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Editorial overview: The aryl hydrocarbon (Ah) receptor: From toxicology to human health

Michael S. Denison and Martin van den Berg

Michael S. Denison

Dr. Michael S. Denison received a Ph.D. in Environmental Toxicology from Cornell University in 1983 and did postdoctoral research in Clinical Pharmacology at the Hospital For Sick Children in Toronto and in Molecular Pharmacology at Stanford University. In 1992, he joined the University of California, Davis, where he is a professor in the Department of Environmental Toxicology. Dr. Michael S. Denison's long-term research focus has been on the biochemical and molecular mechanisms by which the Ah receptor (AhR) mediates the biological/toxicological actions of dioxin-like chemicals and other classes of AhR ligands. He has been investigating the structural diversity of AhR ligands, the molecular interactions of these diverse ligands with residues within the AhR ligand binding domain that lead to activation/inhibition of the AhR and AhR signal transduction and other fun things. His laboratory developed a series of recombinant cell-based bioassays (the so-called CALUX bioassays) that are widely used for high-throughput screening analysis for AhR ligands and the detection and relative quantitation of dioxins and dioxin-like chemicals in extracts of diverse matrices.

Martin van den Berg

Martin van den Berg (1953, The Netherlands) is a professor of toxicology at the Utrecht University (The Netherlands). During the last decades his areas of research include: toxicokinetics, metabolism, reproductive and interactive effects of POPs, effects on steroid hormone synthesis and their relation with hormone dependent tumors, development of in vitro assays to detect endocrine disruptors. He has also been acting as an advisor or chair of several WHO, IARC, EU and US committees dealing with the (environmental) health effects of POPs and endocrine disruptors.

Early studies examining the biochemical and toxicological effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD, dioxin) and related chemicals led to the identification of the aryl hydrocarbon receptor (AhR), a soluble cytosolic protein that binds TCDD specifically and with high affinity. A combination of biochemical, genetic and structure activity relationship studies subsequently provided strong support for a role of the AhR in mediating the diverse spectrum of effects produced by TCDD and related halogenated aromatic hydrocarbons. While the subsequent cloning and characterization of the AhR revealed that it was a ligand-dependent transcription factor and provided details of its detailed molecular mechanism(s) of action, it was the lack of biological and toxic effects of TCDD in AhR knockout mice that definitively demonstrated its role in mediating the action of these chemicals. Since that time, the number of publications on the AhR, AhR signal transduction mechanisms and the effects of AhR ligands have increased exponentially. Beyond new insights into the diversity of AhR ligands, the molecular mechanisms of AhR action, and species differences in AhR response, the AhR has been shown to play key role in a variety of developmental and physiological processes and human diseases. These advances have now led to the identification of the AhR as a target for the development of novel therapeutic agents for a variety of human diseases. In this special issue of *Current Opinion in Toxicology*, "The Aryl Hydrocarbon (Ah) Receptor: From Toxicology to Human Health", world leading experts highlight the current state of knowledge of the AhR, AhR ligands and AhR signal transduction pathways, the role of the AhR in endogenous physiological processes, the adverse and beneficial effects of exogenous and endogenous AhR ligands and the more recent development of AhR-based therapeutic agents.

While understanding the mechanisms and effects of toxic chemicals is important from a potential preventative and therapeutic perspective, it can also reveal previously unknown biological or physiological pathways. Studies into the basis and mechanism of TCDD toxicity and what was responsible for the dramatic differences in TCDD sensitivity across a broad spectrum of species is one such example. How such studies led to the identification of the AhR and the elucidation of its diverse spectrum of biochemical and toxic mechanisms of action is presented in an article by Linda Birnbaum [10.1016/j.cotox.2017.01.009]. The ability of TCDD and other AhR ligands to produce biological and/or toxicological effects in a wide variety of species is not surprising given that phylogenetic analysis suggesting that the AhR is an ancient and evolutionary well conserved protein. The article by Mark Hahn *et al.* [10.1016/j.cotox.2017.02.003] describes the evolution of the AhR and suggests that an AhR homolog was

present in organisms approximately 600 million years ago. At least five different classes of AhR-like proteins have evolved in vertebrates and a given species can contain multiple AhRs or AhR-like proteins that exhibit individual differences in ligand binding, ligand specificity and functional activity. While understanding the similarities and differences in the functional activity of these proteins will likely provide further insights into the diversity of AhR signal transduction, the ability of the AhR and AhR-like proteins to modulate gene expression via distinctly different mechanism has also been observed. The article by Eric Wright *et al*. [10.1016/j.cotox.2017.01.001] describes the current state of knowledge regarding the canonical and non-canonical AhR mechanisms of gene regulation. It also highlights the functional activity of the newly identified AhR:KLF6 heterodimer. In addition to multiple signalling mechanisms, the ability of very structurally diverse ligands to bind and activate an AhR response is notable. Furthermore, the broad range ligand- and species-selective differences suggest additional levels of regulation that can contribute to the diversity in AhR response. The article by Michael S. Denison and Samantha Faber [10.1016/j.cotox.2017.01.006] clearly highlights the diversity in AhR ligands and ligand-dependent AhR responses and it also discusses multiple mechanisms that can contribute to ligand-specific differences in AhR response. While the lack of experimentally determined structures of functional domains of the AhR has hampered detailed analysis of the molecular mechanisms of AhR activation, molecular modelling approaches have provided new insights. The current state-of-the-art of molecular modelling of functional domains of the AhR, the analysis of ligand binding by docking approaches and more recent structural information of AhR related proteins is providing approaches to study ligand-dependent AhR transformation and DNA binding, which is discussed in the article by Laura Bonati *et al*. [10.1016/j.cotox.2017.01.011]. Such experimental approaches will certainly help to elucidate key structural differences that will contribute to our understanding of species differences in AhR ligand selectivity and ligand specific responses.

The ability of TCDD and related TCDD-like chemicals to bind to and activate the AhR and produce AhR-dependent toxicity is well established. This led to the development of toxic equivalency factors (TEFs), values that are used internationally for human risk assessment to predict the toxicity of mixtures of TCDD-like compounds. However, the majority of the TEFs are based on *in vivo* rodent studies. Considering documented differences in ligand specificity and relative effect potencies (REPs) between rodent and human AhRs, there are significant uncertainties in the predictive nature of rodent TEFs for effects in humans. Focusing on dioxin-like polychlorinated biphenyls (DL-PCBs), the article by van Majorie Duursen *et al*. [10.1016/j.cotox.2017.01.005] reviews the TEF approach, its application and limitations with respect to human health effects for these compounds. Moreover, it discusses the impact that ligand- and species-specific differences in human and rodent AhRs and other pathways have on overall estimation of the toxic potency of these chemicals to humans. While a significant amount of information is known about the role that the AhR plays in regulation of gene expression, understanding of the mechanisms by which the AhR mediates the toxicity of TCDD and TCDD-like chemicals lags far behind. Recent advances in our understanding of AhR-dependent hepatotoxicity mechanisms have come from analysis of TCDD-mediated differential gene expression networks and phenotypic analysis. These aspects are discussed further in the article by Kelly Fader and Timothy Zacharewski [10.1016/j.cotox.2017.01.010]. TCDD-dependent, AhR-mediated toxicity is proposed to result from a collective response to cumulative changes in metabolic reprogramming. This involves multiple pathways and variations in effects and is suggested to contribute to documented species and tissues differences in response. Although the ability of the AhR to bind and be activated by structurally diverse ligands, in mammals, AhR-dependent toxicity is observed only with metabolically persistent ligands (e.g. TCDD and TCDD-like chemicals). The reasons for this differential response have remained an open question for many years. The article by Jason Matthews [10.1016/j.cotox.2017.01.013] discusses a new negative feedback loop involving an AhR induced gene product, the TCDD-inducible poly-ADP-ribose polymerase (TIPARP). This protein not only appears to negatively regulate ligand activated AhR activity, but TIPARP is also linked to AhR-dependent toxicity. It was found that the loss of TIPARP results in enhanced ligand-inducible and AhR-dependent toxicity. Based on these observations, the further analysis of the molecular mechanism of TIPARP action may provide a new and novel avenue in which key regulatory events in the molecular mechanisms of AhR-dependent toxicity should be investigated.

Perhaps the most exciting recent development in AhR biology is the demonstration of its role in modulating/mediating a variety of endogenous physiological processes and signalling mechanisms. This may suggest that some of the adverse effects of TCDD and related AhR ligands may result from disruption of normal AhR functions. As such, increased understanding the role of the AhR in normal physiology is providing new avenues of study into how activation or inhibition of AhR can produce its diverse spectrum of biological and toxicological effects. The identification of a variety of indole-containing and/or tryptophan-derived AhR ligands that are produced endogenously as well as by enteric bacteria has further expanded the focus of studies into the endogenous functions of the AhR. These studies suggest that the AhR