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Role of AHR in the control of GBM-associated myeloid cells

Galina Gabriely[1], **Francisco J. Quintana**[1,2]

[1]Ann Romney Center for Neurologic Diseases, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA.

[2]The Broad Institute of MIT and Harvard, Cambridge, MA, USA.

Summary

Glioblastoma (GBM) is an aggressive and incurable brain tumor; its malignancy has been associated with the activity of tumor infiltrating myeloid cells. Myeloid cells play important roles in the tumor control by the immune response, but also in tumor progression. Indeed, GBM exploits multiple mechanisms to recruit and modulate myeloid cells. The Aryl Hydrocarbon Receptor (AHR) is a ligand activated transcription factor implicated in the regulation of myeloid cells. In this review, we will summarize current knowledge on the AHR role in the control of myeloid cells and its impact on GBM pathogenesis.

Myeloid Cells in GBM

Glioblastoma (GBM) is the highest-grade glioma and the most malignant form of brain tumors, still incurable despite the use of multiple immunotherapeutic approaches and combinatorial modalities [1, 2]. The major immune cell population within the GBM microenvironment consists of myeloid cells, which often comprise about one third of the tumor mass. Initially, the heterogeneity of these GBM-infiltrating myeloid cells, denominated glioma-associated macrophages/microglia (GAMs) or tumor-associated macrophages (TAMs) [3–5] was not fully appreciated. However, as specific markers of distinct subsets of myeloid cells have become available, a new picture has emerged revealing the heterogeneity of these GBM infiltrating myeloid cells and their important roles in immunosuppression and tumor progression. Specifically, the GBM-infiltrating myeloid cell compartment comprises brain-derived microglia, as well bone-marrow derived cells including myeloid-derived suppressor cells (MDSCs), macrophages, dendritic cells (DCs), neutrophils, mast cells, basophils, and eosinophils. Here, we summarize current knowledge on the control of main myeloid cell subsets in GBM, including microglia, macrophages, MDSCs, DCs, and neutrophils in GBM. In particular, we will focus on the role of the

Contact Information: Galina Gabriely: ggabriely@bwh.harvard.edu, Francisco J. Quintana: fquintana@rics.bwh.harvard.edu.

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transcription factor aryl hydrocarbon receptor (AHR), its role in disease pathogenesis and its potential as a therapeutic target.

Myeloid cells in GBM can be distinguished based on their location within the tissue, origin and biological function. In terms of location, parenchymal myeloid cells are physically aligned with glioma cells within the tumor parenchyma and mostly include microglia. Conversely, the perivascular myeloid compartment in GBM is thought to include mostly macrophages, similar to those residing along the blood vessels of the brain vascular system [6]. Ontogenetically, two district populations of myeloid cells can be distinguished in GBM: indigenous brain tissue-resident microglia and bone marrow-derived myeloid cells which include MDSCs, macrophages, DCs, neutrophils and other granulocytes. Functionally, myeloid cells can either have anti-tumor properties (usually referred as pro-inflammatory) or support malignant growth (frequently named as anti-inflammatory). Each function can be mediated by multiple mechanisms which affect tumor cells directly or indirectly through the modulation of the tumor microenvironment.

Importantly, the concept of M1 and M2, which thought to describe a dichotomy in the activation of myeloid cells, has been mostly abandoned and a new nomenclature has been suggested [7]. M1 cells were initially described to harbor tumoricidal activity while M2 cells were characterized as immunosuppressive and thus having a pro-tumorigenic role. Multiple lines of evidence, however, indicate that the phenotypic and functional state of myeloid cells in pathological conditions is much more complex. In fact, recent investigations identified mixed M1/2 phenotypic and functional states induced in myeloid cells under certain conditions. Indeed, in the context of GBM, myeloid cells can express both activation and immunosuppression markers, as recently concluded from the single-cell profiling of myeloid cells infiltrating gliomas [8]. Thus, the myeloid compartment in GBM is extremely heterogeneous and dinamic, suggesting that it is succeptible to therapeutic interventions aimed at its modulation to boost anti-tumor immunity.

Role of myeloid cell populations in glioma

Under normal conditions, brain-resident myeloid cells play important roles in tissue homeostasis, neuronal function, and the immune surveillance of the central nervous system (CNS) [6]. Microglia are CNS-resident macrophages which play critical roles in the development of neural circuits, synapse maintenance and neuronal formation. Perivascular macrophages, among others, play an essential role in immune surveillance of the CNS while contributing to maintain blood-brain barrier (BBB) integrity. In the healthy CNS, DCs are found in the choroid plexus and the meninges. Granulocytes, which include neutrophils, are generated in the bone marrow and reside largely in the periphery where they respond to triggers such as infection and tissue damage.

Microglia/macrophages

CNS-resident microglia and peripherally-derived macrophages are actively attracted by gliomas and massively infiltrate GBM. Indeed, these cells comprise the predominant immune cell population in the GBM parenchyma [9, 10] and their abundance correlates with the GBM grade [11–13]. Microglia originate from progenitor cells of embryonic yolk sac

and are maintained in the adult CNS by local proliferation; they are not replenished postnatally from peripheral monocytes [14]. Macrophages, on the other hand, develop in the bone marrow [5]. Of note, it is still unclear whether microglia and peripherally-derived macrophages play different functional roles in gliomagenesis due to the technical challenge associated with specific targeting genes of interest in each of these cell subsets. However, differential functions of microglia and macrophages in GBM are likely to be defined as a result of the identification of unique microglial markers, such as Tmem119 and GpR56 [15–17] and unique markers for peripheral macrophages, such as, CD49d [18]. Nevertheless, it should be keept in mind that, although certain cell markers may be microglia- or macrophage-specific in homeostatic conditions, their expression level and specificity may be altered in pathogenic situations, such as within the tumor microenvironment. The homeostatic microglial marker P2RY12, for example, is downregulated in activated microglia in the context of Multiple Sclerosis (MS) [19].

In response to appropriate stimuli, myeloid cells secrete tumoricidal factors and participate in the presentation of tumor-associated antigens to the adaptive immune system [20]. Indeed, early studies demonstrated that microglia and perivascular macrophages play important roles in antigen presentation in the CNS [21–23]. Within the glioma microenvironment, however, microglia and macrophages are exposed to immunosuppressive cytokines and factors, such as TGF-β, PGE-2, and IL-10 [24, 25], which induce pro-tumorigenic functions that contribute to the suppression of tumor-specific immunity [11, 26]. Moreover, these glioma-infiltrating myeloid cells support cancer formation by increasing angiogenesis, secreting cytokines that support tumor growth, promoting immune suppression, and inhibiting GBM-specific immunity [12, 13, 27]. In addition, these cells facilitate the invasion and spread of glioma cells into brain parenchyma. For example, the upregulation of MT1-MMP in microglia infiltrating GBM activates MMP-2 in glioma cells which, in turn, promotes extracellular matrix (ECM) degradation thus facilitating brain parenchyma invasion by tumor cells [28]. Myeloid cells have also been implicated in glioma-associated angiogenesis and resistance to anti-VEGF therapy [29, 30]. However, glioma-associated macrophages can also suppress glioma growth through T-cell independent mechanisms [31, 32]. Indeed, microglia derived from non-glioma subjects diminished the sphere-forming capacity of brain tumor initiating cells, but myeloid cells derived from glioma patients were inefficient in this process [33]. Furthermore, the re-polarization of GAMs to a pro-inflammatory phenotype with CSF-1R inhibitor inhibits GBM progression in mouse models [31]. Thus, myeloid cells are flexible in nature and their phenotype can potentially be modulated for the treatment of tumors such as glioma [34].

DCs

DCs are highly-potent antigen-presenting cells (APCs) capable of presenting tumor-associated antigens to effector T cells in order to initiate tumor-specific immune responses [35]. Main populations of DCs include classical/conventional DCs (cDC) and plasmacytoid DCs (pDC); both are capable of anti-tumor responses [35]. cDCs can be further divided into subsets. In mice, the CD11b- subsets of cDCs, lymphoid tissue resident CD11c+CD8a+ DCs and non- lymphoid tissue CD11c+CD103+ DCs are among the most effective cross-presenting DCs which are critical in initiating tumor-specific T cells responses [35]. In fact,

Batf3-dependent CD103+ DCs are required for the recruitment of effector T cells to tumors via a CXCL10- dependent mechanism [36].

Poorly defined tolerogenic DCs have been shown to limit excessive immune responses that promote autoimmune disorders [37]. Making use of multiple mechanisms, the tumor microenvironment skews DCs towards a dysfunctional state which exploits their natural tolerogenic abilities and dampens the anti-tumor immune response. For example, IL-10 produced in the tumor environment promotes the generation of tolerogenic DCs [35]. Moreover, tumor derived factors stimulate the expression of PD-L1 and galectin-1 on DCs which contribute to their dysfunction. Furthermore, lipid accumulation impairs the ability of DCs to cross-present tumor antigens. In addition, the hypoxic and acidic tumor microenvironment impairs the ability of DCs to induce effector T cells responses. Finally, pDCs express IDO, which promotes Treg differentiation via AHR-dependent mechanisms [35].

Neutrophils

Neutrophils belong to the most abundant leukocytic cell population in humans, recruited as a first line defense in initial stages of physical injury. The mechanisms by which neutrophils kill pathogens include the secretion of reactive oxygen species (ROS) and extrusion of DNA to generate neutrophils extracellular traps (NETs). While playing a critical role in non-specific clearing of acutely invading pathogens, in the context of cancer, tumor associated neutrophils, also referred as TANs, may play dual roles depending on the tumor microenvironment [38–40]. Neutrophils can produce ROS, induce apoptosis and antibody-dependent cell cytotoxicity (ADCC) of tumor cells. On the other side, neutrophils can promote malignancy by producing MMP9, collagenase and arginase which suppress T-cell responses. Accumulating lines of evidence suggest that neutrophils largely promote tumor growth and metastasis [41–43]. In fact, in GBM patients, a high ratio of neutrophils to lymphocytes in the peripheral blood is associated with diminished survival [44, 45]. Moreover, increased infiltration of neutrophils into glioma tissue correlates with high tumor grade and acquired drug resistance [46]. Indeed, recent studies highlight their promoting role in carcinogenesis [41, 42]. Interestingly, however, high neutrophil counts in the peripheral blood prior to treatment with anti-VEGF antibody bevacizumab are associated with beneficial responses [47]. Collectively, these findings suggest heterogeneity in neutrophil tumor responses, calling for a deep characterization of TAN phenotypic and functional heterogeneity and the molecular dissection of the mechanisms behind them.

MDSCs

MDSCs constitute a population of immature myeloid cells mostly described in pathological conditions, such as cancer and autoimmune disorders. Although they share common markers, MDSCs are distinct from major myeloid cell subsets, such as, macrophages, neutrophils and DCs. MDSCs can be classified into two major groups, called monocytic MDSCs (M-MDSCs) and granulocytic or polymorphonuclear MDSCs (G-MDSCs or PMN-MDSCs, correspondingly). Although both subsets can be found in mice and humans, the phenotypic markers differ in these species. Human M-MDSCs can be phenotypically distinguished as $CD11b^{+}CD14^{+}HLA\text{-}DR^{Io/-}$, while in mice they are $CD11b^{+}Ly6C^{Io}Ly6G^{+}$.

G-MDSCs in humans are defined as $CD11b^{+}CD14^{-}$ $CD33^{+}CD15^{+}$ and, in mice, they are identified as $CD11b^{+}Ly6C^{Hi}Ly6G^{-}$ [48, 49]. An additional subset of MDSCs, $Lin^{-}HLA\text{-}DR^{-}CD33^{+}$, which is enriched in myeloid progenitors has been described in humans.

In mice, M-MDSCs (CD11b+$Ly6C^{Hi}$Ly6G-) and G-MDSCs (CD11b+$Ly6C^{Lo}$Ly6G+) are phenotypically and morphologically similar to monocytes and neutrophils, correspondingly [48]. It is, therefore, very difficult to distinguish these subsets solely based on surface marker expression. For instance, tumor-promoting neutrophils have the same phenotype and function as G-MDSCs.

Functionally, however, MDSCs have been shown to suppress immune responses through various mechanisms involving Arg1, iNOS, TGF-β and IL-10. Interestingly, M-MDSCs are described to harbor stronger suppressive activity than G-MDSCs [48]. In the GL261 glioma model, for example, absolute numbers of MDSCs were reduced with anti-CCL2 antibody administered systemically and this was associated with improved survival of animals [50] suggesting that MDSCs depletion may have beneficial effects for the treatment of human GBM. Indeed, MDSCs have been proposed to be important suppressor of anti-tumor immunity in GBM, their biological roles and regulation have been extensively covered by a recent review [51]. Of note, although MDSCs were initially described in the context of cancer, they have been postulated to contribute to other disorders, including autoimmune disease [52], but these roles are less characterized.

Myeloid cells are controlled by AHR

The glioma microenvironment promotes the proliferation, recruitment, and tumor-supporting polarization of myeloid cells thereby contributing to gliomagenesis. One of the oncometabolites used by glioma cells to control myeloid cells is tryptophan-derived kynurenine [26, 53]. Generated as a byproduct of tryptophan catabolism, kynurenine binds and activates AHR, a ligand activated transcription factor known to play a promoting role in cancer [54].

AHR is a transcription factor expressed in multiple cell types, including glioma and immune cells. Within the cytoplasm, inactive AHR is bound to a protein complex, which consists of a dimer of HSP90, AIP, p23 and c-SRC [55]. AHR becomes activated upon binding to agonists provided by pollutants, the gut flora, the diet and also by the host metabolism, such as kynurenine produced by the activity of TDO in glioma cells [54]. AHR activation triggers conformational changes and its translocation to the nucleus where in association with ARNT and other factors it interacts with regulatory regions of target genes to control their expression. Intriguingly, in addition to its role as a transcription factor, AHR can act as E3 ubiquitin ligase that promotes the degradation of target proteins by the proteasome [56].

AHR activation has been associated with carcinogenesis and its role in cancer, including GBM, is well established. Indeed, AHR can contribute to multiple stages of cancer progression including cancer cell initiation, tumor invasion and metastasis [55, 57]. However, AHR activation and function has been mainly studied within cancer cells themselves and to a lesser degree in stromal cells [58].

Importantly, multiple lines of evidence demonstrate an essential role for AHR in immune regulation [59–61]. AHR controls the differentiation and function of various immune cells, including T cells and DCs [55]. For example, AHR regulates the generation and activity of CD4 T cell subsets and thereby plays an important role in autoimmunity [55]. Although the role of AHR-mediated immune suppression is well established, less is known about the mechanisms by which AHR regulates tumor-specific immunity [62]. Of note, high expression of AHR in GBM is associated with decreased tumor infiltration by CD8+ T cells [54]. In the following sections, we will focus on the role of AHR in the regulation of myeloid cells in GBM (Figure 1).

AHR signaling in DCs

In the context of DCs, Platzer *et al* reported that AHR negatively regulates PU.1 (encoded by the *SPI* gene), a key transcription factor in the regulation of myeloid cell development [63], suggesting that myeloid cell differentiation can be inhibited by AHR. Indeed, AHR activation with its ligand VAF347 blocks the differentiation of human monocytes and the skin resident DCs, Langerhans cells (LCs), from monocytic precursor CD34+ cord blood cells *in vitro* [63]. In a recent study, however, AHR activation with FICZ is reported to promote DC differentiation from blood-derived monocytes by inducing the expression of transcriptional repressor PRDM1 (BLIMP1) [64], suggesting that the role of AHR in DC differentiation is ligand-specific and potentially modulated by other factors.

AHR deficiency impairs LC maturation in mice, as indicated by the decreased expression of costimulatory molecules in LCs from AHR-deficient mice, concomitant with diminished contact hypersensitivity [65]. Later studies further complicated our understanding on the role of AHR in DC maturation and antigen presentation. Bankoti et al, for example, showed opposite responses upon AHR activation on DCs from different sources. Indeed, while TCDD-stimulation decreases the frequency of MHCII positive cells in splenic DCs, it increases the frequencies of DCs expressing MHCII, CD86 and CD40 in lymph node-derived DCs [66]. Stimulation with ITE, however, did not change the frequencies of DCs that express MHCII or co-stimulatory molecules [67]. Hence, the role of AHR in DC maturation in response to different stimulations derived from specific AHR milieu appears to be complex thus deserving further investigation.

Similar to what has been reported in T lymphocytes, AHR signaling in DCs has also been implicated in immune tolerance. Indeed, treatment with the gold-standard AHR agonist TCDD induces the expression of the tolerogenic enzyme IDO in DCs; conversely *Ido* expression is downregulated in AHR-deficient mice [65, 68]. AHR activation with its ligand VAF347 suppresses the production of cytokine IL-6 and co-stimulatory molecules in stimulated human monocyte-derived DCs suggesting that this effect may affect AHR-mediated pro-inflammatory T helper cell function. In addition, AHR agonist VAF347 inhibits allergic lung inflammation in a mouse model, the effect which most likely is mediated by impaired DC function [69]. Moreover, AHR stimulation with the same compound suppresses the DC-driven proliferation of autologous CD4+ T cells [70]. Furthermore, AHR activation has been implicated in pancreatic islet allograft tolerance via a DC-dependent mechanism as VAF347 treated DCs prevented islet graft rejection [71]. LPS

endotoxin and CpG oligonucleotides stimulate AHR expression in mouse bone marrow-derived DCs and blood monocyte-derived human DCs [72, 73]. As Nguyen et al showed, in response to LPS or CpG, AHR is required to induce the expression of IDO in DCs [72]. Indeed, Bessede et al demonstrated that AHR is involved in LPS tolerance, which protects mice against immunopathology to bacterial infection [74]. Initial exposure of mice to LPS leads to the activation of AHR and TDO2 expression which inhibits endotoxaemia in a kynurenine-dependent manner. Indeed, mice deficient for either AHR or TDO2 have increased susceptibility to primary LPS challenge. Endotoxin tolerance to LPS re-challenge, however, requires the activity of IDO1. In cDCs, upon secondary LPS challenge, AHR activation leads to Src-mediated IDO1 phosphorylation followed by production of immunosuppressive cytokine TGF-β, which protects animals from systemic inflammation.

Nguyen et al also reported that treatment of co-cultured DCs and naïve T cells with the AHR ligand kynurenine promotes Treg differentiation while DCs derived from AHR-knockout mice induce less Tregs compared to wild type (WT) DCs [72]. Consequently, this study suggests that AHR in DCs can contribute to kynurenine-driven immunosuppression. In addition, the endogenous AHR ligand ITE induces tolerogenic DCs that promote Treg differentiation via a retinoic acid (RA)-dependent mechanism and suppress autoimmunity in mouse models of MS and type 1 diabetes [67, 75, 76]. In summary, these reports indicate that AHR signaling in DCs can control peripheral tolerance in the context of transplantation, allergy and autoimmunity.

AHR control of macrophages

Similar to what is found in DCs, AHR expression is induced in macrophages by stimulation with the TLR4 agonist LPS; AHR then acts as part of a feedback loop that regulates LPS responses through the transcriptional control of several TLR4-driven genes [77]. Indeed, AHR-deficient mice show increased sensitivity to endotoxin shock compared to WT mice. In combination with STAT1, AHR inhibits the production of pro-inflammatory cytokines by decreasing NF-$_K$B activation after LPS stimulation in macrophages [77]. AHR also negatively regulates IL-6 production via histamine 1 receptor signaling in macrophages following LPS stimulation [78]. Interestingly, a recent study demonstrated that apoptotic cells induce AHR in macrophages via an IL-10 dependent mechanism thus limiting systemic autoimmunity in mice and human [79]. By employing AHR knockout mice, AHR was shown to control the *in vitro* tolerogenic polarization of peritoneal macrophages upon stimulation with IL-4 [80]. Conversely, proinflammatory stimulation with LPS/IFN-γ of AHR-null macrophages resulted in higher expression of IL-1β, IL-6, IL-12 and TNF-α (but NO production and phagocytic abilities were decreased). More recently, it was reported that AHR limits the pro-inflammatory activities of microglia in the context of CNS autoimmunity [81]. Taken together, AHR appears to play a tolerogenic role in macrophages although the specific response may be stimuli and context-dependent.

The abovementioned observations suggest that AHR signaling can promote myeloid cell-driven immune suppression and tumor progression. In fact, a recent study reported that AHR expression is highest in human grade IV glioma. Moreover, high AHR expression in GBM samples is associated with decreased survival [62].

AHR participates in multiple mechanisms involved in the regulation of GBM-specific immune response. Indeed, glioma oncometabolites, such as kynurenine, stimulate AHR expression and activation in TAMs [62]. AHR signaling in myeloid cells promotes the expression of a chemokine receptor CCR2, which mediates their recruitment in response to the chemokine CCL2 produced by gliomas. In addition, AHR drives the expression of the transcription factor KLF4, while it interferes with NF-$_K$B activation via SOCS2-dependent mechanisms to drive a tolerogenic transcriptional program in TAMs. Moreover, AHR signaling in glioma-associated myeloid cells drives the expression of the ectonuclease CD39, which promotes effector T cell dysfunction by catalyzing the synthesis of immunosuppressive adenosine. Accordingly, AHR signaling enhances TAM recruitment to the GBM, promoting their polarization to a tolerogenic phenotype and consequently, interfering with tumor-specific immunity. Thus, AHR signaling modulates multiple myeloid cell functions to promote immune suppression and, ultimately, GBM progression. It would be therefore noteworthy to investigate the role of AHR in myeloid cell populations in different types of cancer.

Conclusions and therapeutic implications

Due to their central role in tumor pathogenesis and dynamic plasticity, myeloid cells have emerged as attractive targets for cancer immunotherapy [31]. Indeed, although myeloid cell depletion improves survival in GBM murine models, better results are obtained with myeloid cell modulation [31]. For example, CSF-1R inhibition promotes the polarization of myeloid cells into a phenotype characterized by robust inhibitory effects on GBM progression; these anti-tumoral effects are stronger than those obtained with myeloid cell depletion [5, 31]. As AHR signaling has been shown to drive a tolerogenic phenotype of myeloid cells [62], these findings identify AHR as an candidate for TAM therapeutic targeting in GBM. In this context, AHR inhibitors may circumvent the limitations associated with the pharmacological inhibition of enzymes involved in the generation of AHR agonists (e.g. IDO), which have failed in recent clinical trials probably reflecting the fact that AHR agonists may be generated by mutliple metabolic pathways [55, 82,83].

Of note, although the role of AHR in the biology of cancer cells is well established, less is known about its contribution to the control of tumor immunity [62]. This is an important point to design effective AHR-targeted therapeutics for the GBM and other malignancies. Indeed, many questions remain open regarding the role of AHR in the control of the immune response in the context of GBM. Does AHR play a role in the control of GBM-associated DCs, neutrophils and MDSCs? Do microglia and peripherally-derived macrophages play distinct functions and does AHR play different roles in these and other myeloid cell subsets?

In conclusion, AHR plays an important role in the control of the myeloid cells in GBM. Accordingly, considering the intrinsic effects of AHR in glioma cells [54], AHR inhibitors may provide useful therapeutic tools targeting both glioma cells and the immune response against them. Thus, AHR may provide a novel target for the modulation of myeloid cells, which could potentially be used in combination with T-cell targeting approaches [84–86] to provide efficacious immunotherapy modalities for the treatment of GBM and other malignancies.

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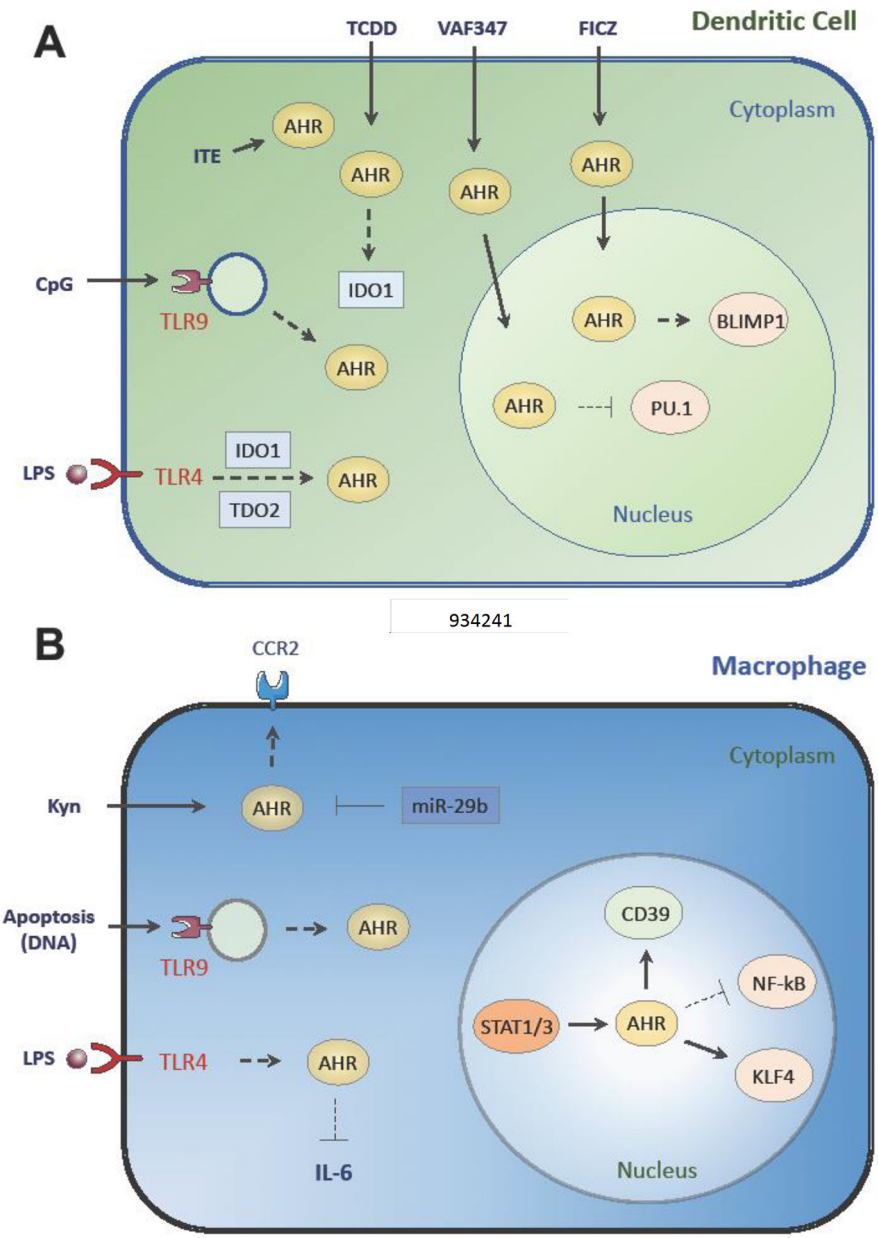

Figure 1. AHR signaling in myeloid cells.

Effects of AHR signaling in a dendritic cell (DC, upper part of the schematic cell) and a macrophage (MF, lower part of the schematic cell). Findings common for both cell types are shown in the middle (in-between two horizontal dashed lines crossing the schematic cell). AHR in the cytoplasm is being activated by its ligands (kynurenine, Kyn; ITE, TICZ, VAF347, TCDD) and translocates to the nucleus to control the expression of its target genes. Dotted arrow lines point on biological functions that AHR regulates in myeloid cells, which are listed on the right side of the figure. TAM, tumor-associated macrophage.