SAR Journal of Medicine

Abbreviated Key Title: *SAR J Med*
Home page: https://sarpublication.com/journal/sarjm/home
DOI: 10.36346/sarjm.2022.v03i02.002

ISSN 2707-773X (P)
ISSN 2709-6920 (O)

Review Article

Perspective of Aryl Hydrocarbon Receptor Exhaustion as Cancer Causative

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Article History: | Received: 09.03.2022 | Accepted: 16.04.2022 | Published: 20.04.2022 |

Over the last decade, Aryl Hydrocarbon Receptor (AHR) dragged the research community's attention due to the associated benefits in physiology and pathology. In this study, the probable role of AHR in cancer development is discussed. The ABCG2 gene that regulates uric acid metabolism is controlled by AHR. The study noticed that the failure of AHR control over ABCG2 leads to the accumulation of uric acid, reduction of vitamin D, and hormonal imbalances that are sequentially associated with several types of cancer. Furthermore, the location of AHR in the cytoplasm and its role in the regulation of the development and differentiation of blood cells, makes it impacts on overall cells of the body, while cancer genes can be transmitted through AHR receptors in the placenta to the offspring. Overtiredness of AHR by aging, microbial, chemical, or other environmental factors escalates the risk of cancer cell growth. Consequently, immune system dysfunction is facilitated by metastasis. Meanwhile, the Tryptophan catabolism indicates the exhaustion of AHR. However, this hypothesis lacks experimental exploration for further validation.

Keywords: Aryl hydrocarbon receptor, Cancer, ABCG2, Uric acid, Vitamin D.

INTRODUCTION

The gene of the breast cancer resistance protein (BCRP/ABCG2) belongs to the ATP-binding cassette family, where the genes in this family instruct for producing proteins that carry molecules across cell membranes. In the bowels, the ABCG2 protein assists in releasing urate into the urine, where urate is a by-product of certain normal biochemical reactions in the body. In the bloodstream it operates as an antioxidant, defending cells from the destructive effects of the free radical unstable molecules. Urate concentrations are synchronized by kidneys, then by intestines with a lower degree. The breast cancer resistance protein (BCRP) is associated with certain drugs transportation out of the cells, which allows them to have their intended effects then to be effectively eliminated from the body [1]. The human direct transcriptional regulator (BCRP/ABCG2) is named aryl hydrocarbon receptor (AhR) [2], in which the fluctuation in the ABCG2 gene is associated with the gout condition [3]. The AhR is first recognized as an intracellular protein that bound and mediated the toxic effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD, dioxin) and dioxin-like compounds (DLCs). Sequential studies demonstrated the significant role of AhR in upholding cellular homeostasis and pathophysiology, whereas rising evidence that AhR is an essential drug target.

Mature studies have established the loss of the AhR in mice resulting in numerous anomalies in organs and tissues, which encompasses liver, heart, multiple adverse female reproductive tract problems, altered mammary gland development, decreased skin barrier integrity, decreased intestinal resilience, extensive immune dysfunctions, modulation of stem cells, enhanced formation of uric acid stones in the bladder, oculomotor deficits and defective optic nerve myelin sheath, and neuronal function deficits [4]. Although the AHR is intelligible practically over mice tissues, for humans it is highly intelligible in the placenta, lungs, thymus, kidney, and liver [5]. ABCG2 contributions overpass hyperuricemia to include gouty inflammation [6], whereas gout patients, due to the high expression of AHR are at escalating risk of cancer, particularly

urological cancers, digestive system cancers, and lung cancer [7]. Preclinical and clinical studies suggest that the AhR is overexpressed in advanced and triple-negative breast cancers, which is due to the high uric acid concentration that degrades survival in patients with breast cancer. Given this, it can be assessed to be employed as an efficient index for the appropriate management of breast cancer patients [8,9]. In addition, the stratified analysis indicated a reverse correlation between uric acid and sickness manifestation in smokers. In particular, each 100 μmol/L increase in uric acid levels for the heavy smoker's lung cancer patients is associated with a 28% reduction in incidence rates. Thus, the serum uric acid level potentially estimates the acceleration in lung function decline in a non-smoking general population [10,11]. Furthermore, the serum uric acid levels rise in patients with metastatic non-small cell lung cancer, in which they responded approvingly to erlotinib and had no progression under erlotinib therapy [12]. In this context, gout raises the incidence of lung cancer, oral cavity, pharynx, colon, liver and biliary tract , pancreas, lung, skin, endometrium and kidney [13]. On the other hand, uric acid is important for maintaining lung function in females with advanced age and diseases. In [14], the study suggested that while females indicated more AHR than males, the frequency of cancer is lower among female than males. Sequentially, authors of [15] have found the incidence of cancer is around 20% higher in males than in females, while the mortality rate is around 40% higher in males in the United States from 2009 to 2013 [15].

ABCG2 rs2231142 olymorphism is accompanied by gout vulnerability, where this connection is influenced by gender and ethnicity diversity. Meanwhile, genetic pieces of evidence supported age as a stimulus the gout susceptibility by rs2231142 [16]. Although females are less probable to have gout than males, in the postmenopausal years the sex difference in disease incidence reduces. Ethnically, blacks have a higher prevalence of gout compared with whites and other ethnic minorities [17]. Another factor is the lack of vitamin D status, which is highly prevalent in postmenopausal females [18]. Stimulation of AHR by xenobiotic substance is stimulating vitamin D3 catabolism in response [19], While xenobiotic directly binds to the AhR. Consequently, its nuclear localization shortens the lifespan of the cell [20].

Due to the secretion of metabolites belonging to the kynurenine pathway into milk being mediated by ABCG2 [21], infants from mothers with ABCG2 defects are more susceptible to communicable and non-communicable diseases. Activation of AHR reduces the *expression* of class II major histocompatibility complex [22], which leads to defects in the main function of major histocompatibility complex (MHC) class II molecules. Given this, the presence of MHC class II molecules processed antigens derives primarily from exogenous sources to CD4(+) T-lymphocytes [23], which is attributed to the capability of aryl hydrocarbon receptor to breakdown vitamin D. Class II molecules are restricted to the immune system cells macrophages and lymphocytes [24]. Thus, AHR takes advantage of the low expression of major histocompatibility class 2 to cause chronic inflammation.

The high levels of serum uric acid were linked with an augmented cancer incidence compared to the normal values, while Hyperuricemia is a potential risk factor for colorectal, hepatobillary, kidney, non-melanoma skin, and other cancers in males, and with head and neck and other cancers in females. Conversely, hyperuricemia may be protective for pulmonary and CNS cancers in men, and for breast, lymphatic and hematological, and CNS cancers in females [25]. Lower 25(OH)D concentrations were accompanied by lower SHBG levels and higher free testosterone levels in both men and females, and lower estradiol and higher DHEA levels in females, independent of adiposity and lifestyle [26], and this accompanied by high expression of AHR. High blood levels of DHEA have been associated with increased risk of breast, ovarian cancers [27] and higher testosterone levels increase the risks of breast and endometrial cancers in females, and prostate cancer in males [28]. SHBG expression levels were higher in females compared with males in the healthy population. In males, SHBG expression levels increased up to the age of 49 then decreased, while in females, SHBG expression levels exhibited a decreased trend up to the age of 49 [29].

In another stream, estrogen plays a vital role in bone growth and maturation, and in the regulation of bone turnover in adult bone. During growth, estrogen is needed for the proper closure of epiphyseal growth plates in both females and males [30]. Acute leukemia is more common in males in a broad age range [31]. This study hypothesized that low levels of estradiol raise the risk of bone-related cancer as a consequence of leukemia. In addition, testosterone exerts a proliferative effect on preadipocytes that may participate in the sex differences in fat distribution [32]. The study hypothesized that a high level of free testosterone is responsible for the cancerous proliferation, while a lower estradiol level is responsible for the immaturity of those cells. Furthermore, long-term testosterone therapy in men with testosterone deficiency produces significant and sustained weight loss [33]. The study hypothesized that weight loss in cancer is attributed to the raise of this hormone in both genders during malignancy. This hypothesis is supported by [34], where suggested that cancer-induced cachexia is commonly occurring between 40–60% of male and 40–50% of female patients above the age of 60. Around 25% of the treated males from cancer during childhood have suffered from a deficiency of the male sex hormone testosterone [35], which enforces the study’s hypothesis on the probable role as reflected in tumour proliferation.

Correspondingly, the high testosterone level is associated with lung cancer [36], colon cancer [37], liver cancer [38], and brain tumours [39]. Additionally, Stomach cancer is associated with low serum testosterone [40], due to the trans-migration of endotoxin directly leading to lower testosterone levels by affecting its production in the testes [41]. *Stomach cancer* is *slow*-growing cancer that usually develops over a year or longer [42], as this study justifies it probably due to lower levels of testosterone.

DISCUSSION

The study hypothesized that Aryl hydrocarbon receptor disturbances by xenobiotics (i.e., uric acid) and toxins (i.e., bacterial endotoxin) lead to hormonal imbalance, which promotes tumour growth. In XuX he study showed that maternal preeclampsia is associated with higher odds of some rare childhood cancers [43], that is linked with XuX study, which suggested that *ABCG2* expression is reduced in pregnancies where the preeclampsia is further complicated by hemolysis elevated liver enzymes and low platelets syndrome.

Smith BW *et al*., [44], showed that AhR has a physiological and functional role in normal hematopoietic development and that modulation of the receptor in HPs can direct cell fate. Gout and kidney stones are associated with polycythemia vera, which occurs due to the high turnover of red blood cells. Consequently, it results in higher-than-normal uric acid production [45], where this implies defects in ABCG2 and AHR due to uric acid disorders.

Furthermore, the metabolism of tryptophan (Trp) is a physiological source of AhR agonists [46], whereas recently it has been recognized that metabolic reprogramming is a complex and multifaceted factor, contributing to the process of lung cancer. Tryptophan (Try) is an essential amino acid with metabolites that can regulate the progression of lung cancer [47]. In addition, tryptophan metabolites especially kynurenic acid in serum and gastric juice is capable to serve as biomarkers for gastric cancer [48].

Tryptophan 2,3-dioxygenase may offer novel insights into the contribution of immunomodulatory enzymatic cascade in acute myeloid leukemia pathogenesis and prognosis [49].

Onesti CE *et al*., [50] justified the significant-high plasmatic kynurenine and tryptophan with the health ratio controls compared to patients with breast cancer, where a lower plasmatic tryptophan and a higher kynurenine/tryptophan ratio in hormone receptor-negative patients were observed compared to hormone receptor-positive cancers.

Li F *et al*., [51] revealed the existence of elevated expression of tryptophan 2, 3-dioxygenase 2 (TDO2), and elevated Trp metabolism in chemo-resistant tumour tissues of prostatic cancer patients. Generally, the tryptophan catabolism pathway is well known to play a role in the aggressive nature of cancer [52].

Based on the literature survey, this study hypothesized that AHR receptors in the placenta are comprised in the transmission of cancerous genes. Sequentially, this is supported given the low expression of ABCG2 in the placenta of pregnant ladies with preeclampsia associated with thrombocytopenia and haemolysis. On the other hand, the presence of AHR permits the cytoplasm influence on the growth and maturation of cells in the human body, which owing to control of the formation and differentiation of hemopoeitic cells. In this study, we conclude that AHR governs the entire health of humans and their breeds.

CONCLUSION

The study concludes that metabolic, environmental, chemical, microbial agents, and other factors which disturb ARH are the keys to tumour growth. The risk increases according to several factors include age, gender, occupation, and lifestyle. The exhaustion of AHR promotes cancerous cell metastasis and facilitates the transmission to the offspring, as a consequence of the immune system improper functioning. And tryptophan breakdown is an indicator of AHR collapse.

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