Biochemical Pharmacology 112 (2016) 1–5

Contents lists available at ScienceDirect

Biochemical Pharmacology

journal homepage: www.elsevier.com/locate/biochempharm

Commentary

Toward elucidation of dioxin-mediated chloracne and Ah receptor functions

Karl Walter Bock

Department of Toxicology, Institute of Experimental and Clinical Pharmacology and Toxicology, Wilhelmstrasse 56, D-72074 Tübingen, Germany

ARTICLE INFO

Article history:
Received 11 December 2015
Accepted 14 January 2016
Available online 23 January 2016

Chemical compounds studied in this article:
2,3,7,8-Tetrachlorodibenzo-p-dioxin = TCDD (PubChem CID 15625)
6-Formylindolo[3,2-b]carbazole = FICZ (PubChem CID 1863)

Keywords:
Chloracne
Ah receptor
TCDD
Sebocyte stem/progenitor cells
Blimp1

ABSTRACT

Target cells and molecular targets responsible for dioxin-mediated chloracne, the hallmark of dioxin toxicity, are reviewed. The dioxin TCDD accumulates in sebum, and thereby persistently activates the Ah receptor (AhR), expressed in bipotential stem/progenitor cells of the sebaceous gland. AhR operates in cooperation with other transcription factors including c-Myc, Blimp1 and ß-Catenin/TCF: c-Myc stimulates exit of stem cells from quiescence to proliferating sebocyte progenitors; Blimp1 is a major c-Myc repressor, and ß-Catenin/TCF represses sebaceous gland differentiation and stimulates differentiation to interfollicular epidermis. TCDD has been demonstrated to induce Blimp1 expression in the sebocyte stem/progenitor cell line SZ95, leading to sebocyte apoptosis and proliferation of interfollicular epidermis cells. These findings explain observations in TCDD-poisoned individuals, and identify target cells and molecular targets of dioxin-mediated chloracne. They clearly demonstrate that the AhR operates in a cell context-dependent manner, and provide hints to homeostatic functions of AhR in stem/progenitor cells.

1. Introduction

Chloracne, a severe and persistent skin disease, is the hallmark of dioxin toxicity [1,2]. Dioxin refers to 2,3,7,8-tetrachlorodibenzo-p-dioxin. Accumulating evidence suggests that stem/progenitor cells represent sensitive AhR targets [3–5]. Dioxin toxicity is known to be remarkably species- and tissue-dependent. In particular, stem/progenitor cells are dependent upon their particular microenvironment or niches. Stem/progenitor cells differentiate along different pathways depending upon the combination of extrinsic factors to which they are exposed [6]. Recently, it has been demonstrated that the AhR is expressed in immortalized human sebocyte SZ95 cells where it induces the c-Myc inhibitor Blimp1, responsible for terminal sebocyte differentiation [7]. Evidence has also been obtained that TCDD treatment of these cells leads to atrophy of sebocytes and increases keratinocyte-like differentiation [8]. In addition, TCDD is known to accumulate in sebum, leading to sustained AhR activation. Bipotential epidermal progenitors from the human sebaceous gland have been identified as well as contrasting roles of c-Myc or ß-Catenin in mediating progenitor differentiation to either sebocytes or interfollicular epidermis, respectively [9]. c-Myc has been demonstrated to be responsible for mobilization of stem cells from quiescence and proliferation of progenitor cells [10].

Due to the well known species and tissue dependence of AhR actions the commentary is focused on human proliferating sebocyte progenitors. Elucidation of mechanisms responsible for dioxin-mediated chloracne is of particular interest since it may hint at physiologic AhR functions [11–13]. Dioxin-mediated chloracne clearly provides an example demonstrating that AhR operates in a cell context-dependent manner.

2. Historical

Numerous examples of dioxin poisoning have been published. Here, two well studied examples are emphasized.

2.1. The Seveso incident 1976

In 1976 an explosion in the herbicide plant of Seveso, Italy, led to a release of up to 30 kg TCDD in an aerosol cloud. The cloud

Abbreviations: AhR, aryl hydrocarbon receptor; FICZ, 6-formylindolo[3,2-b] carbazole; TCDD, 2,3,7,8-tetrachlorodibenzo-p-dioxin.

E-mail address: bock@uni-tuebingen.de

http://dx.doi.org/10.1016/j.bcp.2016.01.010
0006-2952/

deposited over an 18-km^2 area. The contaminated area was divided into three major zones (A, B, R) in decreasing order of contamination. In zones A (n = 736 residents) and zones B (n = 4737 residents) 193 cases of chloracne were observed, almost all diagnosed among children younger than 15 years. The median serum TCDD of a cohort living in zones A and B was 272 ppt (=272 pg/g lipid) and 47 ppt, respectively, with a range from 2.5 to 56,000 ppt [14]. There were children between 2000 and 10,000 ppt with or without chloracne whereas all children above 10,000 ppt had chloracne [15]. For comparison, the reference level is approximately 6 ppt. During the first year after the accident, serum levels of 94–447 ppt were detected in zone A. Levels decreased to 12–73 ppt after 16–20 years [14]. Investigations of the exposed Seveso cohort provide the invaluable opportunity to relate serum TCDD levels with relatively acute (chloracne) and long-term outcomes (cancer and mortality) [16], the latter not in focus of the present review.

2.2. Poisoning of Victor Yushchenko 2004

In 2004 Victor Yushchenko, former president of Ukraine, was poisoned by estimated 1.4 mg TCDD (calculated from serum TCDD levels and the half-life of approximately 7 years for TCDD) during dinner. He became severely ill with gastritis, colitis with multiple ulcers, hepatitis, and pancreatitis. By 6 weeks the digestive tract symptoms had improved. Severe facial edema appeared 2 weeks after the poisoning, chloracne developed and lasted for years. A serum level of 108,000 ppt was detected after he was poisoned [17,48]. The patient allowed to release peer-reviewed scientific information on his case. Skin biopsies revealed sebaceous gland atrophy. This tissue was replaced by cystic lesions with epidermal-like differentiation with the expected distribution of epidermal keratins, termed hamartomas. These hamartomas created a new compartment that concentrated TCDD up to 10-fold compared with serum and strongly expressed cytochrome P4501A1 (CYP1A1) [17].

The chronology of organ involvement after poisoning (described in Figs. 1 and 4 of [17]) clearly demonstrates that the peak of skin involvement is delayed compared with other organs suggesting a 'deep compartment' of TCDD toxicokinetics, i.e. the tissue concentration differs from the blood concentration. It is known that TCDD accumulates in skin and particularly in sebum [17,48].

3. Target cells of TCDD-mediated chloracne

Sebaceous glands are part of the hair follicle of the epidermis producing sebum that lubricates and waterproofs the skin surface [18]. Several different epidermal stem cell clusters have been identified: (i) in the bulge of the hair follicle where stem cells move downward toward the dermal papilla and upward toward the sebaceous gland; (ii) bipotential stem cells have been identified in the sebaceous gland, and (iii) interfollicular epidermis contains separate stem cell clusters [9]. Every SZ95 immortalized human sebocyte that underwent clonal growth generated progeny that differentiated either into sebocytes or cells of the interfollicular epidermis depending upon c-Myc or ß-Catenin signaling, respectively (Fig. 1) [9]. AhR expression has been demonstrated in sebaceous glands in vivo and in SZ95 cells which also express TCDD-induced c-Myc inhibitor Blimp1 [7]. In addition, TCDD treatment of SZ95 cells led to atrophy of sebocytes and increased keratinocyte-like differentiation [8], similar to findings observed in TCDD-poisoned individuals. Hence, SZ95 cells appear to resemble bipotential sebocyte stem/progenitor cells [9].

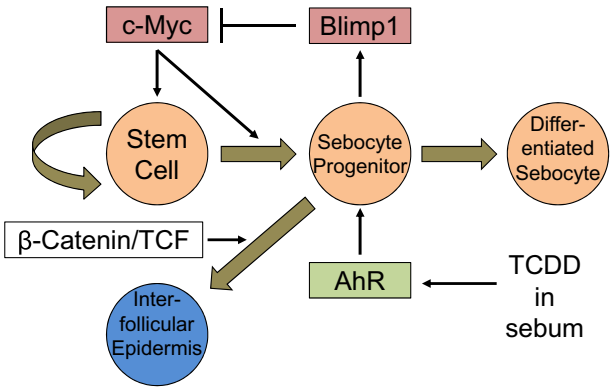

Fig. 1. Simplified model for the role of TCDD-mediated sustained Ah receptor activation in cooperation with c-Myc, Blimp1 and ß-Catenin/TCF on the differentiation pathway to either sebaceous glands or interfollicular epidermis.

4. Molecular targets of sebaceous gland differentiation

After discussion of AhR expression in sebocyte stem/progenitor cells and closely related SZ95 cells, cooperation of AhR with three other transcription factors responsible for sebocyte differentiation is briefly summarized.

4.1. c-Myc

The protooncogene c-Myc is a transcription factor activating its target genes as heterodimer with Max [19]. As shown in the hematopoietic system, c-Myc controls the balance between progenitor cell self-renewal and differentiation [20]. Over-expression of c-Myc leads to proliferation of sebaceous glands [9]. c-Myc contains six AhR-binding XRE-domains in its regulatory region and has been shown to be directly repressed by AhR [21].

4.2. ß-Catenin

ß-Catenin is an essential part of the Wnt signaling pathway. It interacts with members of the LEF/TCF family of transcription factors that regulate hair follicle morphogenesis and skin stem cell differentiation [22], and down-regulates sebocyte differentiation [9]. Studies with liver-specific knockout of the ß-Catenin gene *Ctnnb1* demonstrate that ß-Catenin is also involved in AhR expression [23].

4.3. Blimp1

The transcription factor Blimp is a repressor of c-Myc expression [24]. In addition to being a marker of sebocytes [9,25], it has been shown to be required for postnatal epidermal homeostasis for all epidermal stem cells including terminal differentiation of sebocytes [26].

4.4. Ah receptor

AhR is a multifunctional ligand-activated transcription factor of the bHLH/PAS (basic Helix-Loop-Helix/Per-Arnt-Sim) family that is mostly active at barrier organs including gut, lung and skin [27,28]. In the canonical signaling pathway the AhR/Arnt heterodimer binds to xenobiotic response elements (XREs) in the regulatory region of target genes. AhR is well established to be involved in modulating myriads of cell functions including induction of (i) phase I drug-metabolizing enzymes (mainly CYP1 enzymes), (ii) phase II enzymes including UDP-glucuronosyltransferases (UGTs; in genetic linkage with the antioxidant transcription factor Nrf2), and (iii) a phase III conjugate transporter (Table 1) [29,30]. It is also