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Chapter

Role of Aryl Hydrocarbon-Ligands in the Regulation of Autoimmunity

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Abstract

The aim of this study is to show the effects of activating aryl hydrocarbon receptor (AhR) by specific ligands, on the expression of responsive genes. Specific AhR-ligands were reported to play an important role in immune regulation. This chapter will focus mostly on the effects of activating AhR with different ligands on autoimmunity. Findings showed the possibility of using the AhR to treat inflammatory and autoimmune diseases in mice. AhR ligation with specific ligands can affect T cell differentiation, through activation of $CD4^{+}Foxp3^{+}$ regulatory T cells and downregulation of the pro-inflammatory T helper 17 cells. The results showed the effects of specific AhR-ligands on the production of pro-inflammatory and/or anti-inflammatory T cell subsets, the potential to use AhR-ligands in regulating the inflammation of organ/tissues in various diseases, suggesting that specific AhR-ligands could be used for immune regulation in pathogenesis of autoimmune diseases of human and mice.

Keywords: aryl hydrocarbon receptor, T helper 17, T regulatory cells, autoimmune disease, immune regulation

1. Introduction

The aryl hydrocarbon receptor (AhR) is a ligand-dependent transcription factor that mediates a variety of cellular events in many tissues [1]. AhR expression was found in many vertebrates such as rats and mice including fish. Therefore, it was suggested that AhR has a widespread biological function in animals, but its physiological role is not yet fully known. When AhR binds to xenobiotic ligands, the AhR regulates the expression of many genes including those encoding for cytochrome P450 enzymes. The activation of AhR was linked to variations in cell proliferation, apoptosis, tumor promotion, immune function, development, and reproductive functions [1, 2]. Many studies reported that the phenotype of AhR-deficient mice points to possible physiological functions of the receptor in liver, heart, ovary, vascular, and immune systems [2, 3]. The signaling pathway of AhR starts when AhR-ligand enters the responsive cell and binds with high affinity to the cytosolic AhR. The receptor exists as a multi-protein complex, containing two molecules of the chaperone heat shock protein of 90 kDa, the X-associated protein-2, and a 23-kDa co-chaperone protein [4]. The AhR undergoes conformational changes exposing a specific nuclear localization sequence which results

in the translocation of the complex into the nucleus [5]. The ligand:AhR will then be released from this complex and bind to a related nuclear protein called AhR nuclear translocator (ARNT), which converts the AhR into its high-affinity DNA-binding form [6]. The ligand:AhR:ARNT complex binds to its specific DNA recognition site, the dioxin response elements (DREs), resulting in stimulation of the transcription of cytochrome P450 (CYP1A1) and other AhR-responsive genes. Once the AhR-ligand binds to its receptor, the AhR:ligand complex will translocate into the nucleus. The ligand:AhR will then be released from this complex and bind to ARNT, which converts the AhR into its high-affinity DNA-binding form, and then the ligand:AhR:ARNT complex will bind to the DRE, and as a result, transcription of cytochrome P450 and other AhR-responsive genes will start.

The present chapter highlights the effects of some AhR-ligands both exogenous and endogenous, on the secretion of pro- and/or anti-inflammatory cytokines which control the production of different T helper cell subsets, and consequently affects inflammation, and autoimmunity.

2. Categories of AhR-ligands

There are two major categories of AhR-ligands: exogenous and endogenous ligands. Exogenous ligands are those that are synthetic (formed as a result of non-biological activity) and/or naturally occurring dietary AhR-ligands. Endogenous ligands are those formed in biological systems as a result of natural processes in the body [7].

2.1 Exogenous AhR-ligands

2.1.1 Synthetic AhR-ligands

The synthetic AhR-ligands are in general high-affinity ligands and include halogenated aromatic hydrocarbons (HAHs) such as poly-halogenated dibenzo-*p*-dioxins. Synthetic ligands include also polycyclic aromatic hydrocarbons (PAHs) such as benzathracenes and related compounds [8]. HAHs represent the most potent type of AhR-ligands, with binding affinities in the pM to nM range. In contrast, PAHs bind to the AhR with lower affinity in the nM to μM range. The dioxin 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), which is a member of the HAH group, is considered as one of the most potent AhR agonists known. The potency of TCDD is about 1000-fold greater than that of PAH compounds [9]. It was observed that aryl hydrocarbon receptor-deficient mice, loss of responsiveness to TCDD and related chemicals [10]. Many genes are regulated by the AhR, especially those encoding xenobiotic metabolizing enzymes, such as cyp1a1. The induction of cyp1a1 is AhR-dependent response that has been observed in most species [11].

The physiological role of the AhR remains a key question, and to date no high-affinity endogenous ligand has been identified. The detailed analysis of AhR-ligand binding has mainly focused on the structurally related HAHs and PAHs. However, recent studies have demonstrated the ability of a structurally diverse range of chemicals to bind and/or activate AhR-dependent gene expression [12, 13].

These results suggest that AhR has a ligand-binding site with special characteristics. The identification and characterization of variety of naturally occurring AhR-ligands has started to redefine our ideas as to the structural specificity of AhR-ligand binding.

2.1.2 Naturally occurring dietary AhR-ligands

The major source of exposure of animals and humans to AhR-ligands both synthetic and natural comes from the diet. A number of studies have described and characterized a variety of naturally occurring dietary chemicals that can directly activate and/or inhibit the AhR signaling pathway. Many studies have documented a variety of naturally occurring dietary chemicals that can act as agonist/antagonist to AhR. It was reported that extracts of vegetables or vegetable-derived materials could induce CYP1A1 activity, the hallmark of AhR activation [14]. The ability of several dietary plant compounds, including 7,8-dihydrorutacarpine, indole 3-carbinol (I3C), indolo [3,2-b]carbazole (ICZ), dibenzoylmethanes, curcumin, quercetin, carotinoids (e.g., canthaxanthin and astaxanthin), pro-carotinoid, and *β*-apo-8'carotenal, to competitively bind to the AhR and stimulate AhR-dependent gene expression was also reported [15, 16]. Flavonoids are the largest group of naturally occurring dietary AhR-ligands which include flavones, flavanols, flavanones, and isoflavones. Flavonoids are found in dietary vegetables, fruits, and teas. These chemicals have strong antioxidative activity, anticarcinogenicity, and the ability to inhibit several enzymes such as protein kinases and cytochrome P450 [10, 17]).

Quercetin (3, 3′4′,5,7-pentahydroxy flavonol) is an AhR-ligand which could have both agonist and antagonist activity to AhR depending on the cell context and the experimental conditions [10]. The continuous administration of quercetin following TCDD exposure in C57Bl/6J mice prevented the reduction in body weight due to dioxin exposure [18], and quercetin treatment for 30 days was found to reduce hepatomegaly. Moreover, treating endothelial cells with 100-μM quercetin, following the treatment with the AhR-ligand polychlorinated biphenyls, was found to significantly reduce cyp1a1 mRNA level [19]. In addition to the ability of flavonoids to interact with the AhR, many of these flavonoids are also substrates of the CYP1A1 enzyme [20]. Flavonoid levels in human blood are usually in the μM concentration range, and this amount was reported to be sufficient to either inhibit or activate the AhR [21]. These findings suggest that quercetin could antagonize AhR causing significant suppression in the production of cyp1a1.

Curcumin [1,7-bis(4-hydrosy-3-methoxyphenyl)-1,6-hepta-diene-3,5-dione] is a naturally occurring dietary ligand of AhR. It is the main component (70–75%) of turmeric herb (*Curcuma longa*). Curcumin has a powerful anti-inflammatory, antioxidant, and antimicrobial activities [22, 23]. It has this ability because it can act through many cellular pathways including many transcription factors, hormones, growth factors, and their associated receptors. Also, curcumin is a powerful antitumor agent, due to its ability to dissociate the AhR/ARNT complex inside the nucleus [24]. The administration of curcumin suppresses cyp1a1 and 1b1 mRNA, induced by TCDD treatment. TCDD was reported to enhance AhR/ARNT-mediated cyp1a1 induction, and the expression of indoleamine-2,3-dioxygenase (IDO), which could enhance malignant transformation. In contrast, curcumin was observed to attenuate AhR/ARNT-mediated CYP induction by TCDD; thus, this mode of action may be the reason why curcumin could prevent malignant transformation, suggesting that curcumin could be used as a chemopreventive or anticancer agent.

Thus, plant-derived materials and extracts contain AhR-ligands or products that can promptly be converted into AhR-ligands. They are perhaps the largest class of natural AhR-ligands to which humans and animals are exposed. These chemicals are capable of binding to AhR as ligands, and suppress the transformation of the receptor by simply inhibiting the phosphorylation of AhR and Arnt, by protein kinase C, which is responsible for this process.

2.2 Endogenous ligand/indoles

Recent studies reported that exposing tissue culture media to UV light enhances the induction of AhR-hydroxylase, an enzymatic activity usually associated with CYP1A1 requiring tryptophan for this response [25]. Many studies showed the ability of UV light to induce CYP1A1 in the skin and liver of rats and mice [26], suggesting that a diffusible AhR-ligand was generated in the skin. Thus, FICZ and other photooxidation products of tryptophan may actually be novel chemical messengers of light [25]. The ability of other endogenous indoles and indole metabolites to bind to the AhR has also been reported [27]. These studies demonstrated that tryptophan and naturally occurring tryptophan metabolites (tryptamine and indole acetic acid) can bind to and activate the AhR and AhR-dependent gene expression in both yeast and mammalian cells in culture. Tryptamine was also shown to be a relatively potent competitive inhibitor of CYP1A1-dependent enzymatic activity, suggesting that it may be a substrate for this enzyme [28]. More recently, it was observed that kyneurinine, additional metabolic breakdown products of tryptophan, could activate the AhR signaling pathway [29]. Because these chemicals are relatively weak ligands and only found at low concentration in cells, they are likely not endogenous activators in normal physiological conditions. However, if cellular concentrations of some tryptophan metabolites (i.e., tryptamine) are significantly elevated to 700 nM, for example, in this case, these ligands could activate the AhR receptor [30]. The solar spectrum is composed of various wavelength radiations having specific effects on skin. UV with the wave length between 295 and 215 nm is responsible for most sunburn and DNA damage. UV with the wavelength 315–400 nm could cause immune suppression. The visible light with the wavelength 400–700 nm was reported to enhance the production of reactive oxygen species and cause damage to macromolecules, whereas infrared induces heat damage and also alters mitochondrial integrity in skin cells, resulting in the generation of reactive oxygen species. All the wavelengths in solar spectrum together contribute to skin aging and wrinkling [27]. These findings can change the way we think about skin aging. UV-B was recently shown to interact with AhR in a reaction involving the formation of a tryptophan-derived photoproduct (FICZ) [26, 29]. In other words, the free amino acid tryptophan in skin cell cytoplasm can act as a chromophore to absorb UV-B energy and the resulting photoproduct activates AhR signaling, suggesting that to achieve effective dermo-protection, AhR must be blocked to neutralize some adverse effects of environmental factors.

3. Cytokines controlling T helper 17 and T regulatory cells polarization

3.1 T helper 17 subset (Th17)

There are specific cytokines which are important for the differentiation of naïve T cells into the T helper 17 subset. IL-6 and TGF-β together are important for the development of this population [31]. The blockade of IL-6 through anti-IL-6 antibody was found to inhibit the development of Th17 cells [32]. Furthermore, the addition of IL-1β to culture medium was reported to enhance the development of the Th17 subset. IL-1 receptor knockout mice showed a significant defect in the Th17 population [33]. IL-1β was found to enhance expression of the transcription factors orphan nuclear receptor (ROR-γt) and interferon regulatory factor-4 (IRF-4), which are responsible for the development of the Th17 subset [34]. The Th17 subset could secrete a variety of cytokines including IL-17A, IL-17F, IL-21, and IL-22, which have a pathogenic effect in certain autoimmune mouse models [35].

Moreover, IL-23 which is secreted by antigen-presenting cells (APCs) after pathogen recognition is important for the maintenance of the Th17 population [31]. These data suggested that the Th17 subset is a very sensitive subset requiring specific cytokines for development and maintenance.

3.2 T regulatory subset (Treg)

The presence of IL-10 and TGF-β was reported to skew the development of naïve T cell toward the development of T regulatory cells (Treg) [36]. The main function of Treg is to suppress the immune response, and to inhibit the production of pro-inflammatory cytokines such as IL-2 and IFN-γ. The development of this population could be inhibited in the presence of IL-1β and IL-6 [37]. Treg cells are characterized by the expression of CD25 and the forkhead box p3 (Foxp3) transcription factor [38]. The decreased production of pro-inflammatory cytokines such as IL-6 and IL-1β could help in skewing the differentiation of naïve T cells toward the development of the Treg subset.

4. Role of Th17 in autoimmunity

In some cases, the immune system attacks our own tissues, causing autoimmunity. IL-17-producing cells play important roles in the development of different autoimmune diseases including rheumatoid arthritis (RA), an inflammation disorder which attacks the synovial joints and multiple sclerosis (MS), characterized by inflammation of the myelin sheath, resulting in de-myelination. It was reported that IL-17-knockout mice were protected against these autoimmune diseases [39]. In contrast, a high level of IL-17 was detected in the serum of patients with MS, RA, and systemic lupus erythematous (SLE). This suggests that Th17 cells expressing high levels of ROR-γt and IL-23R could be one of the causes of these diseases [40]. In addition, it was also reported that the Th17 subset increases the severity of EAE, diabetes, and RA [41, 42].

5. Effects of AhR-ligands on the production of Th17/Treg subsets and autoimmunity

Differentiation of Th17 cells depends on the presence of interleukin (IL)-6 and transforming growth factor (TGF)-beta, and it could be regulated by the activation of AhR [43]. The differentiation of Th17 cells could be enhanced by endogenous AhR agonists found normally in culture medium. The RPMI culture medium could support very low levels of Th17 polarization, because it lacks the presence of these ligands. In contrast, Iscove's modified Dulbecco's medium (IMDM) is known to be rich in aromatic amino acids, such as tryptophan, histidine, and phenylalanine, that were thought to be the precursors of endogenous AhR-ligands and therefore significantly increase the development of Th17 cells [43]. In addition, treating naïve $CD4^+$T cells with the AhR-ligand FICZ in Th17 cell polarizing conditions helps in skewing the differentiation of naive $CD4^+$T cells, *in vitro*, toward the development of the Th17 population, and as a result, significant amounts of IL-17*a*, IL-17*f,* and IL-22 cytokines will be secreted. In contrast, a significant reduction in the development of Th17 cells was observed in AhR knockout mice, suggesting that the development of the Th17 cells was AhR dependent [35].

The activation of AhR with different AhR-ligands can regulate Treg/Th17 balance in mice. A significant increase in Treg population was noticed when AhR

is activated with TCDD. In addition, suppression in the severity of EAE disease by a TGF-β1-dependent mechanism [44] was seen. Moreover, C57Bl/6J mice carrying the *d* allele of the Ahr gene (Ahr*d* mice) were characterized by a reduced affinity of about 10–100-fold for AhR-ligands due to a mutation in its ligand-binding site, and treating Ahr*d* mice with (1 μg/mouse) TCDD, had no significant effect on the severity of EAE and the development of Treg cells [44]. In contrast, when AhR binds to FICZ, the activation of the receptor will interfere with the differentiation of Treg development, and cause a significant induction of the Th17 subset and worsen EAE disease which suggests that AhR regulates Treg/Th17 subset differentiation in a ligand-specific manner [44]. These data suggested that different AhR-ligands have different effects on the production of pro- or anti-inflammatory T helper cell subsets, by controlling the production of different cytokines in the surrounding environment.

6. Effects of I3C and indirubin on immunoregulation

Indole-3-carbinol (I3C) (AhR-ligand) is found in cruciferous vegetables. Indirubin (IO) is another AhR-ligand, and is one of the components of the traditional Chinese medicine Danggui Longhui Wan. Although both of them are AhR-ligands, neither of these compounds bind the AhR as potently as TCDD. I3C and IO have anticancer properties, because they could inhibit cyclin dependent kinases that leads to cell cycle arrest in various cell lines. Moreover, both AhR-ligands were used to treat cancer. I3C has been used for the treatment of both breast and prostate cancer [45], while IO has been traditionally used for the treatment of chronic myelocytic leukemia [46]. I3C could downregulate the production of pro-inflammatory cytokines in macrophages [47, 48], whereas IO was reported to suppress these mediators in splenocytes and microglial cells [49].

A study was conducted to evaluate the effects of I3C and IO on specific immune cell populations, such as murine bone marrow-derived DCs, and the effect of these AhR-ligands was tested *in vivo*. The results showed that I3C and IO have immunosuppressive effects on DCs, which could promote a regulatory environment, thus could be useful to suppress chronic inflammatory diseases and/or autoimmunity *in vivo*. In addition, activating DC with lipopolysaccharide (LPS), after treating the cells with both AhR-ligands, suppresses the production of pro-inflammatory mediators including tumor necrosis factor-α (TNF-α), IL-1β, IL-6, IL-12, and nitric oxide but increased IL-10 levels. The DC treated with AhR-ligands was reported to upregulate some immune-regulating genes such as ALDH1A, IDO, and TGFB [50].

Both AhR-ligands were reported to suppress the levels of nuclear factor-kappa B (NF-κB), but only I3C suppressed the LPS-induced activity of RelB transcription factor encoded by the RELB gene. Finally, when naïve T cells were cultured with DCs treated with AhR-ligands, the increased production of $CD4^{+}Foxp3^{+}$ (Treg cells) [50] was seen.

The above observations suggest that I3C and IO have immunosuppressive and anti-inflammatory effects on DCs. Since these ligands are significantly less toxic than TCDD, these natural products may become useful therapeutics for the treatment of autoimmune and inflammatory diseases [50].

7. Effects of curcumin on Treg/Th17 balance and autoimmunity

The protective effect of curcumin was evaluated using ovalbumin (OVA)-induced allergic inflammation in mouse model of allergic asthma. This mouse

model was established by ovalbumin. Mice were treated with different doses of curcumin (50, 100, and 200 mg/kg), and then the level of Treg/Th17-secreted cytokines was measured by enzyme-linked immunosorbent assay (ELISA). In addition, the percentages of Treg and Th17 were measured using flow cytometry assay. Results showed that curcumin caused a significant suppression in the production of Th17 subsets, and the secretion of IL-17 cytokines. In contrast, the AhR-ligand curcumin significantly enhanced the production of $CD4^+CD25^+$ T cell subsets. These findings suggest that curcumin could be used as therapeutic agent for patients with allergic asthma, because of its ability to significantly affect Treg/Th17 balance [51].

Curcumin plays an important role in multiple sclerosis (MS) autoimmune disease. It is characterized by some pathophysiological features such as breaching of blood-brain barrier (BBB) and injury to axons and myelin sheaths. Th17 cells play an important role in the pathophysiological process of MS. Curcumin is well known as active anti-inflammatory and neuroprotective agent if used prophylactically. Curcumin could inhibit neuroinflammation through multiple mechanisms in MS. First, CNS antigens will be captured by DC, and then the antigen will be presented to T cells, which will help in initiating inflammatory response [52]. This action will be followed by the secretion of different pro-inflammatory cytokines and enhancement of production of Th17 cells in circulation. The blood-brain barrier (BBB) usually expresses IL-17R and IL-22R receptors and the expression of these receptors will bridge the gap between Th17 and BBB tight junction that results in the disruption of tight junctions. This action will enhance the transmigration of Th17 across the BBB followed by the enhanced secretion of granzyme-B which in turn is found to initiate the killing of neurons. In contrast, curcumin treatment was found to inhibit the production and expansion of Th17 subsets in circulation. In addition, curcumin was reported to increase the expression of ZO-1 protein, an important tight junction protein, suggesting that curcumin can reduce neuroinflammation in MS autoimmune disease [52].

8. Discussions

How might different AhR-ligands, all with the ability to stimulate AhR-dependant gene transcription and promote Th17 cell development, promote either concomitant increases in Treg cells and lessen autoimmunity, or suppress Treg cell development and increase autoimmune activation? The presumed main function of AhR-induced transcriptional responses is to induce cytochrome P450 (e.g., CYP1A1) for detoxification of the detected aryl hydrocarbon. Indeed, FICZ is rapidly metabolized in a CYP-mediated reaction, within 1–3 hours [53] with a corresponding drop in AhR activation [54]. Thus, a transient AhR activation, even though promoting Th17 development and expansion, may ultimately terminate and allow Treg populations to emerge and dominate. In contrast, sustained AhR signaling might promote Foxp3 suppression and conversion of Treg to Th17 and Th1 cells.

Dietary AhR-ligands have also been suggested to act in an antagonistic manner to TCDD-induced AhR activation [55]. Additionally, although curcumin is able to act as a substrate for CYP1A1-mediated catabolism, it could partially decrease the accumulation of CYP1A1 mRNA [55] and antagonize CYP1A1 activity [56]. Therefore, interference with full AhR function, or metabolism of the inducing AhR-ligand or other endogenous ligands may be important in determining whether AhR-ligands result in regulatory and/or effector T cell development. Alternatively, certain AhR-ligands may induce distinct gene expression profiles [57], some of them promoting Th17 at the expense of Treg and others allowing the emergence of Treg.

The activation of AhR in DCs by some ligands may increase tolerogenic mediators, such as IDO, which promote Treg development. In support of this mechanism,

IDO expression was found to be increased in DCs by TCDD or FICZ [38]. The conversion of Treg to Th17 and Th17 to Th1 profiles has been reported and reprogramming of subsets might be possible by additional cytokine provision, such as IL-23, IL-6, or removal of reinforcement factors, such as IL-23 or AhR-ligands [38]. The reported ability of IDO products (i.e., tryptophan metabolites) to suppress ROR-γt and induce Foxp3$^+$Treg cells [58] may indicate Th17 to Treg conversion, or shift to an IL-10-producing subset might result during exposure to some AhR-ligands. Since some AhR-ligand treatments lead to Th17 responses in the absence of Treg responses, allowing enhanced autoimmunity, this suggests that these ligands may be useful to promote antitumor immunity. It also raises the possibility that the anticancer effects of curcumin and quercetin may be due to their ability to promote potent effector T cell subsets in addition to suppressing some chronic inflammatory states. Another potentially beneficial use of AhR-ligands that have the ability to increase Treg populations is for the prevention or treatment of autoimmune diseases.

Experimental evidence has shown that flavonoids could be used to treat many diseases including cancer [59, 60]. The administration of curcumin was found to block the formation of lesions and tumors in C57Bl/6J mice after implanting murine melanoma B16F10 cells in their neck and brain. Furthermore, curcumin treatment was observed to significantly inhibit the proliferation of PC-3 prostate tumor cells.

The proposed mechanism for this effect of curcumin was its ability to significantly suppress NF-κB and AP-1 signaling pathways in tumor cells [61, 62]. Curcumin was given orally at concentrations in the micro-molar range; however, results showed that the concentration of curcumin was in the nano-molar range in the plasma [63, 64], due to the extensive metabolism of curcumin in the intestine and liver, which prevents the maintenance of high concentration of curcumin in the plasma and tissues after taking it orally [65, 66]. The curcumin is effective on the cancer cells at high concentration which is difficult to be maintained for several hours even in the gastrointestinal tract [63]. This suggests that the potential of using curcumin for cancer treatment is limited when given orally and the intraperitoneal injection may be more effective.

In contrast, other studies have shown that high concentrations of curcumin were found to enhance chromosome malformation in different cell lines. The curcumin could cause DNA damage both *in vivo* and *in vitro* and increase the incidence of thyroid gland follicular cell hyperplasia and carcinogenic activity in the small intestine [67–69]. This was proposed mainly due to its ability to increase the production of reactive oxygen species (ROS) [70]. Other studies have shown that curcumin has the ability to suppress cytochrome P450 enzyme, glutathione, S-transferase, and UDP-glucuronosyltransferase, causing toxicity due to the increased level of drugs in the plasma [71]. Although lower concentrations of curcumin could enhance antioxidant activity, high concentrations of curcumin have shown pro-oxidant effects [63, 72].

Similarly, quercetin is known as an antioxidant, anti-inflammatory, and antimicrobial compound at low doses [73, 74]. In contrast, quercetin can enhance the production of ROS at higher concentrations [75]. ROS production by quercetin was found to kill some cancer cells, and quercetin complexes with bioactive compounds and metal ions such as lanthanum was reported to have powerful cytotoxic and antitumor properties at a concentration in the range of 100–1000 mM and the exposure time of tumor cells was around 3 hours. A quercetin/lanthanum complex was found to have a genotoxic effect on human cervical carcinoma cells due to ROS production [76].

Conflict of interest

There is no conflict of interest in this study.

DOI: http://dx.doi.org/10.5772/intechopen.80840

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