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REVIEW

The interplay between aryl hydrocarbon receptor, H. pylori, tryptophan, and arginine in the pathogenesis of gastric cancer

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ABSTRACT

Several risk factors are known to be involved in the initiation and development of gastric cancer. Among them, H. pylori is one of the most prominent with multiple virulence factors contributing to its pathogenicity. In this study, we have discussed an interesting immunological cycle exploring the interplay between H. pylori, aryl hydrocarbon receptor (AHR), tryptophan, arginine, and the metabolites of these two amino acids in the development of gastric cancer. AHR is a ligand-activated transcription factor which acts as a regulator for a diverse set of genes and has various types of exogenous and endogenous ligands. The tryptophan metabolite, kynurenine, is one of these ligands that can interact with AHR, leading to immune suppression and subsequently, susceptibility to gastric cancer. On the other hand, H. pylori downregulates the expression of AHR and AHR repressor (AHRR), leading to increased inflammatory cytokine production. A metabolite of the kynurenine pathway, xanthurenic acid, is a potent inhibitor of a terminal enzyme in the synthetic pathway of tetrahydrobiopterin (BH4). BH4, itself, is a cofactor in the process of nitric oxide (NO) production from arginine that has been shown to have immune-enhancing properties. Arginine has also been evidenced to have anti-tumoral function through inducing apoptosis in gastric cell lines; however, controversy exists regarding the anti-tumor role of arginine and BH4, since they are also associated with increased NO production, subsequently promoting tumor angiogenesis. Hence, although several synergistic connections result in immunity improvement, these correlations can also act as a double-edged sword, promoting tumor development. This emphasizes on the need for further investigations to better understand this complex interplay.

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Introduction

Gastric cancer is the third cause of cancer death worldwide [1]. In addition to genetic factors, many environmental factors are also involved in the etiology of gastric cancer with the most important being H. pylori infection, gastroesophageal reflux disease, obesity and dietary habits [2,3]. H. pylori is a gram negative bacterium which induces a spectrum of diseases spanning from gastritis and peptic ulcer disease to more severe conditions such as mucosa associated lymphoid tissue lymphoma (MALToma) and non-cardia gastric cancer through its various virulence factors [4]. The two most important virulence factors which are related to the intensity of the bacterial infection include vacuolating cytotoxin A (VacA) and cytotoxin-associated gene A (CagA). H. pylori, with the help of VacA and CagA, induces a defective autophagy process in gastric epithelial cells, which in turn leads to the aggregation of cytotoxic materials such as reactive oxygen species (ROS) [5]. This increases the risk of cancer development due to DNA mutation, possibly affecting the aryl hydrocarbon receptor (AHR) gene [5,6].

The AHR is a ligand-activated transcription factor which belongs to the xenobiotic type receptor family that governs the expression of various set of genes such as cytochrome P450 1A1 (CYP1A1), cytochrome P450 1B1 (CYP1A2), and growth regulatory proteins [7]. AHR also plays a major role in cell homeostasis, covering diverse physiological aspects such as cell proliferation, differentiation, motility, and migration [7]. Moreover, many studies have shown the role of AHR in promoting and modulating antibacterial response [8]. It has been shown that constitutively active AHR

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expression in transgenic mice reduces their life survival and induces tumor formation in the glandular part of the stomach [9]. The observed oncogenic potential of this receptor might possibly be justified by its role in the regulation of cell proliferation [10]. On the other hand, further studies have introduced AHR as a probable therapeutic target for the treatment of gastric cancer due to its contribution to cell cycle arrest [11,12]. A recent study showed that AHR and aryl hydrocarbon receptor repressor (AHRR) expression were reduced in positive H. pylori tissue, and this reduction enhanced tumor necrosis factor-α (TNF-α), IL-8, and IL-1β secretion [6].

Kynurenine, a metabolite of the amino acid tryptophan, is a natural ligand for AHR [13]. Tryptophan dioxygenase, a liver enzyme that drives tryptophan consumption, is upregulated by many cancers, indicating that increased tryptophan consumption might be a possible mechanism of tumors to defeat immune barriers and continue progression [14]. Xanthurenic acid, which is a metabolite of the kynurenine pathway, acts as a potent inhibitor of a terminal enzyme in the synthetic pathway of tetrahydrobiopterin (BH4) named sepiapterin reductase (SPR) [15]. BH4 is a cofactor that is involved in the conversion of amino acids such as phenylalanine, tyrosine, and tryptophan to monoamine neurotransmitters such as dopamine and serotonin [16]. It has been shown that BH4 ameliorates immune response and prevents tumor progression [17]. Thus, the decreased production of BH4 impairs antitumor immune responses and T cell proliferation, resulting in immune suppression. Moreover, BH4 is a cofactor for NO synthesis from arginine [18]. Different studies have implicated that arginine can induce apoptosis in gastric epithelial cells and also mediate NO-induced H. pylori killing[19]. However, being a precursor for NO, a substance which contributes to tumor progression through angiogenesis, suggests a controversial role for BH4 in tumor progression.

Previous studies have discussed the role of AHR and H. pylori in gastric cancer, but the correlation of these two factors in inducing gastric cancer has not been clearly illuminated yet. This review aims to provide a better scope on the initiation and progression of gastric cancer and to clarify the correlation between AHR, H. pylori, arginine, tryptophan metabolism and gastric cancer based on recent investigations.

Gastric cancer and H. pylori

Gastric cancer is the third cause of cancer-related death and the fifth most common diagnosed cancers worldwide [1] . It seems more prevalent in East Europe, Asia, and South America, whereas lower morbidity is seen in North America and most parts of Africa [20,21]. Many risk factors have been related to the development of gastric cancer, classified as either genetic or environmental factors [3]. For instance, salt intake is correlated with gastric cancer development, maybe through destroying gastric mucosa and inducing gastritis [22]. Male sex has also been linked to higher odds of experiencing both cardia and non-cardia gastric cancer compared with females; a finding that is attributed to the protective role of estrogen in the female sex. As shown in a cohort-based study, patients with pernicious anemia are also at a three-fold increased risk of gastric cancer [23]. Moreover, a correlation between cigarette smoking and alcohol consumption with gastric cancer development has also been observed[24]. However, among all known risk factors, H. Pylori infection is recognized as one of the strongest carcinogens of gastric cancer. People usually attain this infection during early years of their lives, and once the bacterium has colonized its host, it can successfully persist for a lifetime unless eradicated [25]. H. pylori infection is associated with low socioeconomic status [26,27] and is more frequently observed in the gastric tissue of individuals from developing countries [28]. Nevertheless, this bacterium is colonized in the gastric tissue of half of the world's population [27]. Previously, Yakoob and colleagues showed that H. pylori infection is correlated with deficiency of several nutrients necessary for immune regulation and homeostasis such as Iron, Copper, B12, vitamin A, C, and E [29].

The H. pylori bacterium is equipped with different virulence factors and enzymes which help it to survive in the host's stomach in a very acidity niche. Some factors which are central to bacterial colonization are Bab A, SabA, OipA, and HopQ. These factors are outer membrane proteins of H. pylori that mediate the adhesion of bacteria to gastric epithelial cells and subsequently facilitate the development of persistent infection; for example, Bab A plays an important role in initial colonization of the bacteria [30]. Urease is one of the most essential enzymes produced by this pathogen which makes the stomach a suitable place for this bacterium by neutralizing gastric acidity [31]. This way, H. pylori can survive and adhere to gastric epithelial cells. But after all, what determines the fate of the infection, whether to develop into gastric cancer or not, is the interaction between the bacterium and the host's immune response [32]. As mentioned previously, the major virulence factors of this microorganism include cytotoxin-associated gene A (CagA)

located within Cag pathogenicity island (cag PAI), vacuolating cytotoxin A (VacA), and lipopolysaccharide (LPS) [5]. Cag PAI cluster gene encodes type IV secretory system (TSS4) which injects LPS and CagA into the host's gastric epithelial cells [33,34]. It has been demonstrated that CagA can drive gastric carcinogenesis when translocating to gastric epithelial cells. This goal is achieved through different pathways; CagA accelerates spermine oxidase production in gastric epithelial cells (an enzyme involved in metabolizing the polyamine spermine into spermidine and generating H2O2), and this acceleration results in oxidative damage to DNA, and finally provokes resistance to apoptosis [35]. Another way in which CagA induces resistance of gastric epithelial cells to apoptosis is through its interaction with a protein named apoptosis-stimulating protein of p53-2 (ASPP2). ASPP2 is a regulator with a central role in controlling apoptosis and cell growth via its association with TP53. ASPP2 contributes to its pro-apoptotic role through various mechanisms such as enhancing the DNA binding and transactivation function of TP53 on the promoters of pro-apoptotic genes, impeding cell cycle progression at G2/M, and decreasing APPBP1 (amyloid beta precursor protein-binding protein 1) ability to induce cell death. The interaction between CagA and ASPP2 leads to the inhibition and degradation of p53, and consequently, results in inhibition of the apoptotic response of the host cell [36]. It also makes epithelial cells lose their polarity and cell to cell adherence, preparing a suitable situation for carcinogens to enter gastric epithelial cells [37]; moreover, this situation leads to increased release of nutrients for bacterial growth [38,39]. Followed by disruption of the adherent junctions, β catenin and p120 are transferred to the nucleus resulting in expression of some genes contributing to disease progression [40]. Besides to CagA, bacterial peptidoglycan is also transferred into gastric epithelial cells. After entering the gastric epithelial cell, peptidoglycan interacts with nucleotide-binding oligomerization domain 1 (NOD1), causing the production of several proinflammatory cytokines such as IL-8 and type I interferon (IFN) [41]. Also, activation of phosphatidylinositol 3-kinase mediated by CagA and peptidoglycan may accelerate the risk for gastric cancer development through inducing apoptotic resistance and increase in cell proliferation [42].

Another virulence factor that plays a role in H.pylori pathogenicity is VacA [43]. It has been evidenced that VacA can prevent the activation and proliferation of T lymphocytes [44,45], induce apoptosis, and also contribute to the intensity of the bacterial infection [5]. VacA induces autophagy in gastric epithelial cells, while CagA plays a reverse role and prevents autophagy [38,46]. CagA and VacA are capable of inducing defective autophagy or inhibiting it. This leads to the accumulation of cytotoxic materials, and reactive oxygen species, subsequently causing mutations in different genes and lowering the threshold for gastric cancer initiation [38]. Although CagA and VacA act reversely most of the time, their cooperation is seen in Iron acquisition from gastric epithelial cells, aiding in bacterial colonization and inducing host Iron deficiency [47]. Noto and colleagues have proposed that Iron deficiency is associated with the augmentation of H. pylori infection in ways such as enhancing the secretion of IL-8, accelerating the risk for developing gastric cancer [48].

It has been reported that in AGS and HGC-27 cell lines, infection with H. pylori upregulates a protein named FAM60A which exists in the SIN3/HDAC deacetylase complex. The upregulation of FAM60A inhibits apoptosis and accelerates cell proliferation, indicating that H. pylori may also induce gastric cancer via the upregulation of this protein [49]. Despite all of the above-mentioned, infection with H. pylori is not the only determinant for developing gastric cancer and the host's immune response plays a major role.

Infection with H. pylori stimulates the host immune response by increasing the secretion of inflammatory cytokines (such as IL-1β, IL-8, IL10, TNF-α) and free radicals, and also activating lymphocytes [6,50,51]. It has been shown that IL-1β and TNF-α suppress acid secretion, and polymorphisms associated with these cytokines are related to a greater risk of gastric cancer development [51–53]. Besides all the effects of H. pylori CagA strains including antiapoptotic activity, ROS production, cell growth and invasion, epithelial-mesenchymal transition (EMT), and activation of NF-κB and PI3K/Akt pathway, CagA can also reduce the expression of GKN1 which is an important tumor suppressor gene. To our understanding, binding of GKN1 to CagA could quell the carcinogenic effect of CagA [54,55].

Aryl hydrocarbon receptor (AHR)

AHR is a ligand-activated transcription factor that belongs to the basic helix-loop-helix (bHLH)/Per-ARNT-Sim family. This transcription factor is expressed in many animal species and humans [56]. AHR has a wide range of endogenous and exogenous ligands [57]. Polycyclic aromatic hydrocarbons (PAHs) and halogenated hydrocarbons (HAHs) are

two types of exogenous ligands for this receptor, with 2,3,7,8-tetrachlorodibenzo-para-dioxin (TCDD) being the most potent [58]. HAHs and PAHs are shown to be important carcinogens that drive gastric cancer development [59].

When there is no ligand to bind to AHR, this receptor forms a complex with two chaperone heat shock protein 90 (HSP90), a small protein named p23, and an immunophilin-like protein known as XAP2 in the cell cytosol. However, upon binding to its ligands, these proteins dissever and AHR translocates to the nucleus and binds to AHR nuclear translocator and forms a heterodimer. This heterodimer attaches to a special part of the DNA named dioxin response element (DRE), and then AHR controls and regulates the expression of a varied set of genes [60]. Some of the important genes that AHR controls are genes that code for xenobiotic metabolizing enzymes such as cytochrome P450 1A1 (CPY1A1), cytochrome P450 1B1 (CPY1B1) and glutathione-S-transferase which detoxify and metabolize drugs and xenobiotics entering the human body [61–63].

Moreover, it has been reported that AHR mediates PAHs' immunotoxicity, leading to susceptibility to different types of cancers. In 2000, Shimizu and colleagues also investigated that treatment of AHR positive mice with benzo[a]pyrene, a PAH, leads to the expression of cytochrome p450 cyp1A1 and promotion of skin tumors, whereas these effects have not been observed in null-AHR mice, indicating AHR requirement for tumor development [64]. Also, AHR ligands such as TCDD may inhibit the expression and activation of p53 and thus induce tumor progression [7].

It has been inquired that AHR plays a role in cell proliferation, differentiation, cell motility, cell migration, immune function, and tumor development, even under normal conditions in the absence of xenobiotics [7]. After AHR finishes transcription of the related genes, the chromosome region maintenance instantly exports the receptor to the cytosol, where proteasomes break it down and prevent its constant activity [65].

AHRR is a protein that negatively controls AHR expressing genes by competing with AHR for binding to the xenobiotic response element. It belongs to the bHLH/Per-ARNT-Sim transcription factor family [66]. Investigations have shown that AHRR is downregulated in many tumor types, including colon, breast, stomach, cervical, and ovarian cancer, and knockdown of this gene leads to significant independent growth in normal mammillary epithelial cells. Similarly, in human lung cancer cell line, downregulation of AHRR, exposed cells to resistance against apoptosis and enhanced their invasiveness [67].

An interesting finding is that the role of AHR in cell proliferation depends on the phenotype of the cell. In other words, cell phenotype can be a strong determinant for AHR to either promote cell proliferation, showing its oncogenic potential or to inhibit proliferation, demonstrating its tumor-suppressive activity [68]. These dual effects of AHR have been investigated in multiple studies. In a study it was reported that treatment with Dioxin, a group of highly toxic chemical compounds, caused the human mammary carcinoma MCF-7 and mouse hepatoma Hepa-1 cells to aggregate in the G1 phase. This aggregation was accomplished through AHR and p300 interaction, which led to p300 displacement from E2F-dependent promoters, driving cell cycle inhibition. This repression is caused through AHR interaction with retinoblastoma protein [69]. A similar study performed by Peng et al. revealed that treatment of AGS cells in a dose and time-dependent manner with TCDD, a potent AHR agonist, puts a growth arrest at the G1-S phase of the cell cycle, implicating AHR as a probable therapeutic target for gastric cancer development [11]. Nevertheless, TCDD itself is a carcinogenic substance inducing a wide range of responses like induction of CYP1A1, immunotoxicity, liver damage, etc. [70]. It has been shown that an AHR modulator, 3,3 Diindolylmethane, also induces apoptosis in gastric cancer SGC7901 cell line [71].

The c-myc oncogene is one of the many genes that are involved in the regulation of cellular proliferation and neoplastic transformation. A previous study on breast cancer cells showed that a physical and functional association exists between the RelA subunit of NF-κB and AHR that is able to induce c-myc gene transcription. This finding suggests the possibility of a novel signaling mechanism whereby the AHR can induce proliferation and tumorigenesis of mammary cells[72].

In human lung carcinoma A549 cells, AHR overexpression caused increased activation of E2F/DP2, leading to DNA synthesis through rising proliferating cell nuclear antigen levels [73]. Also, transgenic mice expressing constitutively active AHR developed liver tumors (about 19-fold) more frequently than the AHR wild-type ones, although both were treated by N-nitrosodiethylamine hepatocarcinogen for thirty-five weeks [74]. Moreover, a similar study on constitutively active AHR in transgenic mice revealed oncogenic potential of the receptor because of the observed reduction in the lifespan of mice and induction of tumors in the glandular part of the stomach [10].

Another investigation reported that the downregulation of AHR expression decreased cellular growth,

prolonged cell cycle, and increased apoptosis, indicating AHR as a tumor growth promotive. It has been announced that AHR activation leads to invasion of gastric cancer cells through c-Jun pathway which induces matrix metallopeptidase-9 (MMP-9) expression [75]. Kuznetsov and colleagues investigated that constitutively active mutant AHR, decreases osteopontin (OPN) expression, a protein involved in different cell functions, including cell motility and cytokine production and this reduction was correlated with the development of stomach tumors [76].

It has been shown that *in vivo* and *in vitro* culture of H pylori, inhibited the expression of both AHR and AHRR in gastric cancer tissues and cells and subsequently resulted in increased production of TNF-α, IL-8, and IL-1β [6]. In another study, human gastric cancer cells SGC-7901 were exposed to Benzo[a]pyrene, a potent carcinogen, in which gastric cancer cells showed an increased capacity in proliferation, migration, and invasion after this exposure. These features were achieved through activation of AHR and ERK pathway, which led to the elevation of MMP-9 and c-myc expression [77]. In 2014, Lai et al. reported that a significant reduction in gastric tumor growth, peritoneal dissemination, and organ metastasis were observed by reducing EMT in mice treated with Biseugenol, a novel AHR inhibitor. Biseugenol mediates AHR inhibition and induces endoplasmic reticulum stress, resulting in Calpain-10 activation, which afterward causes the reversal of EMT and apoptosis [78]. It has been observed that AHR expression is significantly upregulated in gastric cancer tissues. In one study in which small interfering RNAs (siRNAs) were used to silence the expression of AHR in gastric cancer cells, a decrease in cell migration and invasive ability was observed after inhibition of AHR expression. This response was simultaneously accompanied by a decrease in MMP-2 and MMP-9 expression, suggesting that AHR is also probably involved in the expression of MMP enzymes. Moreover, the siRNA-treated cells showed decreased cellular growth, delayed G1-S cell cycle progression and an increase in apoptosis rate[79]. These findings support the role of AHR in promoting the growth and invasiveness of gastric cancer cells and suggest that AHR could serve as a promising candidate for treating gastric cancer.

Tryptophan

Tryptophan is a necessary amino acid in the body with different roles including regulation of nitrogen balance, maintenance of human body weight, and being a precursor for serotonin neurotransmitters [80]. Tryptophan has the lowest concentration between amino acids in the body. It is used in the synthesis of proteins, serotonin, tryptamine, and kynurenine. About ninety percent of tryptophan is catabolized into kynurenine, an endogenous ligand for AHR [81]. Tryptophan catabolites, particularly in the kynurenine pathway, are elevated in different pathological disorders such as cancer, autoimmune disease, and psychiatric disorders. These catabolites have also been observed in inflammation sites and in tumors which abolish antigen specific-T-cell responses [14,82]. This elevation is caused under the influence of pro-inflammatory cytokines including IFNs, the most potent being IFN-ɤ, which finally augments anti-inflammatory and immune-suppressive responses leading to immune tolerance and cancer susceptibility [83,84].

Three enzymes have been reported to catabolize tryptophan to kynurenine: indoleamine-2, 3-dioxygenase 2 (IDO2), tryptophan-2,3- dioxygenase (TDO) and indoleamine-2,3-dioxygenase (IDO). IDO is proposed to occupy the key role [85–87]. IDO is expressed in different cells of the body, such as dendritic cells, macrophages, monocytes, and fibroblasts [88,89]. IFN-α, TNF-α, and in particular IFNϒ, reinforce IDO activation [90], whereas IL-3 and IL-14 have been reported to inhibit IFNϒ-induced IDO activity [91,92]. Kynurenine and IDO have crucial roles in maintaining the homeostasis of the immune system. After activation of antigen-presenting cells by IFNϒ, IDO and kynurenine damp down the immune response, causing suppression of T cell functions, inhibition of natural killer (NK) cells, and activation of T regulatory cells [91]. In addition, kynurenine can suppress NK cells that have an essential role in the immunosurveillance of cancer. L-kynurenine inhibits IL-2-induced upregulation of NKp46 and NKG2D receptors and subsequently results in decreased cytotoxicity and cytokine production of human NK cells *in vitro* [93,94]. Thus, inhibitor molecules that target IDO have recently came into attention for implication in clinical trials.

Moreover, other tryptophan derivatives such as 3-hydroxyanthranilic acid and Quinolinic acid induce apoptosis in T helper cells through employing different mechanisms such as ROS generation and caspase 8 activation which leads to cytochrome c release from the mitochondria [90,95].

In different pathological conditions with T cell interference such as viral infections, autoimmune disorders, and malignancies, a reduction in serum tryptophan level and an increase in kynurenine level due to

IDO activation has been observed [80]. Previously it was believed that IDO functions as an antimicrobial defense because it evacuates tryptophan from intracellular pools and prevents microbial proliferation but soon after it was understood that this theory is only restricted to *in vitro* situations for tryptophan dependent microbes [83].

During an *in vitro* study, Munn et al. investigated that macrophages expressing IDO inhibited T cell proliferation by reducing tryptophan levels. Since T cells are probably dependent on a free tryptophan level for their proliferation checkpoint, this reduction interferes with their proliferation [96]. Platen et al. similarly stated that depletion of tryptophan and accumulation of its catabolites, especially kynurenine, causes T cell anergy and apoptosis. This immunosuppressive function of kynurenine is achieved through AHR [14].

Immunostimulatory cytokines, especially IFN-ɤ, stimulate plasmacytoid dendritic cells to express indoleamine enzyme to drive tryptophan catabolism. This causes T regulatory cells to become more powerful and to cause naïve CD4 T cells to differentiate into T regulatory cells; conclusively restricting immune response [97].

Tryptophan dioxygenase is upregulated by many tumors which survive on tryptophan consumption and kynurenine production. Mezrich et al. announced that kynurenine interacts with AHR and activates the receptor, which leads to the production of regulatory T cells and subsequently weakening of the immune system [98]. In another study, a reduction in serum tryptophan level in both H. pylori seropositive and seronegative patients with gastric cancer was observed compared to the control group with no malignancy. However, a significant increase in kynurenine to tryptophan ratio was only observed in H. pylori seropositive gastric cancer patients [99]. In a later study performed in 2015 by the same author, kynurenine to tryptophan ratio was elevated in both H. pylori-positive and negative patients with colorectal cancer and plasma tryptophan level was diminished in both groups. This elevated kynurenine to tryptophan ratio indicates that H. pylori probably supports immune tolerance to drive cancer development [100].

Tetrahydrobiopterin (BH4)

BH4 is an essential cofactor involved in the synthesis of nitric oxide (NO) species. It is also a cofactor for phenylalanine hydroxylase (conversion of phenylalanine to tyrosine), tyrosine hydroxylase (conversion of tyrosine to L-dopa), tryptophan hydroxylase (conversion of tryptophan to 5-hydroxytryptophan), alkyl glycerol monooxygenase as well as NO synthase [16]. These enzymes are involved in the production of neurotransmitters such as dopamine, serotonin noradrenaline and adrenaline [16,101].

BH4 is present in almost every cell and tissue of the body [102] and plays an important role in pain control, cardiovascular function, [103] endothelial dysfunction (thrombosis, arteriosclerosis), immunity, and production of monoamine neurotransmitters [104]. BH4 is synthesized from guanosine triphosphate (GTP). Three enzymes are involved in the production of BH4. Guanosine triphosphate cyclohydrolase (GCH1) is the first and rate-limiting enzyme in the production of BH4, and sepiapterin reductase (SPR) is the last enzyme in BH4 production pathway [105]. Haruki et al. showed that BH4 production is elevated under the influence of pro-inflammatory cytokines and also implicated that xanthurenic acid, a kynurenine pathway metabolite, inhibits SPR enzyme and subsequently attenuates BH4 synthesis [15]. Werner and colleagues also supported the same idea that cytokines such as TNF-α, IL-1, and IFN-ϒ increase the activity of GTP and subsequent production BH4 [106].

It was also inspected that the inactivation of GCH1 and SPR impairs T-cell proliferation in humans and mice, introducing BH4 as a substance that reinforces immune response and its reduction leads to weakening of autoimmune responses. In an *in vivo* experiment, blockage of BH4 synthesis attenuated allergic inflammations and T cell-mediated immunity. Also, increase of BH4 level through GCH overexpression led to the reinforcement of anti-tumoral activity of CD4 and CD8 T cells [17]. Similarly, treatment of mice with BH4 decreased tumor growth and its influence on effector T cells was observed by their expansion. Nevertheless, it seems that BH4 plays a controversial role in cancer. It has been reported that NO has an important function in tumor angiogenesis. BH4 is an absolute requirement for endothelial NO synthase, thus promoting tumor angiogenesis [107]. Thus, *in vitro* expression of GTP cyclohydrolase I enhances tumorigenesis, tumor cell proliferation, and angiogenesis. [108] In 2016, a study proclaimed that downregulation of GTP cyclohydrolase with 2,4-diamino-6-hydroxypyrimidine (DAHP) in mice with hepatocellular carcinoma reduces BH4 production, NO level, and subsequently NO-mediated angiogenesis by inhibiting Ras-PI3K/Akt pathway [109]. Pickert et al. similarly reported that inhibition of GCH1 decreases tumor growth by employing three ways; killing the

tumor cells directly, ameliorating anti-tumoral immune response, and blockage of angiogenesis [110].

Arginine

Arginine is a semi-essential amino acid and a precursor for protein, polyamine, creatinine, and NO biosynthesis. It also stimulates the release of some hormones such as insulin, insulin-like growth factor1, growth hormone, and prolactin. NO, a product of arginine, can be produced by different cells, including endothelial cells, several tumor cell lines, and human solid tumors [111].Arginine and NO, also play a role in the immune system, such as activation of NK cells, T cells, cytokine production, and stimulating macrophage phagocytic activity [112]. Low levels of arginine induces loss of CD3 ζ chain, suppression of T cell proliferation, and cytokine production [113,114].

Arginine levels are controlled through different pathways in the body including dietary intake, protein catabolism, de novo synthesis from citrulline, and enzymes like arginase I and II, which convert arginine to urea and ornithine, and inducible nitric oxide synthase (iNOS) which converts arginine to NO [115]. Anti-inflammatory cytokines lead to arginase expression while pro-inflammatory cytokines induce iNOS activation and NO production which has a crucial role in eradicating bacteria, parasites, and cancer cells [116]. Of note, the correlation between NO and IDO has also been observed. Several tryptophan metabolites inhibit iNOS activity and reciprocally, NO can inhibit IDO activity [117–119].

Malignant tumors are featured with high metabolic activity, and to meet their drastic growth, they expand nutritional needs [120]. Some tumors named as arginine auxotrophic are not able to synthetize arginine independently. In these tumors, arginine depletion has been described to be a potential anti-tumor treatment [121,122]. It has been investigated that some malignant tumors have high levels of arginase, which converts arginine to urea and ornithine and subsequently causes a reduction in arginine level in tumor margins, leading to immunosuppression [123]. Arginine has a direct effect on tumor growth. Some tumor cells need arginine for their growth; thus, arginine metabolizing enzymes such as arginine deiminase, arginine decarboxylase, and arginase which cause arginine depletion in the tumor microenvironment could be potentially used for arginine deprivation therapy [124–126]. Arginine succinate synthetase 1 (ASS1) is a rate-limiting enzyme in arginine biosynthesis [127]. In gastric cancer cell lines, ASS1 expression is increased. In a recent study, silencing ASS1 through the use of vector-mediated short hairpin RNA expression seemed to notably decrease tumor metastasis and cell migration. Similarly, arginine depletion in gastric cancer cell lines reduced cell migration remarkably [128].

On the other hand, an *in vitro* experiment has inferred that arginine induced apoptosis in AGS cell lines via caspase 8 activation pathway, however, no considerable change in cell invasion was noticed [129]. Both arginine and NO have a wide and contradictory effect on cancer. Although the accurate mechanism of NO in cancer is complicated and has not been discovered totally, it contributes to tumor initiation, progression, tumor cell adhesion, angiogenesis, and differentiation as well as involvement in antitumor responses [112]. A cohort study demonstrated that among patients with hepatocellular carcinoma (HCC) treated with arginine deiminase conjugated to polyethylene glycol for decreasing arginine plasma level, some have responded to therapy [130].

The correlation between H. pylori and arginine has been reported by several studies. In the presence of H. pylori, the generation of NO from L-arginine is disrupted in gastric cells. This is because the presence of H. pylori activates arginase II and ornithine decarboxylase (ODC) in host macrophages, pushing L-arginine into the spermine production pathway. Subsequently, spermine production leads to the inhibition of iNOS translation and eventually results in NO-mediated H. pylori killing [131]. Spermine is oxidized via spermine oxidase (SMO), leading to polyamine-induced oxidative stress and finally, immune dysregulation and probably gastric carcinogenesis [19,132]. Another similar study implicated that SMO production and DNA damage only happens in the case of infection with CagA positive H. pylori but not CagA negative ones [35] (Figure 1).

As mentioned, defining the role of arginine in cancer is controversial as it acts as a double-edged sword toward cancer. It has been shown that daily arginine supplement for seven days significantly stimulates peripheral blood lymphocytes production [133]. Wu et al. performed a study to investigate whether daily arginine supplement could have an effect on advanced gastric cancer patients. Their results showed no effect on total lymphocyte counts in peripheral blood, unlike healthy human beings [134]. Shu et al. announced that L-arginine downregulated the expression of the anti-apoptotic gene, Bcl-2, while at the same time upregulating the expression of p53, a pro-apoptotic protein, in SGC-7901 human gastric cancer cell line; presenting an anti-tumor effect of this amino acid

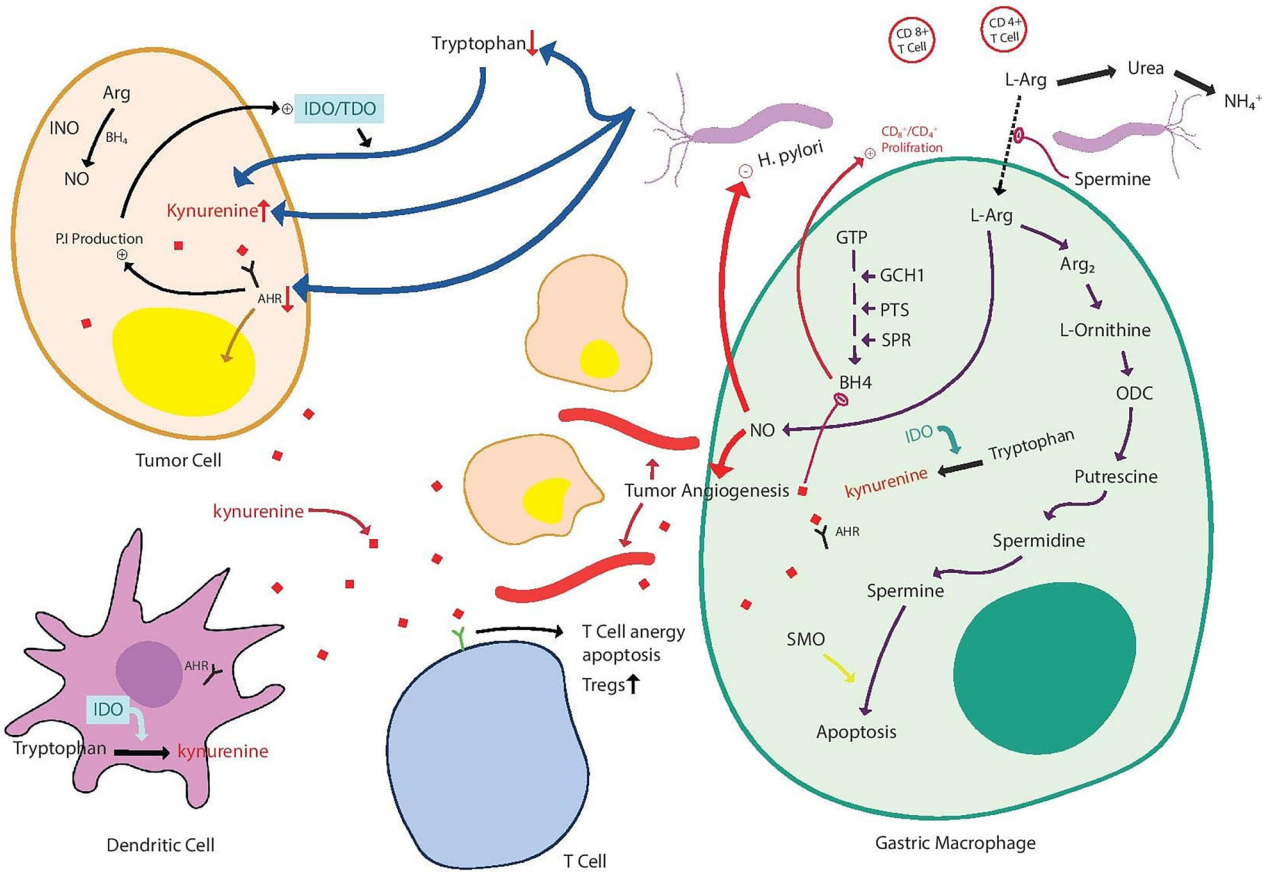

Figure 1. Infection with H. pylori leads to a reduction in AHR level, and subsequently, increased production of pro-inflammatory (PI) cytokines such as TNF-α, IL-8, and IL-1β. TNF-α activates the IDO enzyme, leading to kynurenine production in the gastric tumor microenvironment. Moreover, tryptophan metabolizing enzymes in tumor cells, gastric macrophages, and dendritic cells metabolize tryptophan to kynurenine. Kynurenine is a ligand for AHR and interacts with the receptor. This interaction leads to immune suppression. In the gastric macrophage cytoplasm, H. pylori upregulates arginase II, which in turn converts arginine to ornithine and subsequently into polyamines such as spermine. Spermine inhibits arginine uptake and consequently, NO production, resulting in reduced H. pylori killing and attenuated tumor angiogenesis. BH4, a cofactor for NO production, stimulates the proliferation of CD4+ and CD8+ cells. Xanthurenic acid, a metabolite of tryptophan, inhibits SPR enzyme and BH4 production.

[135]. Plasma arginine level is also reduced in patients with cancer implicating that arginine reduced availability is a specific feature of cancer presence [136].

Conclusion and prospects

Gastric cancer is associated with multiple risk factors, among which infection with H. pylori accounts as one of the strongest. Through applying its different virulence factors, H.pylori becomes capable of inducing gastric cancer. The interaction of H.pylori with AHR, a ligand-activated transcription factor that induces gastric cancer, still remains largely unclear. Although AHR expression is related with reduced cell proliferation, suggesting a possible role as a therapeutic target against cancer, many shreds of evidence also describe AHR to be linked with development of cancer, especially gastric neoplasms. Kynurenine, which is a metabolite of tryptophan, is a potent endogenous ligand of AHR that can weaken the immune system in different ways, including its interaction with AHR. Kynurenine displays elevated levels in pathological conditions such as cancer and autoimmune disorders; evidence shows that many cancers upregulate certain enzymes to drive tryptophan consumption in the kynurenine pathway. Specifically, in patients with gastric cancer and concomitant H. pylori infection, an increase in kynurenine-to-tryptophan ratio is observed; this might be the reason that leads to immune suppression and cancer development. Another mechanism of action of kynurenine is through its metabolite, xanthurenic acid, which can interfere with BH4 production and lead to attenuated anti-tumoral activity. BH4 is a cofactor for NO production from arginine and has immune-enhancing properties. Although the anti-tumoral function of arginine through inducing apoptosis in gastric cell lines has attracted attention, the anti-tumor role of

arginine and BH4 remains controversial since they also contribute to NO production, which is a tumor promotive agent. Upon all that has been discussed, additional investigations are needed to shed light on how these immunological pathways interact and influence each other in the presence of H. pylori and possibly lead to gastric cancer development.

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