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Commentary

Ah receptor- and Nrf2-gene battery members: Modulators of quinone-mediated oxidative and endoplasmic reticulum stress

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ABSTRACT

Quinones are ubiquitously present in mammals and their environment. They are involved in physiologic functions such as electron transport but are also toxic compounds. In particular, quinone–quinol redox cycles may lead to oxidative stress, and arylating quinones have been demonstrated to activate endoplasmic reticulum (ER) stress. To detoxify quinones coordinately regulated Ah receptor and Nrf2 gene batteries evolved. Two pathways are emphasized: (i) glutathione S-transferases, and (ii) NAD(P)H:quinone oxidoreductases NQO1 and NQO2 acting together with UDP-glucuronosyltransferases and sulfotransferases. Coupling between these enzymes may prevent oxidative and ER stress in a tissue-dependent manner, as discussed using benzo[a]pyrene detoxification in enterocytes, catecholestrogen metabolism in breast tissue and endometrium, and aminochromes in neurones and astrocytes. Possible consequences of chronic ER stress such as apoptosis and inflammation as well as therapeutic possibilities of modulating Ah receptor and Nrf2 are discussed. In conclusion, tight coupling of Ah receptor- and Nrf2-regulated enzymes may prevent quinone-mediated oxidative and ER stress.

1. Introduction

Quinones and their phenolic precursors are ubiquitously present in animals and their environment. They include polyphenols and tocopherols in the diet, drugs in medicine, and metabolites of environmental pollutants. Quinones are involved in diverse biologic processes such as electron transport, metabolism of estrogens and catecholamines, and detoxification of aromatic hydrocarbons. Quinone–quinol redox cycles lead to oxidative stress, and some quinones are highly toxic arylating agents, reacting with cellular thiols. Thereby, they activate pathophysiologic processes such as endoplasmic reticulum (ER) stress, inflammation and cancer ([1–3] for references).

Enzyme systems have evolved to detoxify reactive quinones such as multiple glutathione S-transferases (GSTs) [4,5], and the NAD(P)H:quinone oxidoreductases NQO1 and NQO2. The latter enzyme converts quinones by 2-electron reduction to corresponding quinols. Quinols are subsequently conjugated by UDP-glucuronosyltransferases (UGTs) and sulfotransferases (SULTs) [6]. Detoxification enzymes are often termed drug-metabolizing enzymes (DMEs) due to their importance in drug development and therapy. Early studies suggested that benzo[a]pyrene (BaP)-3,6-quinone after reduction to the corresponding quinol, was efficiently detoxified by Ah receptor (AhR)-regulated rat UGT1A6 (in the early publication termed UGT1A1) together with an at that time unknown UGT, now designated rat UGT1A7 [7,8], and by human UGT1A6 and UGT1A9 (the latter termed UGT1.7 in the early publication) [9]. NQO1, UGTs and GSTs are also controlled by the antioxidant Nrf2-Keap1 pathway, in addition to regulation by the AhR [10–13]. Recently, it has been established that both AhR and Nrf2 are required for the induction of these enzymes in mice [14] and possibly humans [15].

It was the aim of the commentary to emphasize two AhR- and Nrf2-regulated pathways which attenuate quinone-mediated oxidative and ER stress: (i) GSTs acting together with glutathione biosynthesis, and (ii) NQO1 and NQO2 acting together with UGTs and SULTs. Tight coupling between these enzymes is necessary to prevent chronic oxidative and ER stress which may lead to tissue-dependent toxicity, exemplified by BaP toxicity in enterocytes, catecholestrogen-mediated genotoxicity in breast tissue and endometrium, and aminochrome-mediated oxidative stress in neurons and astrocytes of substantia nigra.

2. Overview of Ah receptor- and Nrf2-regulated gene batteries

AhR is the only ligand-activated member of the bHLH/PAS (basic helix-loop-helix/Per-Arnt-Sim) family of transcription factors [16].

Abbreviations: AhR, Ah receptor; DME, drug-metabolizing enzyme; ER, endoplasmic reticulum; GSH, reduced glutathione; GST, glutathione S-transferase; NQO, NAD(P)Hquinone oxidoreductase; Nrf2, nuclear erythroid-related factor 2; ROS, reactive oxygen species; SULT, sulfotransferase; UGT, UDP-glucuronosyltransferase.

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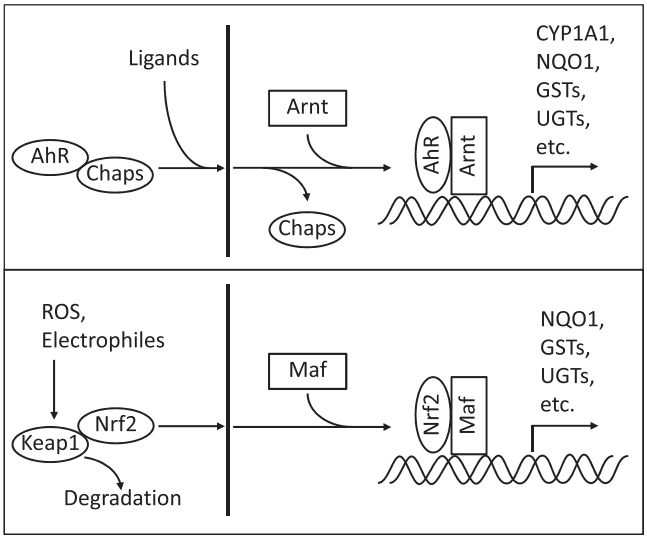

Fig. 1. Activation of Ah receptor (AhR) and Nrf2. (Above) The AhR is normally present in the cytosol guarded by multiple chaperones (Chaps). Upon ligand activation the AhR translocates to the nucleus, sheds the chaperones and associates with its partner Arnt. The heterodimer binds to XREs (xenobiotic response elements) in the regulatory region of target genes. (Below) Nrf2 is inhibited and degraded by Keap1 (part of an ubiquitin E3 ligase). Nrf2 is released following reaction of distinct cyteines of Keap1 with ROS and electrophiles. Nrf2 associates with small Maf proteins and related bZip transcription factors and binds to AREs (antioxidant response elements) in the regulatory region of target genes.

It represents a multifunctional switch involved, for example, in female reproduction, vascular development, inflammation, immunosuppression, and adaptive detoxification of lipophilic endo- and xenobiotics [16,17]. Notably, AhR controls both basal and adaptive DME expression [18]. After ligand binding the AhR translocates to the nucleus, sheds chaperones and associates with its partner protein Arnt. The heterodimer binds to XREs (xenobiotic response elements) with the consensus sequence TnGCGTG in the regulatory region of target genes (Fig. 1). Sustained AhR activation by dioxins may lead to dysregulation of AhR signaling and to dioxin toxicity [17,19]. In addition to classical ligands such as 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) and aromatic hydrocarbons, a number of endogenous AhR agonists have been suggested, including tryptophan metabolites, bilirubin and eicosanoids ([20,21] for references), and evidence for ligand-independent activation of the AhR is accumulating [20].

Nrf2 is a member of a subset of bZip transcription factors, termed CNC bZip family. It is a master regulator of antioxidant defense and cell survival [10–13]. Sequestered in the cytoplasm through binding to Keap1, a key sensor of oxidative/electrophile stress, it is part of the Cul3-dependent ubiquitin E3 ligand complex. In unstressed conditions Nrf2 is constantly degraded. Hence, its level is low. Binding of reactive oxygen species (ROS) and other electrophiles to distinct cysteines of Keap1 releases Nrf2 which translocates to the nucleus, associates with small Maf and related proteins such as c-Jun and ATF4, and binds to AREs (antioxidant response elements) with the consensus sequence TGACnnnGC in the regulatory region of target genes (Fig. 1). Nrf2 is involved in both basal and inducible expression of its target genes such as UGTs [11]. Discovery of Nrf2 and Keap1, their domain structure, mechanisms of activation and functions have been elegantly reviewed ([12] for references).

Transcription factors such as AhR and Nrf2 regulate distinct but overlapping DME gene batteries, involved in endo- and xenobiotic detoxification and antioxidant defense. As mentioned before, both AhR and Nrf2 activation are required for expression of Phase II detoxification enzymes, listed in group B of Table 1. Comprehensive gene batteries have been identified using oligonucleotide microarray analysis in liver of AhR-deficient and TCDD-treated mice [22], and in small intestine of Nrf2-deficient and sulforaphane-treated mice [11]. Similar studies of Nrf2-regulated genes were carried out with cortical neurons and astrocytes [23,24]. However, microarray analysis does not distinguish between primary and secondary effects of transcription factors.

Table 1
Discussed human Ah receptor (AhR) and Nrf2 gene battery members.[a]

AhR gene battery	Nrf2 gene battery
(A) CYP1A1	–
CYP1A2	–
CYP1B1	–
(B) NQO1/NQO2	NQO1/NQO2
AKR1	AKR1
UGT1s	UGT1s
UGT2s	UGT2s
GSTAs	GSTAs
GSTMs	GSTMs
GSTPs	GSTPs
(C) –	GCLC/GCLM
–	GPX2
–	Thioredoxin
HO-1	HO-1
(D) AhR repressor	–
–	AhR
Nrf2	Nrf2

[a] AhR and Nrf2 gene battery members have been grouped into selective AhR- and Nrf2-controlled genes (A and C, respectively), genes requiring both AhR and Nrf2 activation for transcription (B), and genes of transcription factors (D). References are given in the text.

AhR and Nrf2 exhibit multilevel crosstalk. (a) The prototypical AhR-regulated CYP1A1 generates ROS which downregulate CYP1A1 expression [25]. The resulting oxidative stress upregulates Nrf2 [10]. In addition, AhR is controlled by its repressor. (b) Nrf2 has been identified as a downstream target of AhR, based on functional XREs in the promoter of Nrf2 [26]. Interestingly, AhR is also a target of Nrf2 [27]. (c) Coordinate induction of UGTs by AhR and Nrf2 is also possible by direct or indirect (via coregulators) interaction between these two transcription factors [28]. (d) Furthermore, AhR [20] and Nrf2 [29] are embedded in signaling networks. Regulation of UGTs and GSTs by both AhR and Nrf2 has been clearly demonstrated in TCDD-treated, Nrf2-deficient mice [14]. Linked AhR- and Nrf2-regulated genes, i.e., genes containing response elements for binding the AhR and Nrf2 in their regulatory region, include both Phase I and II detoxifying enzymes, such as NQO1 and conjugating enzymes such as GSTs and UGTs [5,10,30]. Other enzymes have been added recently such as aldo-keto reductase (AKR) members [31], discussed in Section 5.1. Subsequently, two groups of AhR- and Nrf2-regulated, quinone-detoxifying DMEs are discussed: (i) GSTs and enzymes of GSH biosynthesis, and (ii) NQO1/NQO2 acting together with UGTs and SULTs.

3. Detoxification of quinones by GSTs

GSTs are multifunctional enzymes, mainly involved in detoxification of ROS and other electrophiles, including metabolites of lipid peroxidation, epoxides and quinones [4,5]. They are present as cytosolic, mitochondrial and microsomal enzymes. Multiple classes of cytosolic GSTs have been characterized, such as GSTA, M and P members, which are expressed in a cell-dependent manner.

In addition to GSTs, GSH homeostasis is also regulated by Nrf2, for example, the rate limiting enzymes of GSH biosynthesis, glutamate-cysteine ligase, catalytic and modifier subunits (GCLC and GCLM) [4]. Nrf2 also facilitates GSH homeostasis in mild

oxidative stress. High intake of vegetables increases GSTA and GSTP in human duodenum [32]. Superoxide generated by oxidative stress is known to be metabolized by superoxide dismutase to hydrogen peroxide which is detoxified by multiple enzymes, such as catalase and glutathione peroxidases (GPX). GPX2 has been demonstrated to be Nrf2-regulated in the gastrointestinal tract and in lungs where it is the major cigarette smoke-inducible GPX [33].

In addition to the GSH system, other redox systems are also Nrf2-regulated, for example, (i) thioredoxin which is evolutionary related to GSTs [4], and (ii) bilirubin, which is generated by the prototypical Nrf2-regulated heme oxygenase-1 (HO-1), the latter also controlled to some extent by the AhR ([34] for references).

4. Quinone detoxification by NQO1 and NQO2 acting together with UGTs and SULTs

Quinones can be reduced (i) by 1-electron transfer pathways to semiquinones, for example, by CYP reductase, leading to semiquinone/quinone redox cycles and oxidative stress, or (ii) by 2-electron transfer, bypassing the semiquinone step via the multifunctional cytosolic flavoprotein NQO1 [6,35]. In support of its detoxification function, a polymorphism of NQO1 in humans (4% in Caucasians and 20% in Chinese) leads to rapid degradation of the enzyme, and has been associated with increased risk of leukemias and benzene-mediated hematotoxicity [36].

Closely related human NQO2 is controlled by AhR and Nrf2 but uses the NADH metabolite N-ribosyldihydronicotinamide as reductant [37,38]. Very little is known about this reductant. In addition, differences in catalytic activity of the two reductases have been observed. For example, NQO1-deletion is associated with increased cancer susceptibility whereas NQO2-deletion was found to be associated with various neurological disorders such as Parkinson's disease ([38] for references). Interestingly, NQO2 has been characterized as ortho-quinone reductase for adrenochrome [37] and estrogen ortho-quinones [39], as discussed in Section 5. Whereas NQO1 is widely expressed, NQO2 is mainly expressed in heart, brain, lung, liver and skeletal muscle. NQO1 and NQO2 are differentially expressed in human hepatocellular and biliary tissue [40]. Interestingly, NQO1 and NQO2 are involved in stabilization of the tumor suppressor p53 [41,42].

UGTs and SULTs represent supergene families [43,44]. They are conjugating, for example, BaP quinols generated by NQO1 [7–9]. UGTs have been classified in two families, UGT1 and UGT2, based on sequence identity of the encoded proteins. As mentioned before, UGT1 members are controlled by linked AhR and Nrf2 transcription factors in mice [14] and humans [15,45]. UGT2 members are also controlled by the two transcription factors in mice [14], but coregulation by AhR remains uncertain. UGT2B7 have been shown to be regulated by Nrf2 [46]. Among the SULTS, SULT1A3 is known to sulfonate catecholamine neurotransmitters such as dopamine, epinephrine and norepinephrine [47].

5. Examples of cell-dependent quinone reductase-coupling with conjugation

Paradoxical effects have been observed when extrapolating in vitro effects of Phase I metabolism to the in vivo situation. The reason was discussed as tight coupling between Phase I and II metabolism [48]. The degree of Phase I and II coupling is expected to be cell specific and depends upon the pharmacokinetics of the particular chemical, as subsequently discussed.

5.1. Benzo[a]pyrene quinones in enterocytes

The ubiquitous environmental pollutant and prototypical carcinogen BaP has been intensely studied. Metabolism of BaP is known to lead to CYP1A1-mediated bioactivation to BaP-7,8-dihydrodiol epoxide (responsible for DNA adducts) and cytotoxic BaP quinones. However, surprising results were obtained with CYP1A1-deficient mice. Contrary to expectation, CYP1A1-induced mice remained healthy when treated orally with BaP whereas enterocyte-specific (but not hepatocyte-specific) CYP1A1-deficient mice died with bone marrow toxicity and immunosuppression under the same conditions [49]. These findings suggest efficient detoxification of oral BaP in intestinal epithelial cells by tight coupling of Phase I and II metabolism. In support, BaP-DNA adducts were not increased in the intestinal epithelium of CYP1A1-deficient mice [50]. Here, the focus is on detoxification of BaP quinones (a major fraction of reactive BaP metabolites) which represent cytotoxins, tumor promoters and progressors [51]. Interestingly, BaP-3,6-quinone has been demonstrated to activate both AhR and Nrf2-Keap1, and expression of their target genes [51]. As discussed before, quinones may either be detoxified by GSTs [4,5] or by NQO1-mediated 2-electron reduction and subsequent conjugation by SULTs and UGTs. Conjugation of BaP quinols appears to be very efficient. Six hours after intratracheal instillation of BaP to rats most of the metabolites were recovered in bile; 30% as GSH conjugates, 6% as sulfate conjugates and 49% as glucuronides. Among the glucuronides, 18% were monoglucuronides, 21% 3,6-quinol diglucuronide, and 10% 1,6/6,12-quinol diglucuronides [52]. Glucuronides are known to be released from enterocytes into the intestinal lumen, e.g., by the AhR-inducible export transporter ABCG2 (previously termed BCRP) ([13] for references).

The CYP1A1-mediated pathway leading to the formation of BaP-7,8-dihydrodiol epoxides is also controlled by detoxification enzymes. For example, BaP-7,8-dihydrodiol can be conjugated by AhR/Nrf2 inducible UGTs [53]. It can also be converted by AhR/Nrf2-controlled aldo-keto reductases (AKRs) to the corresponding catechol which is readily autoxidized to the very reactive ortho-quinone [31]. Ortho-quinones can be detoxified by NQO2 [4,5,37,38] and conjugated by UGTs and SULTs.

5.2. Catecholestrogens in breast tissue and endometrium

Estrogens are essential for development of the reproductive system in women. On the other hand, the proliferation and genetic instability induced by estrogens in breast and uterus may increase the risk that normal cells transform into the malignant phenotype. The complexity of estrogen metabolic pathways has been well studied in postmenopausal woman with breast or endometrial cancer [54,55]. In this population estradiol (E_2) is formed from estrone by 17β-hydroxysteroid dehydrogenase type 12. E_2 is converted to catecholestrogens at two different positions: (i) by AhR-inducible CYP1A1 to mitoinhibitory 2-hydroxy-catecholestrogen, and further metabolized by catecol-O-methyltransferase (COMT) and UGT1A1 and UGT1A3. This metabolic pathway is considered beneficial in carcinogenesis. 2-OH-catecholestrogen is detoxified by UGT1A1. In support of a beneficial role of unconjugated 2-OH-catecholestrogen, less glucuronidation in carriers of UGT1A1*28 is associated with decreased endometrial cancer risk [56]. (ii) On the other hand, CYP1B1 is converting E_2 to genotoxic 4-hydroxy E_2 (4-OH-E_2) which is inactivated by UGT2B7 [54,55]. However, 4-OH-E_2 may also be oxidized to its ortho-quinone which undergoes redox cycles with generation of oxidative stress leading to cytotoxicity, inflammation and genotoxicity (Fig. 2). Several observations suggest that in particular 4-hydroxylated catecholestrogens are important in estrogen-mediated carcinogenesis [57]. 4-Hydroxylated estrogens are oxidized by any oxidative enzyme to reactive ortho-quinones which may bind to estrogen receptors. As a 'Trojan horse' estrogen receptor-bound ortho-quinones may undergo redox cycling with generation of DNA-damaging ROS [58]. The ortho-quinones may be inactivated by GSTs or by reduction to

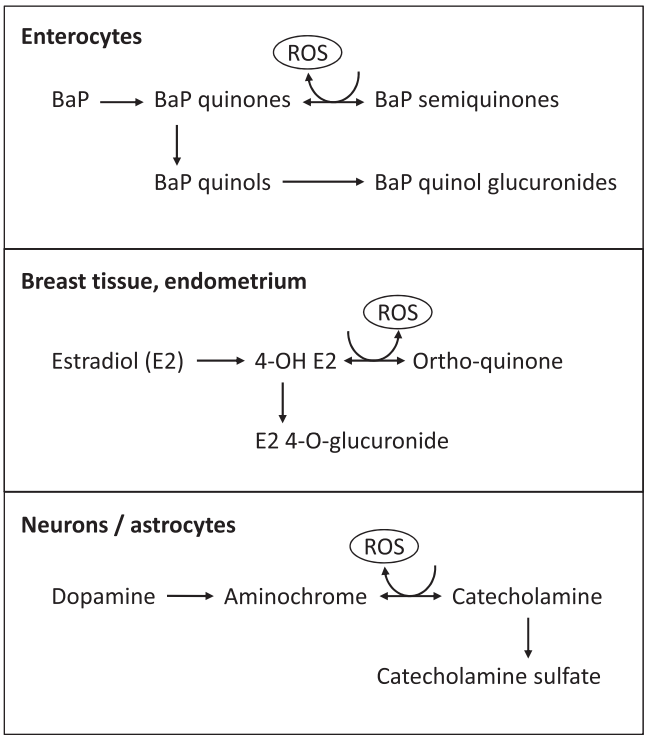

Fig. 2. Examples of cell-dependent enzyme coupling in detoxification of quinone-mediated oxidative stress. Quinones are converted by 2-electron reduction via NQO1 and NQO2 to the corresponding quinols which are subsequently conjugated by UGTs and SULTs. (A) Detoxification of benzo[a]pyrene (BaP) quinones in enterocytes. Redox cycles between quinones and semiquinones lead to generation of oxidative stress. (B) Possible generation of catecholestrogen-mediated oxidative stress in breast tissue and endometrium. (C) Possible aminochrome-mediated oxidative stress in neurones and astrocytes. Details are described in the text.

catechols via NQO1 and NQO2 (the latter enzyme has been characterized as catechol quinone reductase [37,38]). Resulting catechols are inactivated by SULTs and UGTs. Notably, detoxifying UGT2B7 is overexpressed in tumor tissues which may be hijacking the Nrf2-mediated detoxification program [55]. Nevertheless, induction of AhR and Nrf2 pathways may be beneficial at early stages of carcinogenesis (see Section 7).

5.3. Aminochrome in neurons and astrocytes

Parkinson's disease (PD) is characterized by progressive degeneration of the nigrostriatal dopaminergic pathway and formation of inclusions known as Lewy bodies. The frequent sporadic form of PD may result from both genetic and environmental risk factors, including neuroinflammation and oxidative stress [59,60]. The prodrug L-dopa (dihydroxyphenylalanine) is the established treatment of PD. However, dopamine can be oxidized to aminochrome (Fig. 2). This reactive ortho-quinone may be reduced and undergoes redox cycles with generation of oxidative stress [59]. It has been shown to react with α-synuclein, the major component of Lewy bodies [60]. The bioactivating pathway is known to be protected by several detoxification enzymes such as COMT and the monoamine oxidases MAO A and B. Aminochrome is also efficiently conjugated by GSTM2 [61,62]. In addition, it can be reduced by NQO1 and NQO2 [37,38,62,63], and the resulting quinols may be conjugated by SULT1A3 [47]. These metabolic pathways may prevent redox cycling of quinones and oxidative stress. The protective role of NQO2 is supported by an epidemiologic study in Japanese PD patients suggesting that a polymorphism of low activity NQO2 is associated with the disease [64]. Furthermore, it has been shown that dopamine activates Nrf2-regulated neuroprotective pathways in astrocytes and meningeal cells [22,23,65,66]. Hence, tight coupling of bioactivation and detoxification may largely prevent aminochrome-mediated toxicity.

6. Consequences of quinone-mediated oxidative and ER stress

As indicated in the introduction, exposure of cells to arylating quinones may trigger the ER stress response [1]. The ER is involved in processing secretory and integral membrane proteins, for example, in chaperone-mediated protein folding by forming the correct S–S-bonds. Obviously, the latter function is impaired by covalent binding of arylating quinones to cellular thiols. The resulting ER stress response, also termed unfolded protein response, is initiated by activation of three protein kinases: activating transcription factor 6 (ATF6), inositol-requiring protein 1α (IRE1α), and PKR-like ER kinase (PERK). For detailed summaries the reader is referred to excellent reviews [2,3,67]. In brief, (i) ATF6 activates the synthesis of chaperones. Notably, ATF6 has recently been identified to be activated by insertion of integral membrane proteins into ER membranes [68]. Hence, ATF6 contributes to the coupling of ER proliferation to physiological demand. This function may explain ER membrane proliferation following induction of CYPs by phenobarbital [69] and dioxins [70]. (ii) IRE1α regulates degradation of misfolded proteins, and (iii) PERK decreases protein entry into the ER lumen by inhibition of protein translation. Thereby, protein overload in the ER lumen is attenuated. In conclusion, activation of the three kinases may resolve ER stress. However, chronic ER stress leads to pathophysiologic consequences, for example, to inflammation, cirrhosis and cancer in liver [3], and to apoptosis via activation of NFκB in the substantia nigra [71]. Interestingly, PERK has been demonstrated to activate Nrf2 and activate its antioxidative and cell survival pathways [72,73]. Hence, Nrf2 contributes to resolution of ER stress. The AhR is also known to be involved in complex pro- and anti-inflammatory responses [74,75]. Recently, AhR agonists have been shown to activate ER stress resulting in an apoptotic response [76].

7. Therapeutic approaches involving Ah receptor and Nrf2 modulation

AhR- and Nrf2-regulated genes/enzymes are attractive since they can be modulated, for example, by phytochemicals. Phytochemical activators and inhibitors of AhR include DIM (diindolylmethane, the biologically active oligomer of indole-3-carbinol) and resveratrol, respectively. These AhR modulators and activators of Nrf2 such as sulforaphane and epigallocatechin gallate are currently studied in preclinical trials of chemoprevention [77]. In addition, coffee has been demonstrated to induce AhR- and Nrf2-regulated UGTs [78]. Notably, Nrf2 activation by phytochemicals follows a biphasic (U-shaped) dose response relationship: a stimulatory effect at low dose is followed by adverse responses at high doses [79,80]. Hence, there is a pharmacological window of the chemopreventive dose and the maximally tolerated dose. For normal cells it appears that some stress can be good, albeit not too much. On the other hand, constantly stressed cells such as cancer cells appear to hijack Nrf2-mediated detoxification and oxidative stress-preventing pathways. Hence, chemopreventive doses of phytochemicals may not only increase the survival of normal but also of cancer cells [81]. Nevertheless, for the general population and certain moderate at-risk groups, AhR- and Nrf2-activating phytochemicals are considered to be therapeutically beneficial [80].

8. Conclusions

Quinones are involved in physiologic processes but they are also toxic compounds. Quinone–quinol redox cycles produce

oxidative stress, and chronic exposure to arylating quinones may produce ER stress with resulting apoptosis or inflammation. Therefore, detoxifying enzymes evolved to prevent tissue injury. Two pathways are emphasized: (i) GSTs and GSH biosynthesis, and (ii) NQO1 and NQO2 acting together with UGTs and SULTs. Interestingly, these pathways are induced by activating both AhR and Nrf2. Mechanisms of multilevel crosstalk between these transcription factors are discussed. Tight coupling of these enzymes may prevent quinone-mediated toxicity in a tissue-specific manner, exemplified by detoxification of BaP metabolites in enterocytes, of catecholestrogens in breast and endometrium, and aminochrome metabolites in substantia nigra. In these cells/tissues quinones are converted by 2-electron reduction via NQO1 and NQO2 to quinols, bypassing the formation of reactive semiquinones. The resulting quinols are readily conjugated by UGTs and SULTS, thereby preventing reoxidation, redox cycles and resulting oxidative stress.

ER stress, also termed unfolded protein response, results from accumulation of misfolded proteins in the lumen of the ER. Protein kinases have been identified which are sensing and eventually attenuating ER stress. Interestingly, one of these kinases, PERP, has been shown to activate Nrf2 and its ensuing antioxidant functions. Moreover, activation of AhR may contribute to ER stress-mediated apoptosis. Both AhR and the Nrf2-Keap1 pathway can be modulated by a large variety of compounds including many phytochemicals, offering the possibility of therapeutic interventions. Limitations of this approach have also been observed, since cancer cells may hijack AhR- and Nrf2-regulated DMEs. In conclusion, coupling of oxidoreductases with conjugating enzymes is necessary for quinone detoxification. Following 2-electron reduction by NQO1 and NQO2 to quinols, UGTs and SULTs are necessary to prevent redox cycles. In the case of 1-electron reduction to semiquinones GSTs are effective.

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