binds AHR forming the AHR/ARNT complex (Soshilov and Denison 2011; Tsuji et al. 2014). Interestingly, this complex can exert oxidative or anti-oxidative properties in a ligand-specific manner. However, the exact mechanism by which the AHR ligand affects the AHR/ARNT system in different ways remains unclear and needs further investigation. Since AHR is present in many different cell types, and its expression is exceptionally high in some immune cells like DCs, T and B lymphocytes, the activation of AHR by EDCs in these cells could explain the observed immunomodulation. For instance, T-cell differentiation and function can be activated by AHR directly, while indirectly by APCs like DCs (Gutiérrez-Vázquez and Quintana 2018; Trikha and Lee 2020).

In addition, AHR activation has been linked with the NFκB family, which is composed of the transcription factors p50, p52, RelA (or p65), c-Rel, and RelB that share a common binding/dimerization N-terminal domain, which allows the modulation of gene expression by binding to κB sequences in DNA. RelA, RelB, and c-Rel also include C-terminal transcription activation domains. NFκB complexes consist in p50/52 associated with RelA, RelB, or c-Rel and with inhibitory IκB proteins that keep the complex in an inactive state in the cytoplasm. The activation of the NFκB complex can occur by different canonical or non-canonical signals like TLR and CD40 ligation. After activation, IκB is degraded by proteasome followed by phosphorylation by IKK allowing the complex to enter the nucleus. IKK is a complex composed of the kinases IKKα and IKKβ, and the regulatory scaffold protein NEMO. Thus, the activation of p50/RelA and p50/c-Rel occur by the canonical pathway in which IKKβ and NEMO are required, while the activation of p52/RelB is produced through the non-canonical pathway with IKKα alone. Thus, AHR can interact with members of the NFκB family-like RelB and RelA, leading to different outcomes in a ligand- and cell-specific way. For instance, AHR activation by TCDD has been linked with inhibition and activation of NFκB in T cells and DCs respectively, while BPA exposure is related to activation of NFκB in T cells (Vogel et al. 2013; Phadnis-Moghe et al. 2015; Gao et al. 2020).

3.1.1. AHR mechanistic pathway in T cells

This section focuses on the role of AHR activation by EDCs in the activity of T cells, with an emphasis on the Treg and Th17 lymphocyte subsets. Out of 23 articles identified, 19 included TCDD as AHR ligand and 4 included BPs. We could

not find any article associating PFASs and FRs with AHR and Tregs/Th17.

TCDD was initially found to modulate the immune response, and later studies showed the induction of T CD4$^+$ cells with a regulatory phenotype that caused immunosuppression. A concurrent suppression of Th17 cells was also reported after TCDD exposure (Kerkvliet et al. 1990; Quintana et al. 2008; Singh et al. 2011). However, our analysis reveals that 14 from 19 articles state that TCDD exposure results in the increase of Treg and a decrease of Th17 populations (Funatake et al. 2005; Marshall et al. 2008; Vogel et al. 2008; Kerkvliet et al. 2009; Simones and Shepherd 2011; Veiga-Parga et al. 2011; Benson and Shepherd 2011a; Pauly et al. 2012; Schulz et al. 2012; Rohlman et al. 2013; Yang et al. 2016; Ehrlich et al. 2018; Al-Ghezi et al. 2019; Miljkovic et al. 2019), while 5 conclude the contrary (Chmill et al. 2010; Brembilla et al. 2011; Duarte et al. 2013; Liu et al. 2013; Pang et al. 2019). The source of this disagreement may be the different experimental conditions used in each case, such as *in-vitro* or *in-vivo* systems, or different models, which are explained below in detail.

Treg are T lymphocytes known to suppress T effector responses, and their differentiation is regulated by the transcription factor FoxP3. These cells can be classified into two major subsets, the Treg FoxP3+ and the Il-10 producing Tr1 cells, which transiently express FoxP3 but are characterized as FoxP3− (Groux et al. 1997; Fontenot et al. 2017). Their counterparts are the Th17 cells, which are characterized by the production of IL-17 and the expression of the transcription factor RORγδ (Ivanov et al. 2006). Both Tregs and Th17 cells express high levels of AHR and different AHR-dependent mechanisms have been proposed to influence their differentiation, as shown in Figure 2 (Gutiérrez-Vázquez and Quintana 2018). Accordingly, TCDD exposure in mice has been linked with an increase of FoxP3 and a decrease of IL-17 expression, which is related to the induction of Treg and inhibition of Th17 differentiation processes (Kerkvliet et al. 2009; Benson and Shepherd 2011a, 2011b; Schulz et al. 2012; Al-Ghezi et al. 2019). In addition, it has been reported that AHR affects the expression of specific miRNAs that can influence the balance between Treg and Th17. For that matter, TCDD exposure results in downregulation of miR-1224-5p and upregulation of miR-3082-5p, resulting in increased and decreased expression of FoxP3 and IL-17, respectively (Figure 2(B)) (Al-Ghezi et al. 2019).

Cytokines are another major factor controlling the T cell differentiation process and their expression has been shown to be altered by the activation of AHR by TCDD (Figure 2(A)). For instance, TCDD exposure is related to the increased expression of the transcription repressor Blimp-1, resulting in a downregulation of IL-2 and IFNγ, and an upregulation of IL-10 (Martins et al. 2006; Marshall et al. 2008). IL-2 is implied in the growth, survivability, and functions of T cells (Liao et al. 2011) and is also essential for the generation of FoxP3+ Tregs and Tr1 cells (Funatake et al. 2005). A lack of expression of IL-2 has been reported 48 h after TCDD exposure (Marshall et al. 2008; Yang et al. 2016), which may be related to the upregulation of CD25, also known as the IL-2RA (Figure 2(A)). This membrane receptor is especially abundant on Tregs and it is responsible for the depletion of IL-2, which constitutes one of the many immunosuppressive mechanisms of these cells (Triplett et al. 2012). In addition, IL-12 through the IL-12RA signaling pathway results in chromatin remodeling of the *cd25* gene. TCDD induces

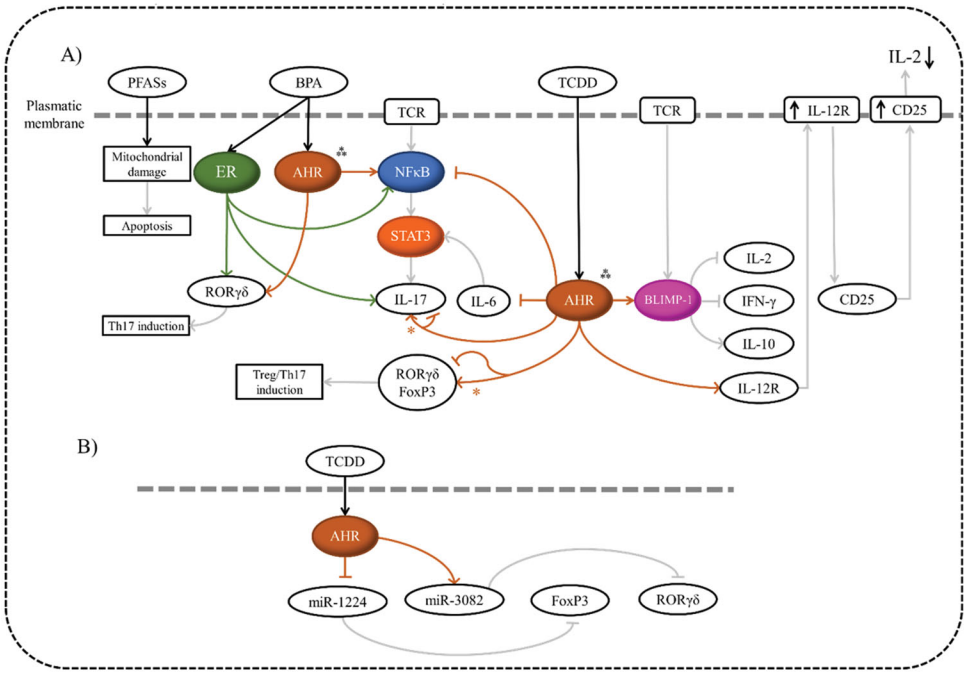

Figure 2. schematic representation of EDCs-induced mechanisms of immunotoxicity in T cells. Gray arrows represent the normal cellular pathways; colored arrows show how each receptor affects the normal pathways. (A) Mechanistic pathways of AHR, ER and PPAR and their respective ligands. "$*$": Both upregulation and downregulation of IL-17, RORγδ and FoxP3 has been reported after AHR activation by TCDD. "$\overset{*}{**}$": The different AHR molecules in the figure are the same and not isoforms. For simplicity they have been drawn at different points of the scheme. (B) Schematic representation of epigenetic regulation of Foxp3 and RORγδ after TCDD exposure through miRNA (taken from section (A)).

upregulation of IL-12RA, thereby resulting in the upregulation of CD25 (Marshall et al. 2008). In addition, TCDD exposure has been linked with the downregulation of NFκB, which is related to reduced activity of STAT-3 and increased levels of IL-10 and TGF-β (Marshall et al. 2008; Gerondakis et al. 2014; Ehrlich et al. 2018). Thus, TCDD exposure leads to a modification of the cytokine profile, resulting in a decrease in the pro-inflammatory cytokines IL-17, IL-6, and IFNγ and an increase in the anti-inflammatory cytokines IL-10 and TGF-β, which is also related to a dysregulation of Treg/Th17 populations (Marshall et al. 2008; Benson and Shepherd 2011b; Yang et al. 2016; Al-Ghezi et al. 2019). Conversely, some authors state that the increase in FoxP3+ Tregs is caused by increased apoptosis of the other T cell subsets rather than by a growth in the absolute number of Tregs (Veiga-Parga et al. 2011; Duarte et al. 2013; Miljkovic et al. 2019).

Despite many pieces of evidence support Treg induction after TCDD exposure, some authors instead have shown an increase of Th17 levels (Chmill et al. 2010; Brembilla et al. 2011; Duarte et al. 2013). For instance, Duarte et al. observed an increase in Th17 cells following *in-vitro* TCDD exposure (Duarte et al. 2013), while *in-vivo* exposure is usually related to suppressing this cell population. TCDD was also found to be species-specific since human exposure seems to have different outcomes as compared to mice (Chmill et al. 2010; Brembilla et al. 2011; Duarte et al. 2013). Brembilla et al. reported an accidental case study of a patient who survived to an extremely high dose of TCDD showed normal levels of Tregs but increased levels of a T cell population IL-22 producer after 4 years of TCDD exposure (Brembilla et al. 2011). Further, the type of *in-vitro* and *in-vivo* model influences the outcomes of chemical exposure (Funatake et al. 2005; Marshall et al. 2008; Kerkvliet et al. 2009; Rohlman et al. 2013). For instance, AHR activation by TCDD in a NOD mouse results in FoxP3 expression, while in an allogeneic GvH mouse FoxP3 is not induced, but Tr1 cells are produced instead (Kerkvliet et al. 2009). On the other hand, it has been shown that TCDD causes a reduction in both Teff and Tregs *in-vitro* when isolated mice CD4+ T cells are used. However, Pang et al. using a more complex *in-vitro* system composed of an isolated mixture of mice splenocytes reported an increased expression of FoxP3 following TCDD exposure (Pang et al. 2019), which emphasize the importance of the microenvironment in T cell differentiation.

On the other hand, our search found 2 papers supporting the suppression of Treg populations and induction of Th17 cells after BPs exposure in an AHR-dependent manner (Gao et al. 2020; Malaisé et al. 2020). The further search string was widened to include 2 more articles related to NFκB activation by BPA (Dong et al. 2020; Wang, Cao, et al. 2020). In fact, it has been reported that AHR activation by BPA resulted in downregulation of FoxP3 and upregulation of RORγδ and into the induction of IL-17 and TNF-α and inhibition of IFN-γ (Figure 2(A)) (Gao et al. 2020). In addition, *in-vitro* studies showed that exposure to low concentrations of BPA and BPF but not BPS significantly increases IL-17 production in T cells isolated from mouse spleen, supporting the induction of Th17 cells by BPs. However, all these BPs, BPS included, used at those concentrations in mouse cells isolated from the gut resulted in an increase of IL-17 and IL-22 levels (Malaisé et al. 2020). Conversely, no modification in IL-17 or IL-22 production has been reported in isolated human T cells exposed to BPA, BPS, or BPF at low concentrations compared to mice. Interestingly, it was observed that exposure to very high concentrations of the three BPs resulted in decreased production of those cytokines both in human and mouse T cells without reducing T cell viability (Malaisé et al. 2020). Moreover, it has been reported that BPA acts through activation of NFκB and STAT3 (Figure 2(A)), which is known to be an essential transcription factor for Th17 differentiation and Treg inhibition. Increased levels of IL-17 and decreased levels of IL-10 and TGF-β have been reported after BPA exposure *in-vivo* in an NFκB-dependent way (Dong et al. 2020; Wang, Cao, et al. 2020). Although some differences between species and *in-vitro* or *in-vivo* conditions have been noticed, BPs induce Th17 cells at low concentrations. While for TCDD, there is an induction of Treg *in-vivo* and an induction of Th17 *in-vitro* (detailed in the discussion section).

3.1.2. AHR mechanistic pathway in dendritic cells

This section focuses on the role of AHR activation by EDCs in the activity of DCs. Our search identified 11 articles, including TCDD as AHR ligand (Kinoshita et al. 2006; Lee et al. 2007; Vogel et al. 2008, 2014, 2013; Chmill et al. 2010; Jin et al. 2010; Simones and Shepherd 2011; Rohlman et al. 2013; Kado et al. 2017; Beamer et al. 2020), 2 for BPs (Bankoti et al. 2010; Švajger et al. 2016; She and Liu 2020) and none for PFAS or FRs.

DCs are professional APCs that have a central role in the regulation of the immune tolerance and in the T cell function and differentiation (Gutiérrez-Vázquez and Quintana 2018). DCs exist as steady-state or immature DCs and as inflammatory or mature DCs. Each differentiation state is characterized by the expression of a different set of biomarkers and the production of different cytokines. For instance, immature DCs are $MHCII^{low}$, $CD80/86^{low}$, IL-12^{-} and IL-10^{-}, while mature DCs are $MHCII^{high}$, $CD80/86^{high}$, IL-12^{+} IL-10^{-}. TCDD has been shown to have different effects on each DC population (Lee et al. 2007; Simones and Shepherd 2011). The AHR-dependent mechanisms of immunotoxicity on DCs are shown in Figure 3. *In-vitro* experiments have revealed that TCDD exposure of mature mouse BMDCs results in reduced levels of the integrins CD11c and CD54 leading to suboptimal T cell activation. In contrast, in immature BMDCs, BMDCs CD54 is increased, which could enhance T cell adhesion. There is an increase in the MHCII and the costimulatory molecules CD80/CD86 and CD40 *in-vitro* in both mature and immature DCs, which has been linked respectively with an increased T cell activation and with inhibition of T cell resulting in induction or Tregs (Lee et al. 2007; Bankoti et al. 2010; Jin et al. 2010; Simones and Shepherd 2011). In addition, suppression of DC-CK1 has been reported following TCDD exposure both in immature and mature BMDCs in humans and mice, resulting in an impaired interaction with T $CD4^{+}$ naïve cells (Vogel et al. 2008, 2013). On the other hand, mature mouse BMDCs exposed to TCDD increased the expression of IL-6 and TNF-α, reduced IL-12 but did not affect IL-10 levels, while in

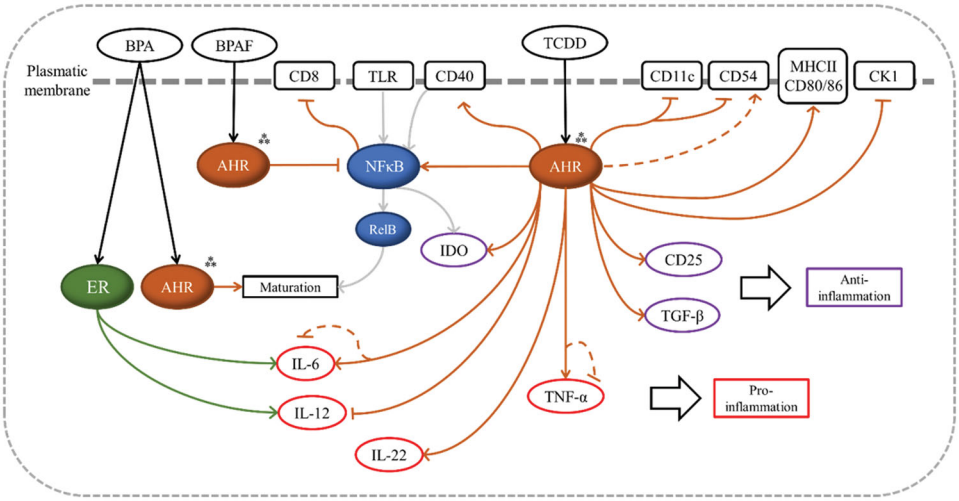

Figure 3. Schematic representation of EDCs-induced mechanisms of immunotoxicity in DCs. Gray arrows represent the normal cellular pathways; colored arrows show how each receptor affects the normal pathways. Discontinuous arrows indicate immature DCs, while continuous arrows indicate mature DCs. The absence of a discontinuous arrow means that there are no differences between mature and immature DCs. Factors labeled in red are related to pro-inflammation, while factors labeled in purple are related to anti-inflammation. "⁂": The different AHR molecules in the figure are the same and not isoforms. For simplicity, they have been drawn at different points of the scheme.

immature BMDCs, the exposure results in a decreased level of all these cytokines, suggesting that TCDD disrupts DC maturation (Bankoti et al. 2010; Simones and Shepherd 2011). Interestingly, an increased expression in regulatory genes was reported, such as TGF-β, IDO, and CD25 in both populations after TCDD exposure, linked with the induction of Tregs (Vogel et al. 2008; Bankoti et al. 2010; Chmill et al. 2010; Simones and Shepherd 2011; Rohlman et al. 2013). An increase in IL-22 levels was reported with both immature and mature BMDCs after TCDD, required to maintain mucosal immunity (Vogel et al. 2013). Similar results were also reported by Kado et al. using mature human moDCs, proving that TCDD exposure resulted in reduced IL-12 and increased IL-22 production (Kado et al. 2017). Other AHR ligands like FICZ and ITE resulted in alterations in BMDCs similar to TCDD (Bankoti et al. 2010). Conversely, *in-vivo* experiments showed no changes in $CD11c^+$ DCs in PPs, MLN, or spleen of mice orally exposed to TCDD (Kinoshita et al. 2006), and ex-vivo TCDD-treated BMDCs failed to suppress T cell responses *in-vivo* (Simones and Shepherd 2011).

The transition from immature to mature DCs primarily occurs through TLR ligation and activation of the NFκB pathway (Simones and Shepherd 2011). In addition, a direct interaction between AHR and the NFκB family members RelA and RelB has been demonstrated and three NFκB binding sites on the promoter sequence of the human AHR gene have been reported (Lee et al. 2007; Chmill et al. 2010; Simones and Shepherd 2011; Vogel et al. 2014; Kado et al. 2017). RelB is the factor that has been associated with DC differentiation and function. Thus, BMDCs maturation by TCDD is related to increased levels and DNA binding of RelB and direct interaction between RelB and AHR (Figure 3) (Vogel et al. 2013). TCDD exposure has also been linked with increased activation of RelB in immature BMDCs, while in mature BMDCs, the outcome seems to be dependent on the TLR ligand used for stimulation (Bankoti et al. 2010; Simones and Shepherd 2011). Recently, it has been demonstrated that the non-canonical NFκB pathway is also critical for the induction of IDO through ligation of CD40, for instance. Therefore it is not unlikely that TCDD-mediated induction of IDO not only requires activation of AHR but also involves RelB (Vogel et al. 2008). It has also been reported a DC population shift from $CD8a^+$ to $CD8a^-$ DCs in mouse thymus after TCDD exposure in a RelB-dependent manner. $CD8a^-$ DCs have been suggested as inducers of Tregs due to their ability to cross-present self-antigens to developing thymocytes (Beamer et al. 2020).

On the other hand, we identified 2 articles reporting that high concentrations of BPs can also affect DCs maturation through AHR activation (Švajger et al. 2016; She and Liu 2020). For instance, it has been shown in humans that BPA exposure results in the induction of moDCs maturation and activation (She and Liu 2020). Exposure of human DCs to high concentrations of BPA and subsequent co-culture with T $CD4^+$ cells has been linked to the induction of a Th17 population with increased production of IL-17 and IL-22 (She and Liu 2020). However, other studies have shown that BPA and BPF have little effect on the maturation of these DCs but BPAF exposure at similar concentration resulted in a significant reduction of RelA and ERK activation in an AHR-dependent way, leading to the inhibition or moDCs maturation (Figure 3) (Švajger et al. 2016). Overall, AHR activation in DCs is related to an increased maturation process but results in regulatory or pro-inflammatory DCs depending on the chemical and biological complexity. *In-vivo*, there is an interplay between T cells and DCs affecting the differentiation process (Kadowaki 2007; Eisenbarth 2019). This could explain why TCDD exposure *in-vivo* is causing Treg induction while exposure *in-vitro* leads to Th17 induction instead. However, this observation does not explain why BPs have the same impact in T cell differentiation both *in-vitro* and *in-vivo* (explained in the discussion section).

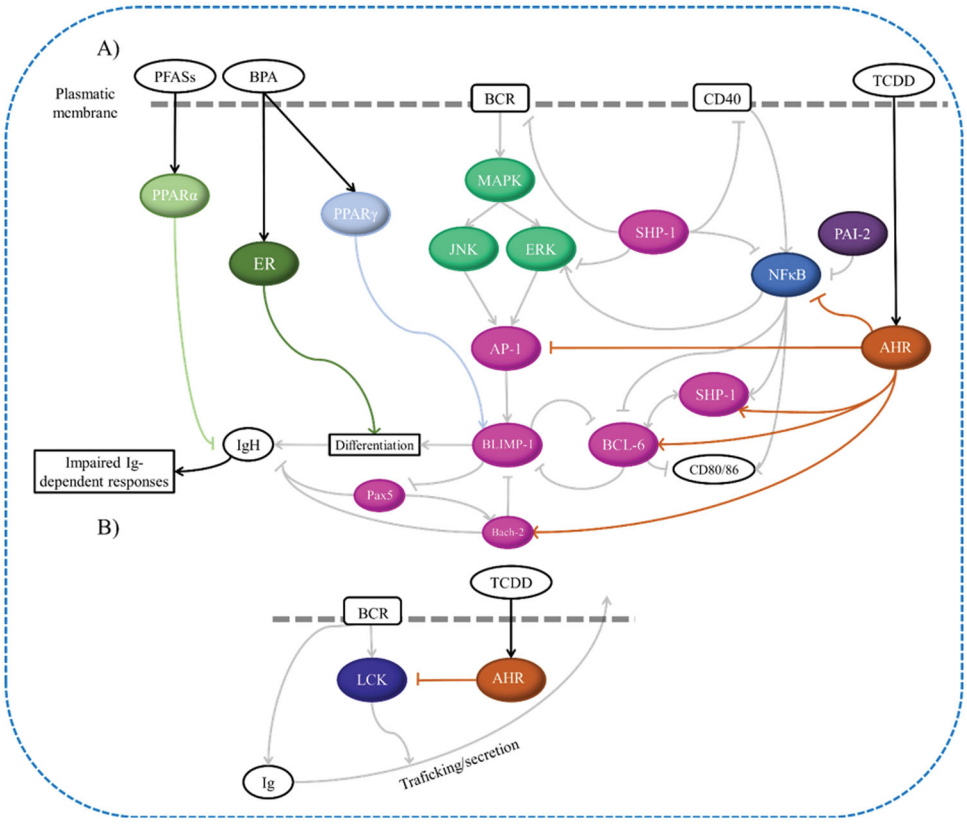

Figure 4. Schematic representation of EDCs-induced mechanisms of immunotoxicity in B cells. Gray arrows represent the normal cellular pathways; colored arrows show how each receptor affects the normal pathways. (A) EDCs mechanistic pathways for mice B cells. Exposure to EDCs in mice affects B cell differentiation to plasmatic cell impairing Ig production. (B) TCDD mechanistic pathways for human B cells. Exposure to TCDD in humans does not affect B cell differentiation but the trafficking/secretion of Igs. For simplicity, only the mechanisms of action affecting B cell differentiation/Ig production have been represented.

3.1.3. AHR mechanistic pathway in B cells

This section focuses on the role of AHR activation by EDCs in the activity of B cells. Our search identified 12 articles, including TCDD as AHR ligand and none for BPA, FRs, and PFASs.

B lymphocytes are specialized cells of adaptive immunity that are characterized by the production and secretion of Igs or antibodies (Lebien and Tedder 2008). TCDD has been found to impair B cell activation and function, mainly affecting IgM levels, by different mechanisms related to AHR activity (Nagai et al. 2005; Kinoshita et al. 2006; Henseler et al. 2009; Lu et al. 2010; Zhang et al. 2013; Phadnis-Moghe et al. 2015, 2016; Kovalova et al. 2017; Dornbos et al. 2016, 2018; Zhou, Henriquez, et al. 2018; Zhou, Zhang, et al. 2018). In B cells, TCDD has been reported to induce CYP1A1 (Nagai et al. 2005) and to impair the expression of different intracellular proteins like the SHP-1, the BCL-6, the Blimp-1, the LCK, and the PAI2, as shown in Figure 4 (Zhang et al. 2013; Phadnis-Moghe et al. 2015, 2016; Dornbos et al. 2018; Zhou, Zhang, et al. 2018). For instance, increased levels of the repressor SHP-1 following TCDD exposure have been reported (Figure 4(A)), resulting in the inhibition of Lyn, Syk, and Btk kinases downstream of BCR, thereby keeping BCR activation at a minimum. This leads to a decrease in ERK activation, which prevents BCL-6 phosphorylation and degradation. Moreover, SHP-1 can inhibit AKT, which is essential for cell survival as well as STAT3/5 (Andjelic et al. 2000; Calò et al. 2003; Reth and Brummer 2004; Han et al. 2006; Lu et al. 2011; Mittal et al. 2011; Phadnis-Moghe et al. 2015, 2016). On the other hand, TCDD can directly induce BCL-6 (Figure 4(A)), which is related to the repression of CD80/86, CD69 and Blimp-1. In addition, Blimp-1 can inhibit BLC-6 expression, so they are mutually exclusive. (Phadnis-Moghe et al. 2015). The PAI2, or Serpinb2 in mice, is upregulated by TCDD and has been proposed to act as a protective mechanism against TCDD-induced immunotoxicity on B cells. For that matter, PAI2 upregulates RB1 leading to an increased B cell survival. In addition, PAI2 can bind CDKN1A resulting in the progression to the G1 phase of replication (Zhang et al. 1994; LaBaer et al. 1997; Dornbos et al. 2018). Furthermore, Blimp-1 is the principal transcription factor that allows differentiation from B cells to plasmatic cells. In mouse B cells, it has been reported that TCDD exposure results in a downregulation of Blimp-1 mainly through the inhibition of the positive regulator AP-1 and the upregulation of the repressor Bach2 (Figure 4(A)), leading to an impaired differentiation toward plasmatic cell and therefore to an impairment in IgM production with a decrease of the IgH, IgJ and Igκ chains and with the inhibition of the 3'IgHRR (Henseler et al. 2009). Zhang et al. also mentioned that B cells that make it into plasma cells have their IgM levels uncompromised by TCDD exposure (Schneider et al. 2009; De Abrew et al. 2010, 2011; Zhang et al. 2013; Zhou, Henriquez, et al. 2018). Moreover, IgG and IgA levels are also affected after TCDD exposure (Kinoshita et al. 2006; Zhou, Henriquez, et al. 2018). Interestingly, a time-dependent mechanism of action of TCDD has been identified in B cells derived from mice. Accordingly, TCDD

can modulate gene expression if the exposure occurs before or during B cell activation. This modulation is maintained for 24 h, but not further. (Zhang et al. 2013; Phadnis-Moghe et al. 2016). Such a study provides better insights into the kinetic perspective, which can improve pharmacokinetic models such as PBPK.

Conversely, it has been reported that the expression of Blimp-1 in human B cells is unaffected by TCDD. Thus the reduced levels of IgM in humans are likely due to an impairment in the Ig pathway rather than a differentiation issue (Lu et al. 2011; Zhou, Henriquez, et al. 2018). In fact, it has been shown that in human cells, TCDD does not affect the synthesis nor assembly of IgM but its secretion (Zhou, Henriquez, et al. 2018). Related to this, LCK is a kinase that plays a major role in vesicular transport and cytoskeleton remodeling in T cells. It is also present in human B cells, and an increased expression following TCDD exposure has been reported (Figure 4(B)). Thus, LCK has been proposed as a modulator of Ig intracellular trafficking/secretion in human B cells. Interestingly, LCK seems not to be directly regulated by the AHR at transcriptional levels but by indirect mechanisms (Kovalova et al. 2017; Zhou, Zhang, et al. 2018). Furthermore, Zhou et al. showed that an excessive inhibition of LCK also resulted in impairment of IgM secretion, suggesting that an optimal level of LCK activity is required (Zhou, Zhang, et al. 2018). On the other hand, $CD5^+$ human B cells (B1 cells in mouse), which are the major IgM-producer cells, are considered principally responsible for the TCDD-dependent effect on Ig responses, proposing that different B cell populations may have different sensitivity to TCDD treatment (Zhou, Zhang, et al. 2018).

The NFκB pathway has also been linked with AHR in B cells (Figure 4(A)). It is primarily induced by CD40 ligation, resulting in the inhibition of BCL-6 and the induction of CD80/86, CD69, ERK, and SHP-1. Furthermore, the AHR activation by TCDD results in the inhibition of NFκB directly and indirectly by SHP-1, which explains the observed outcomes. Although the role of PAI2 seems to be protective against TCDD-dependent mechanisms of immunotoxicity, it has also been presented as a negative regulator of NFκB, therefore contributing to the TCDD-mediated impairment of IgM production (Phadnis-Moghe et al. 2015, 2016; Dornbos et al. 2018).

Furthermore, more evidence has been reported on the different regulations of B cells in humans and mice. In fact, a species-specific regulation by TCDD in B cells has been proposed. For instance, after TCDD exposure, the most upregulated gene in mice was the Serpinb2, while in humans genes related to signal transduction were the most upregulated. However, even with these differences between models, the TCDD exposure results in comparable reduced IgM levels in both cases (although the baseline IgM levels were not the same, the difference between the control and treatment groups was comparable for each species) (Kovalova et al. 2016, 2017). In addition, the interindividual variability in the human population is related to some individuals exhibiting no suppression of the IgM responses, even at high TCDD concentrations (Lu et al. 2010; Dornbos et al. 2016).

3.2. Other mechanistic pathways: estrogen and PPAR receptors

The estrogen receptors α and β are members of the nuclear receptor super family encoded by the ESR1 and ESR2 genes, respectively. They can be found as homodimers (αα or ββ) or as heterodimers (αβ) in the cytoplasm. Upon ligation, ER dimers are stabilized and can be translocated to the nucleus, where they can bind directly to DNA through estrogen response elements (EREs) or indirectly by forming complexes with other transcription factors such NFκB or AP-1. Interestingly, this interaction can have different outcomes since ER activation has been linked both with increased expression and inhibition of NFκB. ERs are widely expressed in different tissues such kidney and brain and in immune cells (Couse et al. 1997; Cunningham and Gilkeson 2011; Kovats 2015; Qiu et al. 2018).

On the other hand, PPAR family members are ligand-activated transcription factors composed of PPARα, PPARβ/δ, and PPARγ that are unequally distributed among the different cellular types. For instance, PPARα is commonly found in hepatocytes, while PPARγ is mainly expressed in adipose tissues. In addition, the expression of PPARγ has been reported in T and B cells and in dendritic cells. Upon ligation, PPAR can exist as a heterodimer formed with the RXR, after which the PPAR/RXR complex migrates to the nucleus and regulates gene expression by binding to PPRE sequences. PPAR activation mainly results in the regulation of energy homeostasis and control of inflammatory processes (Michalik et al. 2006). Besides affecting the immune response through gene regulation, PPAR can also interact with other signaling routes, such as NFκB. For instance, PPARγ activation can inhibit the binding of the NFκB molecules to their target genes resulting in immunomodulation.

3.2.1. ER and PPAR mechanistic pathways in T and B lymphocytes and DCs

This section focuses on the role of the activation of other cellular receptors such ER and PPAR by EDCs on T, B, and dendritic cells. Our search identified 3 articles for BPA and ER or PPAR (Qiu et al. 2018; Avila et al. 2019; Wang, She, et al. 2020) and 5 for PFASs and PPAR (Peden-Adams et al. 2008; Qazi et al. 2009; Corsini et al. 2011; Wang, Wang, Li, et al. 2014; Midgett et al. 2015). No articles for TCDD and FRs as ER or PPAR ligands were found.

Wang et al. reported that BPA exposure could alter the morphogenesis and reduce the antigen-presenting ability of human moDCs through ER activation resulting in an impaired T cell activation. However, it has also been reported a small induction of T $CD4^+$ cells following BPA exposure. In addition, increased secretion of IL-6 and IL-12 by moDCs has been shown (Figure 3), resulting in disturbed differentiation of T cell subsets. Specifically, BPA exposure resulted in increased IL-17 and RORγδ but not IL-10 and FoxP3 expression supporting a role of ER in Th17 induction by BPA (Figure 2(A)) (Wang, She, et al. 2020). Additionally, experiments conducted in zebrafish revealed that BPA, BPF, and BPS exposure induced the expression of ER and NFκB

resulting in increased expression of several cytokines such as IL-10, IL-1β, TNF-α, IL-6, and IL-12 (Qiu et al. 2018). Moreover, ER ligation by BPA has been proposed as a mechanism affecting B cell differentiation to plasma cells (Figure 4(A)) (Avila et al. 2019). Furthermore, Avila et al. demonstrated that prenatal exposure to BPA affects B cell activity through PPAR. BPA can bind PPARγ in B cells, which is related to induction of Blimp-1, resulting in inhibition of B cells proliferation and forcing differentiation toward plasma cells and resulting in a reduction of IgM levels (Figure 4(A)) (Avila et al. 2019).

On the other hand, PFAS can affect the immune system mainly through PPARα. PFOS has been shown to be less effective than PFOA at activation of this receptor and neither PFOS nor PFOA was shown to have a significant activating effect on PPARγ (Takacs and Abbott 2007). For instance, high doses of PFOS and PFOA result in reduced numbers of thymocytes and splenic B cells in mice with suppression of both T cell-dependent and independent IgM responses after long-term exposure (Qazi et al. 2009). In fact, the decrease in the IgM responses after PFOS exposure has been linked with PPARα activation in a still not well-known mechanism (Figure 4(A)) (Peden-Adams et al. 2008). Furthermore, thymic and splenic atrophy has been reported in mice after PFOA/PFOS exposure, likely due to PFAS-dependent mitochondrial damage that results in increased lymphocyte apoptosis (Figure 2(A)) (Wang, Wang, Li, et al. 2014). Additionally, *in-vitro* studies showed some PPARα-independent mechanisms related to PFAS exposure. For instance, the reduced production of IL-6, TNF-α, IL-10, and INF-γ by human leukocytes involves the inhibition of the NFκB pathway. Also, PFOS but not PFOA causes downregulation of IL-2 production by T $CD4^+$ cells in a PPARα-independent way (Corsini et al. 2011; Midgett et al. 2015).

3.3. Proposed AOP network for immunotoxicity

To the best of our knowledge, there were no AOPs for immunotoxicity and EDCs with these NRs as MIEs on AOP-wiki from 2005 to December 2020. Based on the mechanism analyzed during this systematic review, we are proposing a framework for developing AOP networks by which EDCs cause immunotoxicity in a certain group of immune cells. The sustained activation of AHR, PPAR, and ER by EDCs result in different immune-related adverse effects, which ultimately results in immunotoxicity, and this defines the MIE. As a consequence of NRs activation, a series of transcriptional changes and alterations in biochemical pathways ultimately affect cellular function and differentiation, which can be proposed as molecular and cellular KEs. These NRs have already been reported as MIEs by other authors, but not in an immunotoxicity context (Becker et al. 2015; AOP-Wiki 2016; Gust et al. 2019). For instance, Becker et al. reported AHR sustained activation by dioxins (MIE), resulting in hepatocellular damage (KE) and ultimately leading to the development of hepatic tumors (AO) (Becker et al. 2015). In addition, Gust et al. showed that PPARα activation by an antagonist (MIE) resulted in decreased and increased fat and protein metabolisms (KEs), respectively, leading to a general decrease in body weight (Gust et al. 2019).

We propose the molecular mechanisms of immunotoxicity identified in this paper for the different NRs and cell types as potential MIEs and molecular and cellular KEs for immunotoxicity (Table 2). This could be useful to develop an AOP network. Further, in-silico models like PBPK, QIVIVE, QSAR, etc., can improve the existing AOPs and aid in proposing new AOPs. For instance, QSAR models may help screen and identify a molecule as an MIE since they explain dose-response relationships. In addition, the integration of mechanistic data with pharmacokinetic information derived from PBPK modeling, such as time-concentration profiles of chemicals, may help develop complete AOPs and increase the understanding of chemical exposure (Madden et al. 2020). Further, PBPK model-based reverse dosimetry for QIVIVE helps in calculating PODs for risk assessment by predicting BMDLs from dose-response curves (Louisse et al. 2017). This concept could play a role in supporting the choice and relevance of the *in-vitro* bioassay used to identify critical molecular endpoints (Vinken et al. 2020).

Table 2 shows a summary of some proposed MIEs and KEs for Immunotoxicity by EDCs on the studied cell types.

4. Discussion

EDCs include a broad group of chemicals with similar functions but different structures and physicochemical properties. For instance, TCDD and BPs have several aryl rings in their structure, while PFAS is composed of simple hydrocarbon chains (NCBI 2021a, 2021b, 2021c). This molecular structural difference could explain why TCDD and BPs but not PFAS act through AHR, since this receptor is well known for interacting with arylated ligands (Gutiérrez-Vázquez and Quintana 2018). On the other hand, according to a recent report from the EFSA, the exact mechanisms of action of PFAS have not been established yet (Schrenk et al. 2020). However, *in-vivo* and *in-vitro* evidence support that the immunotoxic effects of these chemicals originate from PPARs and NFκB activity and/or regulation of apoptosis (Schrenk et al. 2020). In addition, the United States EPA showed that PFAS immunotoxicity most likely depends on PPARα, although they also reported some other PPARα-independent mechanisms (DeWitt et al. 2009). Numerous articles emphasized the resemblance of PFAS to a fatty acid, which is one of the main ligands of PPARs (Wang, Wang, Liang, et al. 2014; Shabalina et al. 2015; Jacobsen et al. 2018). In addition, Shabalina et al. described PFOS and PFOA as fatty acid-like compounds but with all the hydrogens from the hydrocarbon chain exchanged for fluorine atoms (Shabalina et al. 2016).

This study reviews the role of different NRs such as AHR, ER, and PPAR in the mechanism of immunotoxicity in T, B, and dendritic cells for a selected group of EDCs, including TCDD, BPs, PFAS, and FRs. However, the majority of literature is reporting the role of TCDD and BPs. Therefore, the focus is on TCDD and BPs since we could not find much literature about PFAS and FRs' roles in these specific NRs. To begin with, the primary outcome of AHR activation by EDCs in T

cells is the impairment of the Treg/Th17 balance. T cell differentiation is a very complex process depending on multiple factors that determine the fate of these cells, such as cytokines, cell-to-cell interactions, and epigenetic modifications (Goswami and Awasthi 2020; Singh et al. 2020). AHR-dependent effects are ligand-specific, leading to different outcomes depending on the ligand used, as demonstrated earlier with the role of TCDD and BPA in T cells (Kerkvliet et al. 1990; Quintana et al. 2008; Singh et al. 2011). For instance, the AHR-dependent disturbance of the cytokine profile can lead to anti-inflammatory or pro-inflammatory outcomes depending on the ligand (Marshall et al. 2008; Chmill et al. 2010; Benson and Shepherd 2011a; Yang et al. 2016; Al-Ghezi et al. 2019). This ligand specificity also affects the epigenetic modifications, such as DNA methylation and miRNA expression that occurs after chemical exposure, which makes it more challenging to understand the mechanisms of immunotoxicity of EDCs. In addition, the interaction of AHR with NFκB has been shown to be very important for T cells, also in a ligand-specific way since BPA has been reported to be linked to NFκB induction. It has also been suggested as another mechanism by which TCDD and BPA act through AHR-NFκB controlling Treg/Th17 balance (Marshall et al. 2008; Chmill et al. 2010; Gerondakis et al. 2014; Ehrlich et al. 2018; Gao et al. 2020).

Although the nature of the AHR ligands seemed to determine T cell differentiation, as we have mentioned previously with TCDD and BPs, it is challenging to explain how these ligands acting through the same receptor have opposite outcomes. To explain this contradictory behavior, some authors have proposed that these differences may be determined by the ligand dose and dose-rate used to activate the AHR, rather than by the specific ligand (Ehrlich et al. 2018). For instance, Schulz et al. demonstrated that TCDD induced Tregs while the natural ligand FICZ did not, even at 100 times more concentrated doses. The inability of FICZ to induce Tregs was likely due to its rapid metabolism and inability to maintain the activation of AHR to the same extent as TCDD (Schulz et al. 2012). To prove this hypothesis, Ehrlich et al. designed an experimental approach to further optimize the dose of rapidly metabolized ligands to match the extent of AHR activation using TCDD (Ehrlich et al. 2018). Ehrlich et al. achieved similar *in-vivo* efficacy to induce Tregs with all the AHR ligands tested, including FICZ (Ehrlich et al. 2018). A similar approach can also be applicable to BPs, whose half-life is much shorter than TCDD; however, it has still not been tested. In humans, the half-life of TCDD is years (1–9 years), while for BPs is hours (5–8 h) (Geusau et al. 2002; Kerger et al. 2006; Stahlhut et al. 2009). Thus, BPs are less persistent than TCDD leading to different duration of AHR activation, which could be another explanatory principle for the opposite effects observed on the immune system for each chemical. Given all the complex conditions needed for normal T cell differentiation, it is not surprising that the limitation of the experimental model used can condition the outcomes of chemical exposure. Al-Ghezi et al. demonstrated that the observed decrease in Th17 levels after TCDD exposure was partly due to the reduction in IL-6 levels since IL-6-mediated STAT3 signaling is essential for Th17 differentiation (Park et al. 2014; Al-Ghezi et al. 2019), while Chmill et al. reported a contrary finding (Chmill et al. 2010). Despite both having used similar TCDD concentrations and similar doses, Al-Ghezi et al. used a PTX mouse model and i.p. administration while Chmill et al. used an OVA-immunized mouse model and o.g. administration (Chmill et al. 2010; Al-Ghezi et al. 2019). These contrasting results may, possibly, be due to some differences in their experimental model. Finally, some authors have shown that the specific increase of Tregs after TCDD

Table 2. Summary table of some proposed MIEs and KEs for Immunotoxicity by EDCs on the studied cell types. Each MIE have a series of associated KEs. The cellular KEs arise from the combined effect of the molecular KEs.

Proposed MIE	Proposed molecular KE		Proposed cellular KE	AO
Activation, AHR	Inhibition/Activation NFκB Upregulation/downregulation IL-10 Upregulation/downregulation RORγδ Induction/Inhibition STAT3		Induction/Reduction Treg Induction/Reduction Th17	Immunotoxicity
	Inhibition/Activation NFκB Upregulation IDO		Increase DC maturation Increase tolerogenic DCs	
	Mouse	Inhibition Blimp-1 Upregulation SHP-1	Decrease B cell differentiation Reduction Ig production	
	Human	Downregulation LCK	Impair vesicular trafficking Reduction Ig secretion	
Activation, ER	Upregulation RORγδ Induction NFκB		Induction Th17	
	Upregulation IL-6 Reduction antigen presenting		Increase inflammatory DCs	
	-		Increase B cell differentiation	
Activation, PPAR	Mitochondrial Damage		Cellular death	
	Upregulation Blimp-1		Increase B cell differentiation Reduce B cell numbers Decrease Ig production	

Color code: light grey: T cells; medium grey: DCs; dark grey: B cells.

exposure is the consequence of either or both the inhibitory effect of TCDD on the proliferation and differentiation of Teff cells or the increase in their apoptosis since it has been shown that Tregs are resistant to TCDD-mediated apoptosis and even AHR-independent apoptosis (Banz et al. 2002; Fritzsching et al. 2005; Taylor et al. 2007; Stockinger et al. 2011; Veiga-Parga et al. 2011; Winzler et al. 2011; Che et al. 2015; Miljkovic et al. 2019).

For DCs, TCDD exposure appears to promote a regulatory phenotype, especially in BMDCs subpopulation, by affecting their maturation process and differentially affecting gene expression in each population (Bankoti et al. 2010; Simones and Shepherd 2011; Vogel et al. 2013). The overall effect of AHR activation in mature and immature BMDCs is the increased expression of several membrane receptors and costimulatory factors while reducing the number of integrins and adhesion molecules, resulting in increased capabilities to stimulate T cells, while reducing their binding to both Teffs and T naïve cells (Lee et al. 2007; Bankoti et al. 2010; Jin et al. 2010; Simones and Shepherd 2011). Furthermore, several regulatory genes such as TGF-β, CD25 and IDO are upregulated following TCDD exposure in both types of BMDCs, which has been linked to the induction of Tregs (Vogel et al. 2008; Bankoti et al. 2010; Chmill et al. 2010; Simones and Shepherd 2011; Rohlman et al. 2013). In fact, DCs expressing IDO are regarded as regulatory DCs specialized in causing tolerance through its regulatory effect on T cells (Munn et al. 2002). Interestingly, mature BMDCs showed also induction of pro-inflammatory cytokines like TNF-α and IL-6 (Bankoti et al. 2010; Simones and Shepherd 2011), which are related to Th17 induction, thereby raising doubts about the exact mechanism by which TCDD induces a regulatory phenotype in DCs and suggesting the need of further investigation.

Unlike in T cells, other AHR ligands result in similar outcomes as TCDD in DC maturation as it was demonstrated with FICZ, ITE and certain BPs such as BPA and BPF, proving a relative lack of differential responsiveness of DCs to different AHR ligands. However, DCs exposed to a high concentration of BPA and subsequently co-cultured with T $CD4^+$ resulted in the induction of Th17 cells. Conversely, it is unknown why TCDD and BPA exposure results in this opposite outcome of T cell differentiation despite their similar effect on DCs maturation. In addition, Švajger et al. reported an inhibitory effect of a high concentration of BPAF on moDCs maturation, supporting a complex regulatory interference by BPs in DCs that may influence other intracellular mechanisms (Bankoti et al. 2010; Švajger et al. 2016; She and Liu 2020). NFκB and specially RelB is a major regulator of DC differentiation and function (Vogel et al. 2013). Many reports have provided evidence supporting the importance of this pathway in AHR-related effects on these cells (Simones and Shepherd 2011; Vogel et al. 2013), even suggesting the need for RelB involvement to observe any effect (Vogel et al. 2008). This is an example of how sometimes AHR alone cannot explain every outcome of different chemical exposure. Focusing on other factors, such as NFκB or different NRs (discussed below), may improve the understanding of the mechanisms of action of EDCs on the immune system.

Talking about B cells, the main outcome of AHR activation is the impairment of IgM responses. For this issue, the principal mechanisms of immunotoxicity by TCDD is based on SHP-1, BCL-6, Blimp-1, LCK, PAI2 and IgH and other intracellular factors (Zhang et al. 2013; Phadnis-Moghe et al. 2016, 2015; Dornbos et al. 2018; Zhou, Zhang, et al. 2018). Ultimately, the inhibition of Blimp-1 and IgH in mice results in the inhibition of B cell differentiation and Ig production. Interestingly, the direct inhibition of IgH is unlikely since it would imply that the TCDD-mediated suppression of the antibody response could happen even after B cell differentiation to plasma cells (Zhang et al. 2013). PAI2 has been associated with a dual effect in B cells, protecting against TCDD-dependent immunotoxicity but also inhibiting NFκB, therefore contributing to the negative effects previously described. This duality was explained by studies performed by Dornbos et al., probing that the serpin2/PAI2-dependent protection against TCDD is time-specific since the levels of IgM were maintained in normal mice for 3 days but not for 4 days (Dornbos et al. 2018). A curious finding is that many authors reported that the timing of chemical exposure has major effects on the outcomes for B cells, making the intracellular alterations detectable only if TCDD is added before or during B cell activation (Zhang et al. 2013; Phadnis-Moghe et al. 2016). Zhang et al. explained that this is likely due to alterations in early signaling events on these cells. Thus, once B cells are committed to the plasma cell fate, TCDD can no longer influence their differentiation program (Zhang et al. 2013). On the other hand, AHR ligation in humans is not related to a defect in the Blimp-1-dependent differentiation process but rather to an IgM secretion/trafficking impairment (Lu et al. 2011; Zhou, Henriquez, et al. 2018). For that matter, LCK is very important in vesicular trafficking and its expression is increased by TCDD. Therefore, since IgM assembly occurs between the endoplasmic reticulum and the Golgi apparatus, the IgM protein trafficking is likely to be affected after Golgi-associated processes have been completed in an LCK-dependent way (Zhou, Henriquez, et al. 2018). Furthermore, B1 cells have been presented as a more sensitive subpopulation of B cells to TCDD likely due to their higher expression levels of LCK compared with B2 cells (Kinoshita et al. 2006; Zhou, Zhang, et al. 2018). Despite much information about TCDD and AHR for B cells, there was not much about other EDCs. However, some evidence supports that BPA exposure results in enhanced production of IgM by B1 cells in both *in-vitro* and *in-vivo* in a murine model of lupus (Yurino et al. 2004) are in line with the observed outcomes for BPs in T cells.

EDCs interacting with other NRs can also contribute to the observed outcomes of chemical exposure. For instance, after TCDD exposure DCs acquired a more anti-inflammatory phenotype even though they did not stop producing some amount of pro-inflammatory cytokines. For BPA, similar outcomes were reported in an ER-dependent manner but more inclined to a pro-inflammatory response (Qiu et al. 2018; Wang, She, et al. 2020). Since BPs can also interact with AHR, each EDC may move the balance to one side or another depending on their properties and way of affecting the different NRs, making it even more challenging to understand

their molecular mechanisms of immunotoxicity and more difficult to know whether the observed outcomes depend on one or another NR or arise from a combined effect. T cells are another example in which BPA acting through ER and AHR contribute to the induction of Th17 cells, although little is known about whether there is direct cooperation between these two NRs or they reach the same outcome by different pathways (Dong et al. 2020; Gao et al. 2020; Wang, Cao, et al. 2020; Wang, She, et al. 2020). Moreover, Avila et al. showed that PPARγ activation by prenatal exposure to BPA is related to an induction of Blimp-1, leading to an increased B cell differentiation to plasma cells. This results in less B cell proliferation leading to a general decrease in the numbers of plasma cells and lower levels of circulating IgM (Avila et al. 2019). Since this is a developmental study, it does not contradict what was observed by Yurino et al. in adult mice (discussed above). The immune system of the fetus and the adult are in a different state of maturity and development, so it can be expected to find different responses to chemical exposure.

PFAS compounds have been shown to impact the immune system mainly through PPARα interaction resulting in different outcomes such as splenic and thymic atrophy (Qazi et al. 2009). Wang et al. tried to support these observations by linking PFAS exposure with the reported increase in apoptosis in these tissues and suggesting that PFAS likely affects mitochondria integrity. In addition, they showed an upregulation of PPARα, which was not apparently linked with the increased apoptosis, but it may be causing depletion of the necessary physiological lipids associated with the immune system and therefore contributing to the reported outcomes since it is well known that PPARs are related to lipid metabolism (Wang, Wang, Li, et al. 2014). Nevertheless, the exact role of PPARα in the PFAS mechanism of immunotoxicity is not yet clear, since PPARα is not upregulated with low doses of PFOS (Peden-Adams et al. 2008) and the immunosuppressive effects of PFOS seem to be independent of PPARα activity (Corsini et al. 2011). In addition, Midgett et al. reported that PFOS and PFOA affect cytokine production in T cells in a PPARα-independent way but involving inhibition of the NFκB pathway (Midgett et al. 2015), suggesting that other factors may be involved for PFAS-dependent immunotoxicity.

Interspecies and intercell-type differences exist in different models (*in-vitro*, *in-vivo*, and human), leading to variation in the production of immune cells. Choice of models can result in similar or different outcomes depending on the cell type used in the study (Deepika et al. 2020). Accordingly, as it was demonstrated with B cells, TCDD exposure results in an impaired IgM response both in mice and humans by affecting the Blimp-1-dependent differentiation toward plasmatic cell (Zhang et al. 2013; Phadnis-Moghe et al. 2015, 2016) and by impairing the LCK-dependent IgM secretion/trafficking, respectively (Zhou, Zhang, et al. 2018). For T cells, a different response to TCDD between humans and mice have also been reported (Chmill et al. 2010; Duarte et al. 2013). The variance between species probably arises from the inherent differences in complexity and regulation of the immune system. This is further supported by Kovalova et al., who proposed that even though comparable functions and pathways are affected between the species, different orthologues within common pathways and biological processes are differentially regulated indicating that TCDD may use species-specific mechanisms to suppress the IgM response (Kovalova et al. 2017). In addition, it is well known that AHR affinity in humans is lower than in mice while the half-life of TCDD is higher in humans than in mice (years and days respectively) (Chmill et al. 2010; Lu et al. 2010; Duarte et al. 2013), which can be determining the observed differences. Furthermore, interindividual variance in AHR expression in humans is something that must be accounted for and can determine the outcomes. For instance, some studies reported the presence of individuals who did not respond to TCDD exposure likely due to polymorphisms in the AHR gene, such as 554 G > A, which has been linked with a failure to induce CYPA1A (Lu et al. 2010; Dornbos et al. 2016). Interestingly, no major differences have been reported for DCs between humans and mice. On the other hand, *in-vitro* exposure to TCDD is linked with Th17 induction, while *in-vivo* exposure is related to increased levels of Tregs, as was previously discussed. Further investigation is needed to completely understand why these differences are produced, but they are likely dependent on the distinct microenvironment of the T cells in each model. As it was commented previously, DCs exposed to TCDD acquire a regulatory phenotype that is related to the induction of Tregs. Thus, the observed induction of Tregs *in-vivo* after TCDD exposure may be dependent on the presence of those regulatory DCs, among other factors, that are not present *in-vitro*. Another possibility is the different dose duration and way of administration of the chemicals (Connor and Aylward 2006; Chmill et al. 2010; Stockinger et al. 2011; Schulz et al. 2012; Duarte et al. 2013; Ehrlich et al. 2018; Singh et al. 2020). In fact, different routes of administration in combination with different doses will lead to different pharmacokinetics, and thus to different amounts of ligand that reaches the target cells (Duarte et al. 2013). In addition, studies conducted with BPA added further factors that bias T cell differentiation. Thereby, Malaisé et al. demonstrated that cell location (i.e. gut or spleen) determines whether a specific AHR ligand results in one or another outcome. For instance, the exposure of isolated mouse immune cells from the gut to BPS results in increased levels of IL-17 and IL-22. but the exposure of cells isolated from the spleen did not, thus suggesting that tissue-specific signals affecting T cells are important in AHR-dependent effects (Malaisé et al. 2020). Furthermore, model-specific outcomes have been reported (Kerkvliet et al. 2009; Pang et al. 2019). For instance, using a NOD mouse model, an increase in Tregs is produced, while with a GVH mouse, Tr1 cells are induced instead (Kerkvliet et al. 2009). No explanation has been provided for this, but it may be dependent on specific characteristics of each model since there is evidence pointing at a protective role of Tr1 cells in transplantation and a positive correlation between the number of Tr1 cells and a stable graft function (Song et al. 2021). In addition, Pang et al. proved that using an isolated mixture of mice splenocytes, an induction of Treg *in-vitro* was produced after TCDD exposure unlike when using only isolated T $CD4^+$ cells, supporting that differences

observed between *in-vitro* and *in-vivo* systems may arise from differences in the microenvironment (Pang et al. 2019). In case of DCs, Simones and Shepherd demonstrated that TCDD-treated BMDCs displayed tolerogenic properties in *in-vitro* model, and failed to suppress T cell responses in *in-vivo* model, most likely due to a defective migration to the lymph nodes or the need for additional stimulatory signals for acquiring functional immunosuppressive capabilities (Simones and Shepherd 2011). No differences between *in-vitro* and *in-vivo* models have been reported for B cells.

To the best of our knowledge, there is no information about FRs in the context of NRs. However, some reports have provided evidence about the immunotoxic properties of the former compounds. For instance, exposure to the BFR TBBPA *in-vitro* induces the expression of pro-inflammatory cytokines by innate immune cells through AKT/MAPK/NF-kB/AP-1 signaling, in a similar way as BPA does in T cells. TBBPA also resulted in the induction of Th1 responses in mice (Hall et al. 2017). Interestingly, the chlorinated FR Dec602 shows the opposite effect, leading to the increased expression of some anti-inflammatory cytokines, such as IL10 and IL4, causing increased Th2 responses (Canbaz et al. 2017). This suggests that different types of FRs may have different effects on the immune system. Moreover, the OPFR TPHP has similar effects on DCs, like the ones observed with TCDD. Thereby, TPHP exposure in mice cause increased expression of MHCII, CD80/86, and CD40 in DCs, also inducing their maturation (Feng et al. 2016).

There is a need for more research to completely understand the mechanisms of immunotoxicity of EDCs. Due to limited data availability, the number of chemicals is often very low to assess consistency, strength, and specificity for associating the last KE to MIE. Another significant gap is the considerable uncertainty associated with results limiting the proper characterization of the proposed AOP. Application of in silico translational models can reduce some of these knowledge gaps. For instance, Hernández-Jerez et al. applied PBPK model for deltamethrin and performed reverse dosimetry to find the dose for the specific effect (developmental neurotoxicity). The observed equivocal *in-vivo* effects found that only direct exposure with relatively higher concentration to pups could initiate MIE of the proposed AOP network. Kinetic assessment in this study can support the decision-making as a dose range leading to adverse effects was established (Hernández-Jerez et al. 2021). Further, the construction of AOP networks may help identify other possible unnoticed mechanisms. For instance, SHP-1 is also present in T cells and can inhibit STAT3 (Lorenz 2009), making it possible that the TCDD-dependent downregulation of Th17 cells could be happening through SHP-1 induction by AHR as it was described for B cells (Phadnis-Moghe et al. 2016).

Moreover, BPA has been shown to affect Blimp-1 expression through PPARγ (Avila et al. 2019), controlling B cell differentiation, which was also reported for TCDD and AHR (Zhang et al. 2013). Since BPA can bind to AHR (Švajger et al. 2016; Gao et al. 2020; Malaisé et al. 2020; She and Liu 2020), it is not unlikely that BPA can also control B cell differentiation in an AHR-dependent way. This cooperation between receptors may also explain the contrasting outcomes observed in DC-dependent T cell maturation comparing TCDD and BPA since TCDD act through AHR while BPA can additionally bind to ER and PPAR.

5. Conclusion

This systematic study has shown that the immunotoxicity mechanisms of EDCs are mainly determined by the activation of several NRs such as AHR, ER, and PPAR in a cell-, tissue- and ligand-specific way. Although most of the researchers focus on one specific NR to investigate immunotoxicity, it has been shown that the outcomes of chemical exposure depend on more than one activation signal in some cases. TCDD and PFAS were reported to only interact with one receptor, AHR, and PPARs, respectively. Whereas BPs can interact with the AHR, ER, and PPAR, more research is needed to prove if their effects on the immune system arise from the combined activation of several NRs. In addition, species-specific differences have been found, as well as a translational gap between *in-vitro* and *in-vivo* models, and between different *in-vivo* models and *in-vitro* models, especially in T cells, which may depend on their complex regulation and differentiation requirements. The development of AOP networks for EDCs-induced immunotoxicity will help in the further development of integrated PBPK/PD modeling applying a broader systems biology approach and delivering IATA for better quantification of human health risk assessment. Development of this kind of model could also be helpful to design better *in-vitro* strategies by introducing relevant factors that otherwise would be difficult to determine.

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Supplemental material

Supplemental data for this article can be accessed here.

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