HHS Public Access

Author manuscript

Nucl Receptor Res. Author manuscript; available in PMC 2019 December 06.

Published in final edited form as:

Nucl Receptor Res. 2019 ; 6: . doi:10.32527/2019/101447.

Phase 0 of the Xenobiotic Response: Nuclear Receptors and Other Transcription Factors as a First Step in Protection from Xenobiotics.

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Abstract

This mini-review examines the crucial importance of transcription factors as a first line of defense in the detoxication of xenobiotics. Key transcription factors that recognize xenobiotics or xenobiotic-induced stress such as reactive oxygen species (ROS), include AhR, PXR, CAR, MTF, Nrf2, NF-κB, and AP-1. These transcription factors constitute a significant portion of the pathways induced by toxicants as they regulate phase I-III detoxication enzymes and transporters as well as other protective proteins such as heat shock proteins, chaperones, and anti-oxidants. Because they are often the first line of defense and induce phase I-III metabolism, could these transcription factors be considered the phase 0 of xenobiotic response?

Introduction:

The term phase I and phase II detoxication have been a part of the lexicon of the toxicology vocabulary since first coined by R.T. Williams in 1959 [1]. Phase I and II enzymes include the cytochrome P450s (CYPs), flavin-containing mono-oxygenases (FMOs), peroxidases, dismutases, and conjugases [glutathione S-transferase (GST), uridine diphospho-glucuronosyltransferases (UDPGT; UGT), and sulfotransferases (SULTs)] that hydroxylate, oxidize, reduce, desulfurize, epoxidate, and conjugate xenobiotics [2]. Phase I refers to the early oxidative metabolism of the xenobiotic, and phase II typically refers to conjugation but potentially to a second oxidative reaction such as de-epoxidation by epoxide hydrolase [3].

Later the discovery of xenobiotic transporters led to the term phase III and refers to proteins that eliminate xenobiotics from cells through membrane transport pumps [4]. Phase III transporters include key members of ATP-binding cassette (ABC) transporters primarily in groups ABCB and ABCC such as multidrug resistance associated protein 2 (MRP2), multidrug resistance protein (MDR1), and bile salt export pump (BSEP) [5–8] (Fig. 1). Additional phase III transporters can also be found in groups such as ABCG (ABCG2; breast cancer resistance protein)[9]. Phase III transport can occur first, prior to transcription factor activation or phase I metabolism, as some xenobiotics are pumped out shortly after entering the cell by transporters such as MDR1 (also known as P-glycoprotein (PGP)).

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Therefore, phase III has been recently referred to as “phase 0 transport” because these transporters eliminate chemicals from the cell without prior phase I and II metabolism [10, 11]. However, for clarity and recognition of “transport”, I propose that phase III be used whether or not metabolism occurs prior to membrane transport. Similarly, conjugation of xenobiotics (phase II) can also occur prior to phase I metabolism if the proper leaving group is available and yet conjugation is still called phase II [12–14].

Most of these phase I-III detoxification enzymes and transporters are inducible and elegantly regulated by a suite of transcription factors. We often refer to specific pathways in transcriptomics based on the transcription factor activated. Thus, given that transcription factors are often our first responders following chemical exposure, they could be considered our first phase of detoxication. However, the term phase I is already taken and well established in the literature. Therefore, transcription factors that initiate our molecular response to chemical intrusion and help individuals acclimate to xenobiotic insults be identified as “phase 0”, “phase 0 detoxication” or “phase 0 xenobiotic response” because these transcription factors act as the initial response that increases phase I-III metabolism (Fig. 1)?

Xenobiotic-responsive transcription factors:

Transcription factors are any number of proteins that can help initiate or regulate transcription by binding DNA at specific promoter or enhancer sites [15]. The transcription factors crucial in toxicology can respond directly to xenobiotic exposure or respond to adverse metabolites or reactions caused by the chemicals such as increased ROS or perturbations in mitochondrial viability [16, 17]. The list of transcription factors presented below is not exhaustive, but includes the most prominent transcription factors in acclimating to chemical stress.

Transcription factors typically perturbed by endo- or xenobiotic-mediated stress are *trans*-acting elements that can be activated by ROS, hormones, xenobiotics or any number of extracellular stress signals. In turn, the transcription factor activates transcription by binding to DNA at specific *cis*-elements (i.e. response elements; consensus sequences) sometimes called a Xenobiotic Response Element (XRE) when dealing with the response element is unique to a xenobiotic responsive transcription factor. There are several groups of transcription factors often classified based on the type of DNA binding motif that they contain such as zinc fingers (nuclear receptors), basic leucine zippers (bZIP), or basic helix-loop-helix (bHLH). An example is the bHLH group of transcription factors containing a basic region adjacent to a helix-loop-helix (HLH) domain [15]. HLH members include the aryl hydrocarbon receptor (AhR), a key transcription factor in toxicology [18].

AhR:

The aryl hydrocarbon receptor (AhR), also known as the dioxin receptor, is a bHLH transcription factor in the Per-Arnt-Sim (PAS) family. It is an established xenobiotic receptor, as it is bound and activated by polycyclic aromatic hydrocarbons (PAHs), dioxins, and other coplanar aromatic compounds. It has additional functions based on the phenotype of untreated AhR-null mice, which include roles in the immune system, cardiac hypertrophy,

cardiac development, hepatic growth, and oocyte development [19–23]. Cardiac toxicity is common in animals exposed to TCDD and other AhR agonists during development [24, 25] and recent work shows mice treated with AhR agonists have a propensity towards obesity [26] and non-alcoholic fatty liver disease [27, 28]. AhR is also involved in regulating tryptophan metabolism through the kynurenine pathway [29].

The AhR binds to a number of xenobiotics such as the halogenated aromatic hydrocarbons (HAHs), (i.e the dibenzo-*p*-dioxins, dibenzofurans, and polychlorinated biphenyls (PCBs)), and the polycyclic aromatic hydrocarbons (i.e. pyrene, 3-methylcholanthrene, benzo[a]pyrene) [30]. HAHs have higher affinities for the AhR than PAHs and this difference is strongly associated with toxicity [31, 32]. It is assumed that the toxicity of HAHs and PAHs is due to the inappropriate expression of specific genes induced by AhR.

Following ligand activation, the AhR translocates to the nucleus, and mediates the transcription of a number of genes. Many of the proteins induced by AhR activation are detoxication enzymes and include CYP1A, CYP1B, NADPH:quinone oxidoreductase 1, and UDP-glucuronosyltransferase 1 [32–34] of which several are necessary for the metabolism of the xenobiotic and protection from its adverse effects. There is also data implicating AhR activity in the down-regulation of the estrogen receptor, glucocorticoid receptor, epidermal growth factor receptor, and CYP2C11 in mammals [35, 36].

Activation of AhR in the cytosol displaces it from heat shock proteins (HSP90), HSP23 and the immunophilin chaperone Ara9 (also known as XAP2) [29, 37]. This allows for translocation to the nucleus and association with the aryl hydrocarbon receptor nuclear translocator (ARNT). The AhR/ARNT complex binds to the xenobiotic response element (XRE, also known as the dioxin responsive element, DRE) and in turn activates basal transcription factors, the transcription of CYP1A, and other target genes (Fig. 2). In addition, ligand binding to AhR also releases proto-oncogene tyrosine kinase (SRC), which is a tyrosine kinase that phosphorylates and activates the ERK1/2 pathway. SRC can also phosphorylate AhR, increasing nuclear translocation [38].

Interestingly, reported cardiotoxicity mediated by benzo(a)pyrene is significantly reduced in zebrafish lacking AhR activity and in turn Cyp1a induction; however, this is not true for all PAHs tested [39]. 2,3,7,8-tetrachlorodibenzo-p-dioxin's (TCDD) teratogenicity is significantly ameliorated in AhR-null mice demonstrating a role for the AhR and its transcriptional response in mediatiating toxicity [40, 41]. Furthermore, a poor response to AhR agonists is associated with tolerance to dioxin and dioxin-like chemicals [18, 42, 43]. For example, *Fundulus heteroclitus* resistant to PAHs, polychlorinated biphenyls, and dioxins have been found in New Bedford Harbor, MA, Newark Bay, NJ, and the Elizabeth River, VA, and each of these populations demonstrate weak induction of CYP1A following chemical exposures primarily due to mutant AhRs [43–49].

Nuclear Receptors (PXR, CAR, HR96):

The nuclear receptor superfamily contains several transcription factors of which most are activated by small lipophilic ligands such as steroids, bile acids, bilirubin, fatty acids, heme, and xenobiotics [50–52]. Several nuclear receptors have a role in protecting individuals from

the build-up of toxic endobiotics, including farnesoid X-receptor (FXR) liver X-receptor (LXR), and the peroxisome proliferator activated receptors (PPARs); however, their role in xenobiotic metabolism and elimination is limited [53–62]. We will not consider these nuclear receptors for this review but it should be noted that they are crucial in the detoxication of endobiotics including bile acids, bilirubin, fatty acids, and oxysterols [53, 58, 60, 63–65].

PPARs, Vitamin D receptor (VDR), GR, and the retinoid receptors; RAR and RXR, are considered new targets for endocrine disruption by xenobiotics, in addition to the traditional endocrine targets such as estrogen receptors, thyroid hormone receptors and androgen receptors (all within the nuclear receptor family)[58]. In addition, new nuclear receptors have been discovered recently in several invertebrate species including some within the xeno-sensing clade [51, 66–68]. Of these “non-toxicology” nuclear receptors, the PPARs (PPARα/δ/γ) are of special interest in toxicology because several chemicals activate various PPARs including tributyltin, perfluoronated compounds such as PFOS, mono-2-ethylhexylphthalate, and atrazine [54, 58, 69–72]. Activation of PPARα causes peroxisome proliferation in the mouse liver, which is associated with rodent liver cancer [73, 74]. However, PPARα is highly expressed in rodent liver, but weakly expressed in human liver and this difference in expression is thought to be the underlying cause of specie’s differences in PPARα-mediated liver cancer, which is not observed in humans [75]. PPARγ activation is associated with obesity in multiple species. Current research suggests that PPARγ-mediated obesogens work in conjunction with RXR activation [54, 76]. However, there is little data indicating that activation of the PPARs provides a toxicokinetic effect by altering the metabolism, distribution, or clearance of most chemicals.

Confirmed xenobiotic sensing nuclear receptors include the pregnane X-receptor (PXR), its relative the constitutive androstane receptor (CAR), and their invertebrate ortholog, HR96 [68, 77–83]. Because of their impact on toxicology there are extensive reviews available on the wide range of ligands and indirect activators that mediate transcriptional activation through these nuclear receptors. For an overall review of these nuclear receptors and their ligands see the following manuscripts [84–87].

PXR and CAR are primarily expessed in the liver but show limited expression in other tissues such as the intestines, urinary tract, brain, and fish gills [78, 81, 88–92]. PXR and CAR act as master regulators of phase I and phase II metabolism enzymes and phase III transporters (Fig. 3). This includes CYP3A, CYP2B, UDPGT, GSTA2, SULT2A, and MRP2 [79, 93–98] with significant overlapping ligand specificities and gene regulation [86, 99]. There are several manuscripts and reviews that have taken a comprehensive look at environmental chemicals, nutrients, and pharmaceuticals that activate CAR and PXR [86, 100–104].

PXR is considered promiscuous because it binds a variety of bile acids, steroids and xenobiotics in mammals, including a large number of endocrine disrupting chemicals [105–109], providing circumstantial evidence that the PXR and its close relative, CAR, are protectors of the endocrine system [3]. Xenobiotics that bind and activate PXR in mammals include rifampicin, hyperforin, bisphenol A, 4-nonylphenol, phthalic acid, 1,1-dichloro-2,2-

bis (p-chlorophenyl)ethylene (DDE), methoxychlor, vinclozolin, alachlor, cyperterone acetate, trifluralin, and non-planar polychlorinated biphenyls (PCBs) [3, 79, 86, 104, 107–114].

PXR binds to a larger number of diverse chemicals than other receptors [86, 115]. PXR's promiscuity is attributed to its large and flexible ligand binding domain (LBD). PXR only needs to use a portion of its ligand binding pocket for chemical activation, and it has polar residues spaced through a smooth, multi-regional hydrophobic ligand-binding domain [112, 116, 117]. In addition, PXR has alpha helices that are flexible or can unwind, which allows for PXR to contract or expand in order to bind ligands of different sizes [117]. PXR also forms homodimers and a PXR-RXR heterotetramer complex that is crucial in the recruitment of coactivators and stabilization of the AF-2 domain [118, 119].

CAR is also promiscuous, however it is for reasons related to phosphorylation rather than its binding domain. CAR's ligand binding pocket is smaller and less flexible than PXR's, and in turn CAR is less promiscuous than PXR [3, 116, 120, 121]. TCPOBOP is one of a small number of true ligands for CAR. [122]. However, CAR can also be activated indirectly through changes in phosphorlylation status (i.e. phenobarbital) leading to translocation to the nucleus [16, 123, 124]. Under normal (inactivated) conditions, CAR is phosphorylated at Thr^{38}. Dephosphorylation occurs through a Receptor for Activated C Tyrosine Kinase 1 (RACK1) - Protein Phosphatase 2 A (PP2A) cascade [125] that is inhibited by Epidermal Growth Factor (EGF) signaling [126]. Phenobarbital binds the EGFR near the EGF binding site and reduces bound EGF [127] thus inhibiting downstream actions of EGF on SRC and subsequent phosphorylation of RACK-1 allowing for increased dephosphorylation by PPA2 [126]. This blocks EGF action and increases CAR activity.

Another putative mechanism for CAR activation by phenobarbital involves AMP activated protein Kinase (AMPK) [128]. However, downstream functions such as translocation of CAR or induction of CYP2B have varied depending on the system. Inhibition of CAR translocation and CYP2B expression have also been observed following AMPK activation providing contradictory results [129]. In summary, removal of the phosphate group from Thr^{38} triggers nuclear translocation of CAR. CAR in turn forms a heterodimer with RXR in the nucleus and binds PBREM/DR4 enhancer modules that induce gene transcription of CYP2B6 in humans, Cyp2b10 in mice [80], along with a host of other genes required for cell growth, metabolic activity, and detoxification [86, 130, 131].

Given CAR and PXR's role in the induction of crucial phase I-III detoxication proteins, it is not surprising that CAR and PXR are associated with protection from anthropogenic pollutants and endobiotics. For example, CAR or PXR activation increases the metabolism, detoxication, and clearance of bile acids [132, 133]. PXR expression increases in response to higher steroid levels during pregnancy presumably to protect the mother from the increased steroid load [134]. Lycopene is in part protective from atrazine toxicity due to its actions on CAR and PXR, and in turn increased metabolism of atrazine [70]. PXR also protects from benzo(a)pyrene toxicity by repressing AhR-mediated transcription [135]. CAR-null mice show significantly increased sensitivity to parathion due to decreased metabolism of parathion to *p*-nitrophenol, the key detoxication product of parathion [136]. In addition,

PXR-null mice showed greater hepatic damage following nonylphenol exposure than wildtype mice, presumably due to a repressed transcriptional response and lower hepatic detoxication enzyme levels in PXR-null mice. PXR-null mice also had greater serum nonylphenol concentrations than wildtype mice, providing further evidence that PXR-null mice were unable to transcriptionally respond and detoxify nonylphenol [137]. Interestingly, human PXR (hPXR) mice showed responses in between wildtype and PXR-null mice indicating that hPXR is less responsive to nonylphenol than murine PXR [137]. Overall, these xenobiotics showed greater toxic effects probably due to the lack of the proper regulation or induction of key detoxification enzymes [136–139].

However, sometimes PXR or CAR activation increases metabolic activation and the toxicity of the chemical. For example, thalidomide activation of PXR increases the production of its teratogenic metabolite, 5-hydroxy-thalidomide through CYP induction [140]. PXR also mediates rifampin toxicity through its actions on aldosterone [141]. CAR-null and PXR-null mice are also less sensitive to acetaminophen, and activation of these receptors and subsequent CYP induction increases NAPQI production and toxicity [142, 143]. PXR activation has also been associated with drug-drug interactions. For example, PXR activation by hyperforin increases clearance of warfarin, estradiol, and other drugs leading to reduced efficacy and poor clinical outcomes [3, 111, 144]. Overall, the discovery of PXR (and to a lesser extent CAR) has provided crucial information on drug-drug interactions and therefore saved lives.

HR96, as well as the *C. elegans* receptors, NRH48 and NHR8, are the invertebrate homologs to CAR, PXR, and VDR [51, 77, 145]. Similar to CAR and PXR, HR96 regulates lipid homeostasis [146–150]. HR96 also mediates the induction of phase I-III detoxication genes [68, 151, 152] following activation by endogenous or exogenous chemicals [68, 77, 83]. Recent studies indicate that activation of HR96 by atrazine provides protection from some chemicals such as docosahexaenoic acid and triclosan, but increases toxicity to others such as endosulfan and parathion [83, 152]. Thus, many invertebrates also contain nuclear receptors responsive to anthropogenic stress that induce phase I-III metabolism.

Nrf2, AP-1 and NF-kB:

Nrf2, AP-1, and NF-κB are transcription factors that respond to oxidative stress and are important regulators of GSTs, superoxide dismutase (SOD), catalase, and other protective proteins involved in the detoxification of ROS. The toxicant-induced formation of reactive oxygen species (ROS) has been associated with reduced fitness, apoptosis, cancer, and death. For example, pulp and paper mill and sewage effluents induce ROS and fatty acyl-CoA oxidase activity (an enzyme that produces the oxidant H_2O_2 from O_2) in exposed Longnose sucker (*Catostomus catostomus*) [153]. Several metals including iron, copper, nickel, chromium, cadmium and possibly arsenic mediate toxic effects through oxidative mechanisms and alter redox-sensitive signaling through Nrf2, AP-1 and NF-κB [154–159]. Of these metals, chromium and arsenic have also been shown to block AP-1 and NF-κB activity by binding their respective response elements [160], and the lack of Nrf2 increases sensitivity of cells to metals and a variety of other pro-oxidants [155]. Furthermore, cadmium-induced oxidative stress increases cytochrome c and activated caspase 3, 8 and 9,

causing apoptosis through the mitochondrial pathway. Anti-oxidants were able to alleviate the effects of cadmium on apoptosis demonstrating the role of ROS in cadmium-induced apoptosis [161].

The induction of antioxidant enzymes is also associated with protection from toxicants in vivo; a concept supported by the presence of a resistant population of *Fundulus heteroclitus* from the Elizabeth River, VA, USA that exhibits high glutathione peroxidase and reductase activities, along with high glutathione concentrations [162]. In addition, this population demonstrates both induction and a heritable increase in manganese superoxide dismutase (MnSOD) and glutathione concentrations, which may play a key role in their tolerance to PAHs [163]. Overall, the induction of anti-oxidant defenses is key in protecting individuals from chemical stress and there are three key transcription factors involved in their induction with Nrf2 as the primary protective sensor for ROS.

NF-κB: Nuclear factor-kappa B (NF-κB) is a transcription factor complex that can be activated by a number of different external signals, including several cytokines, bacterial and viral products, ultraviolet irradiation, oxidative stress, environmental chemicals such as arsenic, chromium, and diesel exhaust, and some therapeutic pharmaceuticals [164–172]. NF-κB in turn regulates the transcription of cytokines, cell adhesion molecules, stress response proteins, acute phase proteins, and regulators of apoptosis. Genes regulated by NF-κB include GSTP 1–1, COX-2, IL-1, C-reactive protein, phospholipase A2, DT-diaphorase, superoxide dismutase, α−1-antichymotrypsin, caspase 10, and IGF-BP1 [173–181] Comprehensive reviews on NF-κB can be found at [164, 173], or a website maintained by Dr. Thomas Gilmore, Boston University (www.NF-kB.org).

NF-κB is typically found in the cytosol in its inactive state where it is bound to inhibitory IκB proteins such as IκBα. Extracellular stimuli cause the activation of IKK, a kinase that phosphorylates IκB and targets it for ubiquination and proteosomal degradation [182]. This releases the NF-κB and allows it to enter the nucleus, bind DNA and activate transcription. Interestingly, NF-κB induces the transcription of IkBα that causes an inhibitory auto-regulatory cascade. IkBα enters the nucleus following translation, binds and inactivates NF-κB, and removes it from the nucleus [183, 184]. Thus, the transcriptional activation of the NF-κB pathway is often a short, transient process in cells. Figure 4 provides an overview of NF-κB action.

NF-κB refers to a family of proteins that control transcription and are involved in development, immune system functions, inflammation, cellular growth and apoptosis. Many of these proteins are referred to as Rel proteins and include RelA, Rel2, c-Rel, p105/p50, and p100/p52. The p105/p50 and p100/p52 proteins are inactive in the cell in their larger form and when the C-terminus is cleaved (p105 cleaved to p50) they become active, shorter DNA-binding proteins. The p105/p50 and p100/p52 proteins are not generally active in transcription unless bound to the Rel proteins. Rel/NF-κB proteins can regulate a large number of different genes because Rel proteins can form homodimers or heterodimers and the individual dimers have distinct DNA-binding sites. The most studied and most common of these dimers is the p50-RelA heterodimer [185].

Interestingly, NF-κB increases the transcription of several genes such as *elk-1* and *c-fos* involved in the Activation Protein-1 (AP-1) transcriptional pathway, another sensor of oxidative stress. Thus, NF-kB can increase stress responses by activating transcription factors that bind other responses elements such as the antioxidant response element (ARE) and tetradecanoyl-phorbol-13-acetate (TPA)-response element [186]. This cross activation increases the number of genes transcribed following a stress event.

AP-1: Activation Protein-1 (AP-1) belongs to a family of transcription factors characterized by a basic domain and a region of leucine and hydrophobic residue repeats (bZIP family) [187]. AP-1 is a complex comprised of two main proteins, a Jun and a Fos, where Jun may include c-Jun, JunB, or JunD and Fos may include c-Fos, FosB, Fra1, or Fra2 [188]. These proteins may form homo- or heterodimers among themselves such as Jun-Jun or Jun-Fos dimers, and in turn interact with additional proteins to initiate transcription at sites containing an AP-1 consensus sequence. There are several different AP-1 DNA binding sites, including a “classical” AP-1 (TPA-response element) binding site and the antioxidant response element (ARE) [189, 190].

Like NF-κB, AP-1 plays a vital role in increasing the expression of antioxidant enzymes, phase II detoxification enzymes, and cytoprotective genes in order to protect the cell from ROS. Genes thought to be regulated by AP-1 binding to the ARE include GST Ya subunits, NAD(P)H:quinine oxidoreductase (NQO1), Cu/ZnSOD, MnSOD, glutathione peroxidase, catalase, glutathione reductase, and heme oxygenase [187, 191].

Nrf2: NF-E2 p45-related factor 2 (Nrf2) is a bZIP transcription factor with a cap’n’collar (CNC) structure that also binds several AREs [192]. Similar to NF-κB, Nrf2 is activated by the release of its inhibitor, in this case Keap-1, in the presence of ROS and then heterodimerizes with bZIP proteins such as Fos, Jun, Activating Transcription Factor-4 (ATF4), and most likely musculoaponeurotic fibrosarcoma (Maf) proteins at a variety of AREs [193–195]. AREs include classical antioxidant response elements, electrophile-response elements, β-napthoflavone-response elements, Maf-recognition elements, and AP-1 sites found within the AREs. Greater insight into all of these AREs is available in a recent review [195].

Mice lacking Nrf2 (Nrf2 −/−) show decreased mRNA transcript levels of catalase, NQO1, SOD1, heme oxygenase, stress protein A170, GST alpha and mu, and peroxiredoxin MSP 23. Furthermore, hyperoxia induced levels of NQO1, GST Ya, and glucuronosyltransferase were significantly lower in Nrf2 −/− mice compared with Nrf +/+ mice [192, 196, 197]. Mechanistic studies demonstrate the role of Nrf2 in the regulation of phase I-III detoxication enzymes, primarily conjugases and anti-oxidant defenses, but also MRP transporters [194, 198–200]. These studies and others [155, 156, 201–203] have made it increasingly obvious that Nrf2 is a key transcriptional regulation of oxidative balance. For example, acetaminophen is tolerated in wildtype mice at doses that kill Nrf2-null mice due to their inability to respond to oxidative stress [204].

Nrf2 is activated endogenously by a number of polyunsaturated fatty acid (PUFA) metabolites such as the oxylipins [205], including key oxo-DHA metabolites [158]. DHA,

EPA, and other PUFAs are metabolized to several different oxylipins of which some activate Nrf2 such as 15-J2-IsoP [158, 205]. The production of these oxylipins and subsequent activation of Nrf2 may play a protective role in several diseases including mitochondrial disfunction and cardiovascular disease [206]. Other diseases in which Nrf2 plays a protective role because of transcriptional regulation of anti-oxidant defenses include fatty liver disease, cancer, diabetes, emphysema, and chronic obstructive pulmonary disease [207–209].

Nrf2 is also activated exogenously by a host of chemicals that perturb redox status. These include several metals, PFOS, paraquat, MPTP, and other chemicals [155, 156, 201, 210]. Nrf2 also crosstalks with the AhR and nuclear receptors such as CAR. Thus, the activation of AhR and CAR causes the subsequent activation of Nrf2 for protection of oxidative stress [194, 203]. AhR or CAR activation probably activates Nrf2 due to the formation of reactive metabolites produced by CYPs following AhR/CAR-mediated CYP induction [194, 203] (Fig. 5). It has been hypothesized, but not definitely demonstrated, that ROS may be directly produced by specific CYPs such as Cyp2b or Cyp2e in a substrate-independent manner and this in turn activates Nrf2 [203]. More likely, Nrf2 activation following AhR or CAR-mediated CYP induction occurs due to increased ROS due to reactive metabolites or CYP-mediated oxylipin formation. The potential role of CYP induction in the activation of anti-oxidant defenses following activation by traditional xeno-sensing receptors is an interesting concept in need of more research [203]. Overall, most toxicology studies would indicate that Nrf2 is the most important of the anti-oxidant transcription factors.

Metal-responsive transcription factor-1 (MTF-1):

Metallothionein is primarily regulated by metal-responsive transcription factor-1 (MTF-1) [211]. Metallthioneins (MT) are ubiquitous, low molecular weight, cysteine-rich proteins that bind and regulate the available concentrations of many metals. The primary role of MTs is to regulate concentrations of the essential trace metals, copper and zinc. At high concentrations, even essential trace metals can bind macromolecules and elicit toxicity and MT ensures a stable bioavailable population of these metals by binding excess essential metals. MT also provides protection from similar toxic metals such as Cd and Hg. For example, Cd-resistant populations of fish express high levels of metallothionein [212], and MT −/− mice show increased sensitivity to many different metals [213].

Zinc and other divalent metals bind MTF-1, which in turn binds DNA at the metal responsive element (MRE) and promotes transcription of MT. MTF-1 is also activiated by oxidative stress [214]. The promoter region of the zebrafish MT gene contains four MREs, three AP-1s and a SP-1 site. However, only the MREs and in particular the distal MRE is required for induction of MT by Zn^{+2}, Cd^{+2}, Cu^{+2}, or Hg^{+2}. MT was not induced by Ni^{+2}, Pb^{+2}, and Co^{+2} in cell culture [215]. Interestingly, while cadmium is a potent inducer of MT, it does not appear to bind MTF-1 in mammals or yeast, indicating that cadmium indirectly activates MTF-1 [216, 217].

Biomarkers of Exposure are Often Regulated Through Transcription Factors:

The transcription factors described above regulate the expression of genes involved in xenobiotic responses, including several established biomarkers of chemical exposure (Table 1). It is the transcriptional regulation by chemical stress that provides the basis for many of the biomarkers. The toxicant binds to the appropriate receptor, which when bound to the promoter region of DNA, initiates the transcription of genes that can be used as biomarkers. Some of biomarkers are indicative of exposure to a specific toxicant or class of toxicants, while others are much more general and suggest oxidative or physiological stress. MT, for example, is a well established biomarker of exposure to metals due to activation of MTF-1 [211, 218, 219]. CYP1A induction is a well established biomarker of exposure to PAHs and HAHs and has been used as a biomarker in multiple species (AhR activation) [92, 220, 221]. Cyp2b and Cyp3a are biomarkers of CAR and PXR activation, respectively [78, 81, 222, 223]. Cyp4a is induced by PPAR and vitellogenin induction provides a specific biomarker for estrogenic chemicals (estrogen receptor; ER activation)[224–226]. Although altered expression of GSTs, SOD, and other antioxidant enzymes provides information about the general physiological state or stress level of the organism, they typically do not indicate exposure to a particular toxicant, but instead production of ROS (Nrf2; other ROS sensors) [203, 209]. Taken together, transcription factors provide the basis for the biomarker responses toxicologists have been measuring for decades and will continue to use.

In conclusion, there are a number of crucial transcription factors that activate detoxication pathways through their regulation of key phase I-III detoxication enzymes and transporters as well as other protective proteins such as heat shock proteins, chaperones, and anti-oxidants. These transcription factors induce enzymes that protect individuals from xeno- and endobiotic stressors, including activation of AhR by members of the tryptophan-kynurenine pathway [29, 227], activation of Nrf2 by oxylipins [158, 205, 228], activation and inactivation of PXR and CAR by steroids, steroid precursors, and bile acids [78, 101, 134, 229], and of course numerous xenobiotic chemicals that activate all of the transcription factors mentioned previously. In conclusion, transcription factors are often an initial line of defense from toxic xeno- and endobiotics because their activation leads to a response to chemical stress that allows individuals to acclimate to the chemical insult, and therefore are the phase 0 xenobiotic response.

Acknowledgements:

Research support was provided in part by National Institutes of Environmental Health Sciencs grant R15ES017321. The author would like to thank Melissa Heintz, Matt Hamilton, Emily Gessner, and Emily Olack for reading over the manuscript and providing valuable insight.

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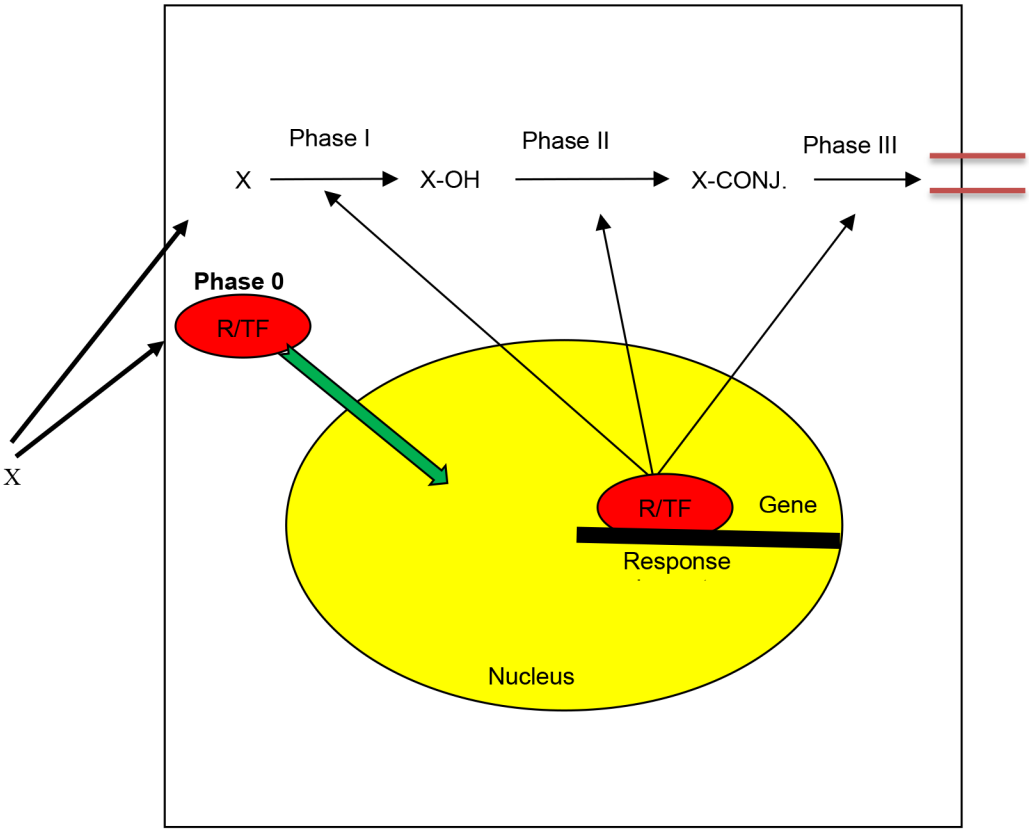

Figure 1. Phase 0 response to xenobiotics is activation of a transcriptional response by xenobiotic responsive transcription factors.

Phase I-III detoxication is well documented and relatively well defined as oxidative metabolism, conjugation, and transport, respectively. Phase 0 xenobiotic response is defined as the transcriptional response of and initial acclimation of the cell to xenobiotics leading to increased phase I-III detoxication through gene regulation. R/TF = receptor/transcription factor.

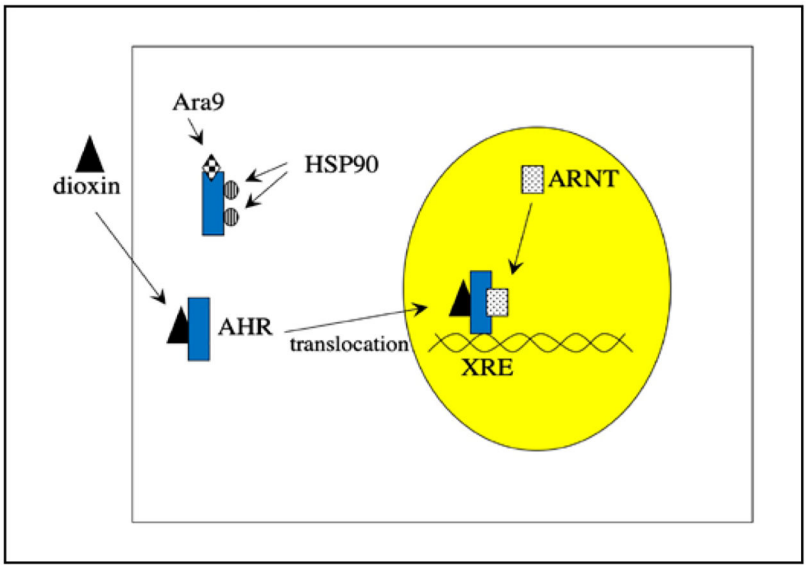

Figure 2. The AhR is activated by ligands such as dioxin.

Ligand activation induces the release of HSP90 and Ara9 and allows for translocation of the AhR into the nucleus. In the nucleus, the AhR binds ARNT and this complex binds the xenobiotic response element (XRE) and regulates transcription of CYP1A and other detoxification genes.

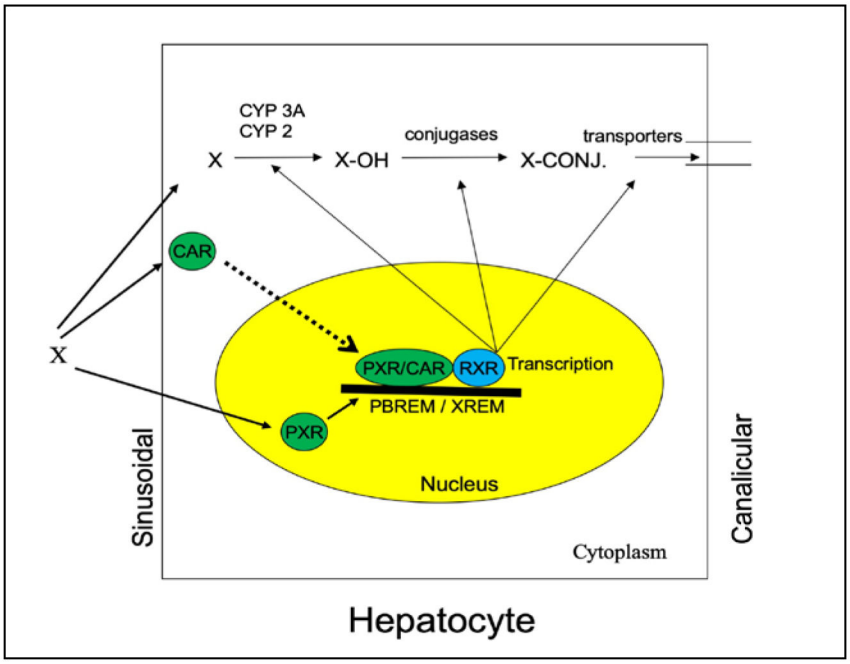

Figure 3. Function of CAR and PXR in xenobiotic metabolism.

CAR and PXR are activated by specific xenobiotics (X). In turn they dimerize with RXR, act on consensus sequences (XREM/PBREM), and initiate transcription of phase I and II enzymes involved in the hydroxylation and conjugation of xenobiotics, and phase III transporters that eliminate the xenobiotics. Indirect activatin of CAR and its subsequent translocation to the nucleus is key in its transcriptional activity.

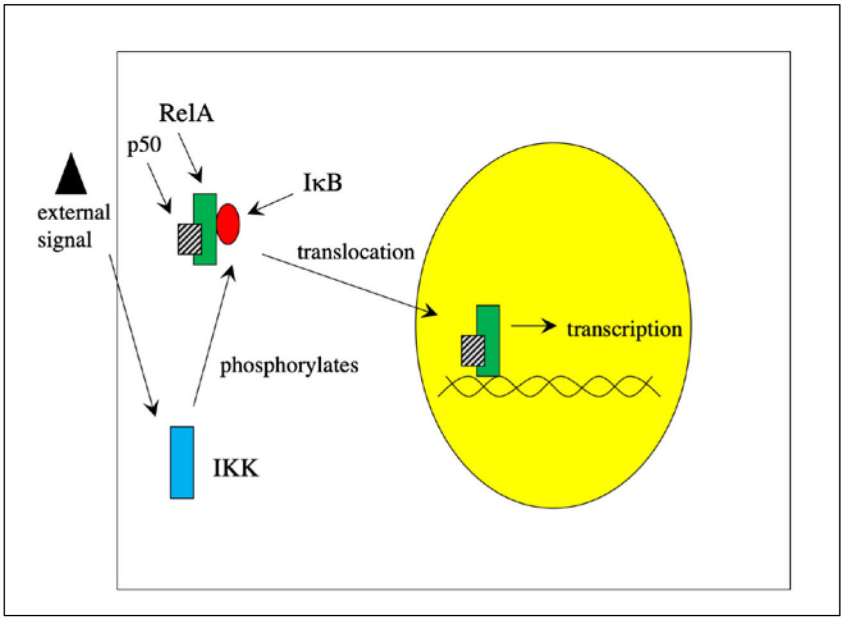

Figure 4. Activation of transcription factors by external and internal stress reponses – NF-κB.
External stimuli such as environmental toxicants and oxidative stress activate IKK which phosphorylates IkB, targeting it for proteosomal degradation. The release of the inhibitory IkB allows for the NF-kB complex (RelA/p50) to enter the nucleus and initiate transcription. Interestingly, one of the genes transcribed following NF-kB activation is IkBa, which can in turn inhibit NF-kB.

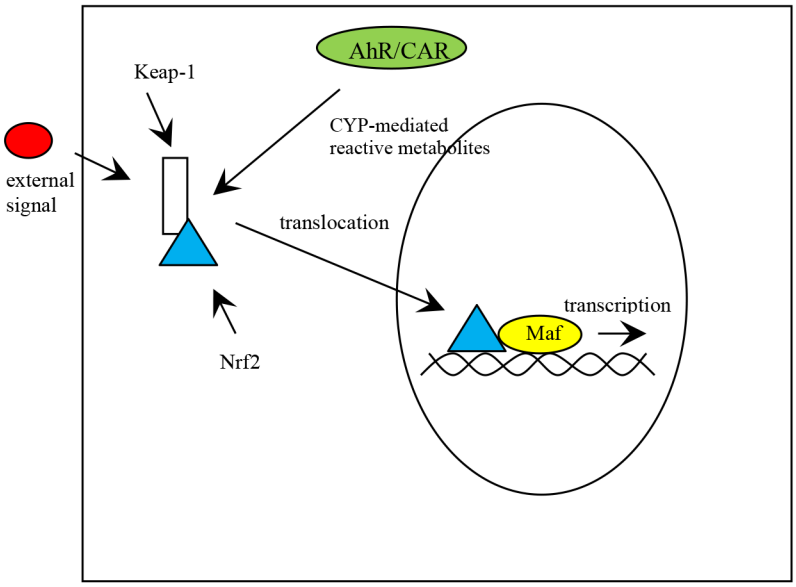

Figure 5. Activation of transcription factors by external and internal stress reponses – Nrf2.
Reactive oxygen species modify central cysteine species on Keap-1 that leads to the decoupling of Keap-1 and Nrf2. Alternatively, Nrf2 can be phosphorylated by kinases. In turn, Nrf2 is decoupled from Keap-1 and translocates to the nucleus where it binds Maf, JunD, or ATF4 and initiates transcription of a variety of antioxidant enzymes and transporters.

Table 1:

Some currently used molecular biomarkers of exposure and the transcription factors that govern their response.

Biomarker	Chemical	Transcription factor
CYP1A	PAHs, HAHs	AhR
CYP2B	Pharmaceuticals, pesticides	CAR
CYP3A	Pharmaceuticals, some EDCs	PXR
Vitellogenin	estrogens	ER
CYP4A	lipids, some organic pollutants	PPAR
Peroximsome proliferation	lipids, some organic pollutants	PPAR
Metalliothionein	Zn, Cd, Hg, Cu	MTF-1
GSTs	ROS, metals, HAHs, PAHs	Nrf2, AP-1, AhR, PXR/CAR
C-reactive protein	stress	NF-κB
Superoxide dismutase	ROS, physiological stress	Nrf2,NF-κb, AP-1
Heat shock proteins	stress, metals, ROS	HSF