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The Role of Ahr in Anticancer Drug Resistance in Breast Cancer

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Abstract

Breast cancer has been a significant health problem in terms of both morbidity and mortality and has been the second leading cause of cancer deaths worldwide. Exploring and understanding the cellular and molecular mechanisms of BC tumorigenesis and progression as well as resistance to chemotherapeutic drugs involved will be critically important for advancing the overall efficacy of BC therapy. The increasing data demonstrates high levels of constitutively active AhR in mammary tumors, suggesting there is a putative role for the AhR in mammary gland tumorigenesis, while target the AhR for new drug discovery and development has been payed more attention in recent years. The present review aims to provide a relative detailed understanding and progression on the integrated role of AhR in BC tumorigenesis and in BC resistance to chemotherapeutic drugs.

Keywords: Aryl hydrocarbon receptor; Breast cancer; Drug resistance

Introduction

Non-communicable diseases (NCDs) were responsible for two-thirds of all deaths globally in 2011, while cancer has been one of the four main NCDs in the world according to the statistic of the WHO major cause of death 2012. Based on the GLOBOCAN 2014 estimates, the lung, breast, colorectal, stomach, and prostate cancers cause the majority of cancer deaths, although there is a regional difference. Breast cancer (BC) has been a significant health problem in terms of both morbidity and mortality and has been the second leading cause of cancer deaths worldwide [1].

Through the improvement and development of cancer biological medicine, new therapeutic strategies, and cancer epidemiology have been made in the last few decades, BC is truly a multidisciplinary problem and also is a multifactor and multi-stage process. Many aspects including genetic factors, physiological factors, life behaviors, environmental factors are involved in its tumorigenesis and progression. Although many tumor-related genes and molecular signaling pathways have been found in recent years, the pathogenesis and the genetic molecular alterations underlying BC tumorigenesis and its progression are still not clearly understood yet. In addition, the survival benefit of the BC patients was not satisfactory for the present first-line therapeutic strategy in clinic, while the drug resistance has been an important problem in BC treatment [2]. Thus, exploring and understanding the molecular mechanisms of tumorigenesis and progression of BC, as well as the mechanism of resistance to chemotherapeutic drugs involved, will be very important for advancing the overall efficacy of BC therapy.

Aryl hydrocarbon receptor (AhR) is a ligand dependent transcription factor that mediates many of the toxic and biological effects of environmental chemicals such as polycyclic aromatic hydrocarbons (PAHs), which are important potential carcinogens for the mammalians. Besides, previous studies have shown that AhR is expressed in multiple organs and tissues, the AhR and its signaling pathway play an important role in cellular homeostasis [3,4] and disease occurrence including human caner [5]. The increasing data demonstrates high levels of constitutively active AhR in mammary tumors, suggesting there is a putative role for the AhR in mammary gland tumorigenesis [3,6], while target the AhR for new drug discovery and development has been paid more attention in recent years [7,8]. The present review aims to provide a relative detailed understanding and progression on the integrated role of AhR in tumorigenesis and resistance to chemotherapeutic drugs in BC.

AhR was Involved in the Resistance to Cancer Chemotherapy

AhR regulated phase I, phase II enzymes and/or transporters playing important role in mediating the chemotherapeutic drug resistance

Chemotherapy is one of the three most common treatment modalities for cancer including BC [9]. Despite improvements of methods in BC therapy and advances in the development of new chemotherapeutic drugs, conventional cancer therapy often falls the goal of controlling tumor progression, while the drug resistance usually plays an important role in the process. Notably, P450 enzymes regulated by the AhR, play an important role not only in metabolically activating carcinogens but also in the detoxication process of the exogenous chemicals as well as drugs [10,11]. For example, AhR knockout significantly decreased the TCDD induced toxicity in mouse liver, thymus, heart, kidney, pancreas, spleen, lymph nodes, and uterus, and the reduced expression of AhR decreased the expression of enzyme CYP1A1, which plays an important role in metabolizing and transforming the exogenous compounds into active products, might be a potential mechanism of drug resistance [12].

Tamoxifen (Tam) is widely used for BC chemotherapy especially for the prevention and treatment of steroid hormone receptor-positive BC [13]. However, prolonged treatment of women with Tam may be a risk factor for endometrial cancer [14] and may contribute to cancer progression in recurring cancers through the accumulation

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of drug-resistant cancer progenitors [15], making Tam resistance an important clinical problem [16]. Tam requires enzymatic activation by cytochrome P450 (CYP) enzymes for the formation of active metabolites 4-hydroxytamoxifen and endoxifen. As compared with the parent drug, both of the metabolites have 30- to 100-fold greater affinity to the ER greater and the ability to inhibit cell proliferation, and the genetic variations and functional activity of these drug-metabolizing enzymes have the potential to affect Tam metabolism [17]. Recent pharmacologic and clinical evidence suggests CYP2D6 is the key enzyme in this biotransformation, the genetic variants and drug interaction by CYP2D6 inhibitors directly influence the outcomes of Tam treated patients [13]. Nuclear receptors like AhR, PXR, CAR have been shown to be the key mediator of both metabolizing enzymes and transporters [11,18]. Besides, the exogenous environmental compounds might activate the nuclear receptors that trigger cellular "stress" response leading to the increase metabolizing enzyme genes expression. This lead to, on one hand, enhance the elimination and clearance of these xenobiotics and/or other "cellular stressors" (including harmful reactive intermediates) and, on the other hand, contribute to accelerate the elimination of potential pharmaceutical chemicals and decrease drug activity, demonstrating drug resistance [19]. These suggest that the AhR regulated phase I, phase II enzymes playing important role in mediating the chemotherapeutic drug resistance. Besides, the expression of drug-metabolizing enzymes and/or transporters at sites of absorption and/or their tissue distribution can play an important role in drug metabolism and elimination, and their difference in expression or functions may account for the inter-individual difference in drug response [20], the disturbance of their homeostatic response might results in unpredictable exposure and tissue distribution of drugs and may manifest as adverse effects or therapeutic failure.

Breast cancer resistance protein (BCRP)/ATP-binding cassette subfamily G member 2 (ABCG2) is an ATP-binding cassette (ABC) transporter identified as a molecular cause of multidrug resistance (MDR) in a diverse cancer including BC, the ABCG2 physiologically functions as a part of a self-defense mechanism for the organism, enhances elimination of toxic xenobiotic substances and harmful agents in the gut and biliary tract, as well as through the blood-brain, placental, and possibly blood-testis barriers, suggesting it is a multidrug resistance transporter shown to control oral bioavailability and central nervous system (CNS) penetration [21]. It has been found that the ABCG2 expression could be induced in various tissues and cell-types after exposure to exogenous activators of AhR like TCDD, 3-MC, suggesting that specific ligand activated AhR could contribute to induce drug resistance mediated by the ABCG2 or by the transporter-associated drug-drug interactions [22,23]. These findings also suggest a new paradigm for drug resistance, i.e., environmental chemicals acting through AhR to target xenobiotic efflux transporter and thus reduce brain accumulation of CNS-acting therapeutic drugs.

A recent study has been confirmed AhR dependence of ABCG2 gene regulation using RNA interference and ectopic expression techniques to manipulate cellular AhR status in human-derived tumor cells including BC cell [24]. The constitutive activation of AhR contribute to up-regulate expression of ABCG2 and promote MDR phenotype in esophageal squamous cell carcinoma cells with acquired cisplatin resistance, and they found that AhR antagonists demonstrated inhibition effect on ABCG2 up-regulation and reversion of the ABCG2 mediated MDR [25]. These results further suggest AhR is a direct transcriptional regulator of human BCRP and provide an unprecedented role of AhR in cellular adaptive response and cytoprotection as well as drug resistance effect.

AhR impacts the drug resistance through interacting with other transcription factors directly or indirectly

In addition, AhR can also impacts the drug metabolizing enzymes (DMEs) and the transporters through interacting with other transcription factors, to promote the expression of MDR genes or MDR-associated proteins [23,26-28]. The 3MC or BaP but not the TCDD activated AhR contribute to formation of functional compound (Ahr/*ARNT*/p53), which can binding to the promoter region of multidrug resistance gene 1 (*mdr1*), then induced the *mdr1* transcription in hepatoma cell lines, suggesting a ligand specific manner [26]. The metabolic activation of these exogenous compounds into reactive species is necessary to trigger the p53 activation, that's why TCDD (resistant to metabolic breakdown) cannot induce such effect [26].

Cell proliferation dropout and apoptosis escape are the basic characteristics of cancers, while tumor progression and presumably also tumor promotion are triggered by loss of cell-cell contact [29]. The high frequency of mutations in cancer cells which result in altered cell cycle regulation and growth signal transduction, conferring a proliferative advantage, not only indicates that many of these aberrant mechanisms may be strategic targets for cancer therapy, but also suggests a potential way to explore and combat drug resistance. It has been demonstrated that the AhR itself or interacting with other transcription factors involves in cell cycle regulation, mitogen-activated protein kinase cascades, immediate-early gene induction, and the functions of the Rb protein [30], and is responsive to changes in matrix composition as well as cell-cell and cell-matrix interactions [31], suggesting potential ability to be an drug target for cancer therapy and combating drug resistance.

The pharmacological effect of Tam is mainly manifested through inhibiting proliferation and induces apoptosis of BC cells by ER-dependent modulation of gene expression [32], while specific exogenous ligands of AhR can impact the effects of ER signaling directly or indirectly [33], suggesting that the AhR might involve in Tam resistance through a non-classical transcriptional regulation. It has been demonstrated that the AhR signaling manifests difference in Tam-sensitive and Tam-resistant (Tam-R) breast cancer MCF7 cells, small molecule antagonists of AhR specifically inhibit the progenitor population in MCF7 (Tam-R) cells and growth of MCF7 (Tam-R) xenografts *in vivo*. At the same time, small molecule antagonist AMD3100 specifically inhibit the progenitor population in MCF7 (Tam-R) cells and growth of MCF7 (Tam-R) xenografts *in vivo*, through AhR mediated down-regulating of the chemokine receptor CXCR4 signaling [15].

Basic researches and clinical studies suggest that although the frequency of amplification of proto-oncogene *c-myc* and prognostic relevance in human studies have been inconsistent, it is important in BC pathogenesis [34] and is often associated with poor prognosis [35]. As a target gene of transcription factor NF-κB, the activated NF- B translocated into the nucleus where it can bind to NF-κB responsive elements and regulate the transcription of proto-oncogene *c-myc* [36]. Classical NF-κB is a heterodimer transcription factors composed of p65 (or RelA) and p50 (or NF-κB1) subunits, while the former subunit has potent transactivation potential. However, the coexisting high levels of constitutively active AhR and constitutively active NF-B in PAH-induced rat mammary tumors suggested that there was a potential interaction between the two transcription factors. Further in vitro study found that RelA and AhR cooperate to positively transactivate the *c-myc* gene and promote proliferation and neoplastic transformation, apparently via direct binding to NF-κB elements [37].

Besides AhR itself, the aryl hydrocarbon receptor nuclear

translocator (*Arnt*) [38,39] and the aryl hydrocarbon receptor repressor (Ahrr) [40] are also critical during the development of drug resistance, and have been treated as putative new tumor suppressor gene in multiple types of human cancer, highlighting their potential as a therapeutic target in an important subset of cancers. It has been demonstrated that the reduced expression of *Arnt* was correlated with cisplatin-induced cell death in drug-sensitive cells while suppression of *Arnt* reversed the characteristics of cisplatin-resistant cells through down-regulation of *mdr1* expression, suggesting the expression of *Arnt* is critical during the development of cisplatin resistance [41]. Previous study also showed that the increased abundance of *Arnt* transcripts and protein contributes to induce troglitazone and daunorubicin resistance through increasing expression of SOD2 and Nrf2 transcripts and elevating intracellular GSH concentration [39].

Conclusion and Prospective

BC is the most common cancer in women worldwide, but established risk factors account for a relatively small proportion of cases and causative factors remain ambiguous and poorly defined [41]. Environmental factors including environmental endocrine disrupting chemicals have been implicated in cancer development [42]. There are at least two types of problems during the process of BC research and therapy in the current era. One is the studies on mechanism of tumorigenesis of BC and the development of new therapeutic drugs or strategies. The other one is the studies on mechanism of anti-cancer drug resistance and the exploration of new methods to combat drug resistance.

The AhR is responsible to mediating the multiple effects resulting from exposure to environmental chemicals. Apart from mediating the adverse effects of diverse effects of environmental chemicals, the AhR play an important role for cell normal homeostasis through the classical and non-classical signaling pathway [43,44]. The increasing epidemiological and experimental data demonstrates the AhR should be a potential target of BC therapy [3,5,45]. In addition, the extensive data showing the interaction between the AhR and other nuclear receptors including ER, further underlines the its potential role in the normal physiological and tumor pathological process [33,46-48]. By far the most extensive studies involving cross talk between AhR and another transcription factor are those involving the estrogen receptor alpha (ERα), and such non classical pathways of AhR signaling also play an important role in carcinogenesis/tumorigenesis, and tumor progression.

AhR mediates both ligand-dependent and independent toxic and therapeutic responses especially to xenobiotic, demonstrate both toxicological and physiological function, indicating the importance for continued research and development of new drug candidates targeted AhR, and the deep understanding of mechanism of its action in BC will contribute to develop new anti-cancer drug and to combat the problem of drug-resistance during cancer chemotherapy.

However, considering the important dual role of AhR regulated phase I, phase II metabolic enzymes and the complicated interaction with other transcription factors, it is really difficult to determine whether the AhR acts as an oncogene or as a tumor suppressor gene. Thus, it is still a large challenge to uncover the underlying molecular mechanisms of action of AhR both in BC tumorigenesis/development and in mediating drug.

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