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The Aryl Hydrocarbon Receptor as a Possible Novel Immunotherapy Target in Myeloma

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Abstract

Epidemiologic studies have demonstrated a possible association between exposure to environmental aromatic hydrocarbons and the development of monoclonal gammopathy of undetermined significance (MGUS) and multiple myeloma (MM). These aromatic hydrocarbons bind the aryl hydrocarbon receptor (AHR) expressed by plasma cells that seem to promote development and survival of malignant cells. Our group recently demonstrated that antagonism of AHR decreases viability of MM cells while increasing MM cell susceptibility to immune-mediated cytotoxicity whereas AHR antagonism enhances normal lymphocyte development and function. AHR may represent a novel therapeutic target in MM.

Keywords: Immune cells and organs, Immunotherapy, Tumor immunology

Introduction

Multiple myeloma (MM) remains an incurable plasma cell malignancy associated with progressive immune dysfunction. This immune dysfunction leads to infectious complications and progression of disease via impairment of immune surveillance and rejection of MM cells [1].

While the pathogenesis of MM remains incompletely understood, multiple studies (**Table 1**) suggest that environmental aromatic hydrocarbons (such as dioxins, benzenes, and pesticides) are linked to the development of plasma cell dyscrasias [2,3]. For example, an epidemiologic study of US Veterans found that veterans exposed to Agent Orange (2,3,7,8-tetrachlorodibenzo- p-dioxin, TCDD) were at significantly increased risk of developing MGUS, the precursor condition to MM [2]. Additionally, because of the extraordinarily high concentration of aromatic hydrocarbons at the disaster site, firefighters who worked during the World Trade Center disaster site have been reported to have an elevated rate of plasma cell dyscrasias [3].

Environmental aromatic hydrocarbons bind the aryl hydrocarbon receptor (AHR), first described in relation to TCDD poisoning [4]. Because the half-life of dioxins is quite long in humans, the persistent activation of AHR may contribute to myelomagenesis by perpetuating ongoing viability of cells expressing high levels of AHR [5]. Researchers have found that AHR activation and signaling plays a fundamental role in normal hematopoiesis, lymphocyte development, and tumor-specific immunity [4]. Hughes *et al.* have demonstrated through *in vitro* studies that the AHR is functionally expressed by MM cells and that AHR antagonism causes MM cell death while enhancing NK cell-mediated cytotoxicity [5].

Structure and Function of AHR

AHR is a nuclear hormone receptor and ligand-binding transcription factor that regulates xenobiotic-metabolizing enzymes [15]. Upon ligand binding, substrates for AHR including dietary substances, endogenous metabolites required for host metabolism, and environmental pollutants, lead to nuclear localization and transcription of so-called

Table 1. Studies examining a causal relationship between environmental aromatic hydrocarbon exposure and development of MGUS or MM.

Article	Population Studied	Statistical Analysis
Kogevinas et al. (1997) [6]	Workers from multiple countries exposed to phenoxy herbicides and chlorophenols manufacturing	SMR = 1.21 (0.55-2.29)
Mannetje et al. (2005) [7]	New Zealand workers exposed to phenoxy herbicides	SMR = 5.51 (1.14-16.1)
McBride et al. (2009) [8]	New Zealand workers involved with TCP production (TCDD exposure)	SMR = 2.2 (0.2-8.1)
Yi et al. (2013) [9]	Korean veterans of Vietnam War with self-reported exposure to TCDD	OR = 3.69 (3.02-4.52)
Yi et al. (2014) [10]	Korean veterans of Vietnam War with self-reported exposure to TCDD	AHR = 1.14 (0.65-2.01)
Landgren et al. (2015) [2]	US Operation Ranch Hand Vietnam Veterans with AO exposure	OR = 2.37 (CI: 1.27-4.44)
Landgren et al. (2018) [3]	US World Trade Center Firefighters exposed to polycyclic aromatic hydrocarbons	RR = 3.13 (CI: 1.99-4.93)
Liu et al. (2023) [11]	US Vietnam Veterans with MGUS who were exposed to high levels of AO	AHR = 1.48 (CI: 1.02-2.16)

MGUS: Monoclonal Gammopathy of Unknown Significance, AO: Agent Orange, TCDD: Tetrachlorodibenzo-p-dioxin, TCP: Trichloropropane, AHR: Adjusted Hazard Ratio, OR: Odds Ratio, SMR: Standardized Mortality Ratio, RR: Relative Risk

dioxin responsive elements (DREs) [4]. The AHR is implicated in a wide variety of biologic mechanisms, including cellular metabolism and regulation of the immune response [16]. AHR is also intimately involved in normal hematopoiesis and lymphocyte development. For example, AHR regulates gene transcription in many immune cell types, including IL-22 producing TH17 cells [17]. AHR also prevents IL-22 producing innate lymphoid cells (ILC3s) from differentiating into mature NK cells in the presence of IL-15. The ILC3 phenotype and expression of IL-22 is dependent on expression of AHR, which is ultimately maintained by IL-1β [17]. AHR is constitutively active in rapidly growing tumors and immortalized tumor cell lines, which results in cancer cell invasion, survival, and promotion of stem-cell characteristics through regulation of cell cycle progression [18]. Certain genetic polymorphisms, specifically those that result in higher levels of AHR activity, are also associated with increased risk of developing certain cancers [18].

AHR in Myeloma

AHR transcript and protein is expressed in normal B cells and plasma cells but is more pronounced in myeloma cells and appears to be integral to MM phenotype, proliferation, and cytokine production. MM cells secrete endogenous AHR ligands (kynurenin and kynurenic acid) that correlate with clinical disease burden [19]. Interestingly, the chromosomal translocation, t(14;16), which has been implicated in MM pathogenesis and associated with high-risk clinical disease, results in overexpression of cyclin D2 and subsequent increased AHR expression [20]. AHR promotes transcription of cytokines integral to the MM tumor microenvironment including IL-6, IL-21, and TGF-β. Additionally, AHR promotes other transcription factors involved with MM including c-MAF, c-MYC, and NFKB [4]. AHR expression in MM has been documented from the MM "stem cell" compartment to samples from patients with clinically advanced plasma cell leukemia [5]. Provocatively, while AHR activation promotes MM proliferation and survival, AHR activation also impairs normal immune function.

Relationship between NK Cells and MM

Natural killer (NK) cells are large granular lymphocytes of the innate immune system. NK cells are well-known for eliciting an immune response to viral infection and malignant transformation via antibody-dependent cellular cytotoxicity (ADCC), complement-mediated cellular cytotoxicity, and various other mechanisms leading to lysis of the target cell [12].

Through a complex expression of inhibitory and activating factors, NK cells are able to discriminate host from non-host antigens [13]. It has been suggested that NK cells also have similar characteristics to cells of the adaptive immune system, including regulatory function, adaptation, and antigen-specific memory [14].

Research has demonstrated that patients with MGUS or newly diagnosed MM have increased amount of NK cells with optimal cytotoxic ability. However, as the disease progresses, NK cells decline with reduced surveillance ability and cytotoxic effect against MM cells [5]. The cellular microenvironment of MM promotes tumor progression through immunoevasive mechanisms (e.g., TGF-β, IL-10, and IL-6 production) and associated activation of signaling intermediates (e.g., STAT3) that support MM cell growth while hindering NK cell function [5]. Excessive serum immunoglobulins produced by MM interfere with NK-cell mediated ADCC, and MM cytokines interfere with NK cell activation, proliferation, and function. MM cells also express inhibitory ligands that prevent NK cell surveillance and cytotoxicity [12].

Antagonism of AHR

The antagonism of AHR may be a promising therapeutic approach in MM. Hughes *et al.* demonstrated that AHR is functionally active in MM cell lines and primary MM cells [5]. AHR antagonism resulted in prevention of AHR translocation from the cytoplasm to the nucleus, ultimately blocking transcriptional function. AHR antagonism altered MM cell surface phenotype by increasing expression of differentiation markers like CD138, CD19, CD20, CD56, and CD11a and decreasing expression of CD9 and ITGB7. On the contrary, AHR agonism promotes a more immature, highly proliferative phenotype with decreased expression of CD38 and increased expression of CD13, CD27, and CD117. Therefore, AHR antagonism may promote subclones that are more differentiated with reduced proliferative propensity [5].

AHR antagonism also leads to apoptosis of MM cells with high levels of AHR expression while sparing healthy cells. While promoting MM cell apoptosis, AHR antagonism increased the relative and absolute quantity of NK cells. Lastly, AHR antagonism sensitizes myeloma cells to NK cell-mediated cytotoxicity. [5] Hughes *et al.* [5] revealed that cells that remained viable after AHR antagonism demonstrated an increased susceptibility to NK cell-mediated cytotoxicity. Pre-treatment of cell lines known to be resistant to NK cell-mediated cytotoxicity with an AHR antagonist enhanced lysis by NK cells. This is thought to be due to upregulation of NK cell activating receptors (particularly DR4 – ligand for TRAIL, CD112 and CD155 – ligands for DNAM-1, MICA/B and ULBP proteins – ligands for NKG2D) on the surface of MM cells [5]. Inhibiting AHR ultimately promotes the development and cytolytic potential of NK cells, which improves antitumor function.

As well as modulating MM cell surface and cytokine expression, AHR antagonism upregulates antigens for which there are FDA approved, targeted therapeutic monoclonal antibodies. For instance, treatment with AHR antagonists upregulates CD38 expression, the target of the monoclonal antibodies, isatuximab and daratumumab [5]. AHR antagonism has a direct apoptotic effect on myeloma cells while promoting immune-mediated lysis via NK cells, suppressing myeloma cytokine pathways, and promoting healthy immune cell development and function.

Future Prospects in MM

There is an emerging, multifunctional role for AHR in immune biology and pathogenesis of multiple myeloma. Through transcriptional regulation, AHR plays a major role in the MM cell immunophenotype. Endogenous AHR ligands are secreted by MM tumor cells and serve as an autocrine loop that facilitates MM cell proliferation and survival. Soluble, endogenous AHR ligands even correlate with clinical disease stage and burden in MM patients [21]. In addition to the effects on myeloma cells, AHR signaling dampens the immune response to the disease, particularly NK cell function. Therefore, antagonism of AHR should selectively target MM cells while enhancing antitumor lymphocyte subtypes. Blockade of AHR simultaneously promotes MM cell death while facilitating the ability of the immune system to detect and ultimately kill MM cells. By these complementary mechanisms, AHR may be a novel therapeutic target that may be utilized alone or alongside other targeted therapies to boost NK cell function and inhibit MM cell survival simultaneously. *In vitro* combination treatment with CH-223191 (AHR antagonist) and daratumumab (anti-CD38 monoclonal antibody) resulted in enhanced NK cell-mediated killing as demonstrated in an ADCC assay [5]. An anti-leprosy drug, clofazimine, has AHR antagonist effects and has been studied in treatment-refractory myeloma phenotypes. Kumar *et al.* [22] demonstrated that clofazimine had the potential to improve the therapeutic efficacy of proteasome inhibitors and immunomodulators, especially in treatment-resistance myeloma [22]. Therefore, pre-treatment with an AHR antagonism may prove to be a useful strategy in promoting differentiation of myeloma cells to those that are more susceptible to targeted therapies, like monoclonal antibodies, or through priming the immune system's ability to recognize and kill myeloma cells in combination with proteosome inhibitors and immunomodulators.

The AHR antagonist has yet to be utilized in clinical trials for hematologic malignancies. However, an oral AHR inhibitor, BAY2416964, has been studied in phase 1 clinical trials for advanced solid tumor malignancies that were resistant to prior therapies [23]. This clinical trial demonstrated that BAY2416964 was well tolerated across all dose levels and regimens tested. The treatment-emergent adverse events (TEAEs) of all grades were mostly grade 1 or 2, but patients did experience grade 3 nausea and fatigue [23]. There is an additional phase 1 clinical trial involving an oral small molecule inhibitor of AHR, IK-175, alone and in combination with nivolumab for recurrent or treatment-resistant solid tumor malignancies [24]. The tolerability and side effect profile for IK-175 has yet to be disclosed. In ongoing clinical trials, vigilance is warranted in monitoring for adverse events and unexpected toxicities, especially in combination immunotherapy settings. Ultimately, ongoing research will help elucidate the clinical feasibility of aryl hydrocarbon receptor antagonists and their usefulness in treating multiple myeloma.

Author Contributions Statement

OK, PG, DB, and AK wrote and edited the commentary. DB conducted research referenced in the commentary. All authors approved the final version of the commentary.

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