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Aryl hydrocarbon receptor and liver fibrosis

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Abstract

The concept of toxicant-associated liver disease (TALD) has recently emerged linking exposure to pollutants to the development of chronic liver diseases (CLD) including fibrosis. Among such pollutants, ligands of the Aryl hydrocarbon Receptor (AhR), a transcriptional factor involved in detoxification processes, have been suspected to trigger multiple mechanisms (oxidative stress, epithelial and mesenchymal transition) associated with the occurrence of such pathologies. However, AhR knockout-mice also could develop liver fibrosis, an observation which might first be described as a paradox. In this review, we will present the different mechanisms linking AhR ligands and CLD and provide a hypothesis to solve this paradox.

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1. Introduction

Liver fibrosis is defined as a response to a sustained cell injury and chronic inflammation that leads to the activation of pro-fibrotic cells and the excessive deposition of extracellular matrix. While reversible, it often leads to fatal complications or increases the risk of hepatocellular carcinoma (HCC). To study the mechanisms which lead to this pathology, experimental animal models have been developed mostly implicating rodents, and can be chemically-induced, surgically-based, diet-based or genetically-modified [1]. Several types of etiologic factors have been identified such as alcohol consumption or viral exposure. However, the contribution of environmental causes such as exposure to persistent organic pollutants (POPs), has been recently documented (TALD: toxicant-associated liver disease) [2]. In this review, we will focus on the specific contribution of the Aryl hydrocarbon Receptor (AhR), which can bind some of these POPs, on the occurrence of liver fibrosis.

2. AhR ligands, mechanism of action and functions (Fig. 1)

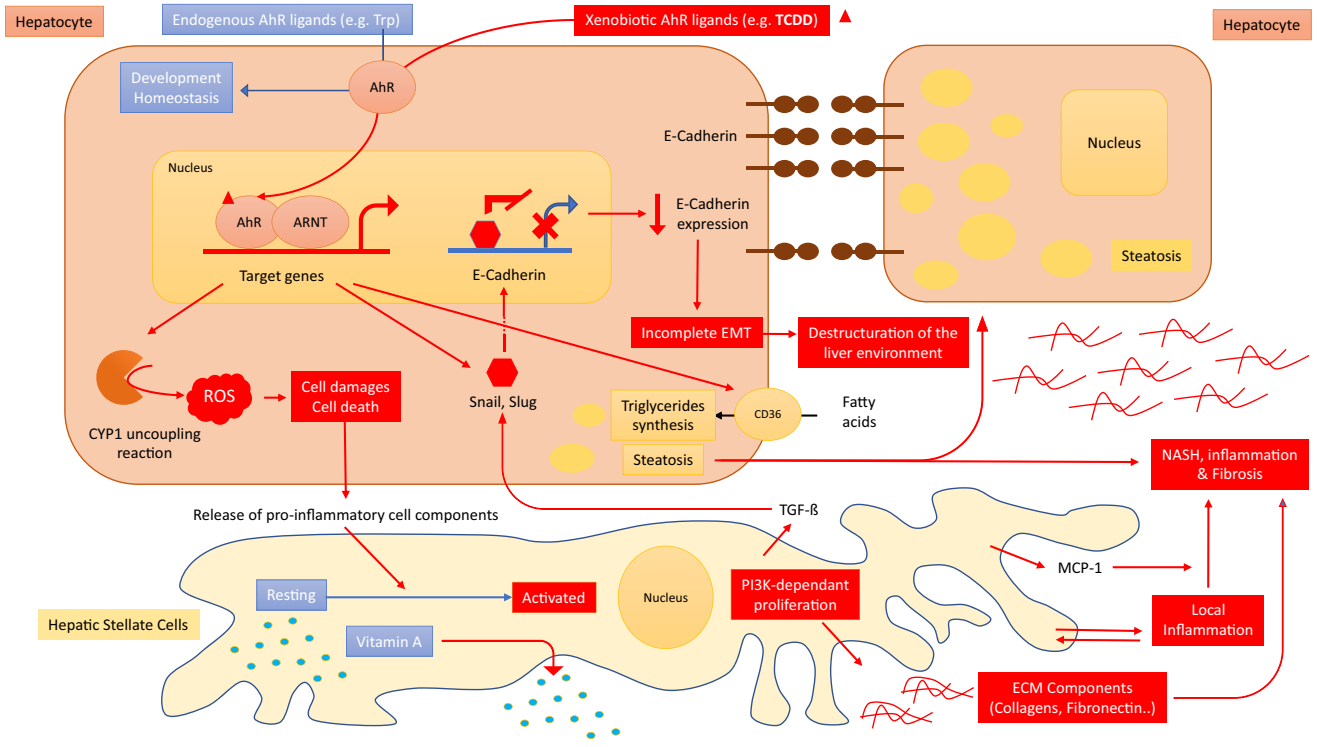
The AhR has been identified in the 90's as a xenobiotic receptor which detects many organic pollutants (some of them persistent) such as dioxins, furans, some polychlorinated biphenyls (PCBs) and polycyclic aromatic hydrocarbons and triggers a transcriptional program leading to the expression of xenobiotic metabolizing enzymes such as cytochromes P450 (CYP) or UDP-glucuronosyltransferases (UGT), that metabolize the pre-cited ligands, favoring their elimination in wasting fluids (e.g. urine). This elegant mechanism of action (detection/metabolism/elimination) historically strengths the idea that the AhR displayed only one unique function, dedicated to the regulation of xenobiotic metabolism. However, the development of knock-out models in vertebrates and invertebrates led to the suspicion of alternative functions of this receptor. Endogenous ligands including tryptophan metabolites started to be identified [3]. During the 00's with the emergence of large-scale omics-based technologies, several teams started to decipher other AhR functions such as the regulation of the epithelial–mesenchymal transition (EMT associated to cell adhesion/migration, and to the regulated expression of epithelial/mesenchymal markers) [4–6]. Non-genomic pathways and complex interactions with nuclear receptors were then identified. Thus, the AhR appears to be a far more complex protein than initially expected [4,6].

3. Chemically-activated AhR and liver fibrosis

3.1. Epidemiological and animal models-based evidence

Epidemiological studies reported previously a potential link between environmental or accidental exposure to dioxins or AhR ligands and CLDs. Studies on US veterans (Operation Ranch Hand) exposed to TCDD (2,3,7,8-TetraChloroDibenzo-p-Dioxin, a contaminant of Agent Orange), did not show any increase of the expected mortality compared to the overall population but

Fig. 1



The AhR regulates a diversity of signaling pathways in hepatocytes and in hepatic stellate cells which can contribute to the development of liver fibrosis including epithelial–mesenchymal transition, oxidative stress, secretion of extracellular matrix components and local inflammation.

they identified an increased number of deaths due to digestive diseases especially caused by CLDs such as cirrhosis (the highest grade of fibrosis) [7–9]. This was also observed in cohorts of workers potentially-exposed to dioxins (e.g., resulting from manipulation of pentachlorophenol) [10–12] or on accidently-exposed horses, which displayed centrilobular fibrosis as the most predominant liver lesion [13].

Animal models exposed to TCDD (and subsequently activating the AhR) were also reported to develop liver fibrosis [14–16]. For example, the US National Toxicology Program (NTP), a 2-years study on TCDD or binary mixtures of dioxin-like compounds such as PCBs or furans, reveals a hepatotoxicity in several female rats, including liver fibrosis (mostly portal, sometimes centrilobular) [17–22].

3.2. TCDD-activated AhR and oxidative stress (Fig. 1)

One of the first legitimated mechanisms that could link AhR ligands with liver fibrosis, is oxidative stress [23]. Indeed, TCDD is known to produce reactive oxygen species (ROS) through transcriptional and translational induction of CYP1 enzymes which catalyze uncoupling reactions [23]. Such a CYP-related oxidative stress mechanism is already firmly suspected in the chemically-induced CCl_4-experimental model of liver fibrosis as CCl_4 is metabolized notably by cytochrome P450 2E1 (CYP2E1), leading to lipid peroxidation by the production of ROS. In addition, TCDD promotes a decreased glycolytic flux with a switch of pyruvate kinases, favoring the production of $NADPH,H^+$ used by CYP-based catalytic reactions [24,25]. Furthermore, TCDD represses the level of expression of hepcidin (involved in the regulation of intracellular iron levels) which indirectly contributes to oxidative stress through iron-related Fenton reactions [26]. Moreover, a tight and complex interplay between the AhR and the Nrf2 signaling pathways (known to activate antioxidant enzymes) has been described, with direct consequences on TCDD-induced oxidative stress and fibrosis in the liver [27].

Over-production of ROS induces cell death (apoptosis/necrosis) and as a consequence, the release of pro-inflammatory and pro-fibrotic mediators by dying cells activates hepatic stellate cells (HSCs) which acquire a myofibroblastic phenotype (expressing alpha-smooth muscle actin (alpha-SMA), producing pro-fibrotic factors, e.g., TGF-β, and components of the extracellular matrix such as collagens type I, III and IV; fibronectin and proteoglycans). Additionally, TCDD favors the recruitment of inflammatory cells and the development of a local inflammation in the liver through AhR