Role of indoleamine 2,3-dioxygenase 1 (IDO1) and kynurenine pathway in the regulation of the aging process

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ABSTRACT

Indoleamine 2,3-dioxygenase 1 (IDO1) is activated in chronic inflammatory states, e.g., in the aging process and age-related diseases. IDO1 enzyme catabolizes L-tryptophan (L-Trp) into kynurenine (KYN) thus stimulating the KYN pathway. The depletion of L-Trp inhibits the proliferation of immune cells in inflamed tissues and it also reduces serotonin synthesis predisposing to psychiatric disorders. Interestingly, IDO1 protein contains two immunoreceptor tyrosine-based inhibitory motifs (ITIM) which trigger suppressive signaling through the binding of PI3K p110 and SHP-1 proteins. This immunosuppressive activity is not dependent on the catalytic activity of IDO1. KYN and its metabolite, kynurenic acid (KYNA), are potent activators of the aryl hydrocarbon receptor (AhR) which can enhance immunosuppression. IDO1-KYN-AhR signaling counteracts excessive pro-inflammatory responses in acute inflammation but in chronic inflammatory states it has many harmful effects. A chronic low-grade inflammation is associated with the aging process, a state called inflammaging. There is substantial evidence that the activation of the IDO1-KYN-AhR pathway robustly increases with the aging process. The activation of IDO1-KYN-AhR signaling does not only suppress the functions of effector immune cells, probably promoting immunosenescence, but it also impairs autophagy, induces cellular senescence, and remodels the extracellular matrix as well as enhancing the development of osteoporosis and vascular diseases. I will review the function of IDO1-KYN-AhR signaling and discuss its activation with aging as an enhancer of the aging process.

1. Introduction

Chronic low-grade inflammation is associated with the aging process, i.e., the state has been called inflammaging (Franceschi et al., 2000). Several studies have revealed that the aging process not only remodels the immune system but also triggers pro-inflammatory changes in senescent non-immune cells (Freund et al., 2010). For instance, Benayoun et al. (2019) reported that the aging process induced significant epigenetic and transcriptional changes in mouse and human tissues, e.g., in the myocardium, liver, and cerebellum. They revealed that the most robust age-related alterations occurred in the responses of immune system, such as an increased expression of interferon α (IFNα) as well as the activation of the JAK/STAT3 signaling pathway. The age-related inflammatory changes displayed common signatures across the tissues and species (Benayoun et al., 2019). Interestingly, inflammatory mediators stimulate the expression of indoleamine 2,3-dioxygenase 1 (IDO1) which catabolizes the conversion of L-tryptophan (L-Trp) into kynurenine (KYN) (Section 3.1) (Fig. 1). The activation of IDO1 stimulates the KYN pathway which generates a diverse set of physiologically active metabolites (Section 3.2.1) (Fig. 2). KYN and its metabolite kynurenic acid (KYNA) activate the aryl hydrocarbon receptor (AhR) which is a potent immunosuppressive transcription factor (Section 3.2.2) (Fig. 2). The activation of IDO1/KYN/AhR signaling is significantly increased in chronic inflammatory diseases. It is known that increased activation of AhR signaling increases tissue degeneration and thus promotes the aging process (Section 6). I will shortly review the function of IDO1-KYN-AhR signaling and discuss its activation with aging as an enhancer of the aging process.

2. Tryptophan catabolism via the activation of IDO1

L-Trp is an essential amino acid which cannot be synthesized in the human body. L-Trp is not only a building block in protein synthesis but it is also a precursor in the synthesis of serotonin and melatonin (Richard et al., 2009; Hoglund et al., 2019; Comai et al., 2020) (Fig. 1). However, the major metabolic route of L-Trp is the catabolic pathway mediated by IDO1 enzyme which converts L-Trp into KYN and its metabolites, especially under inflammatory conditions (Zeden et al., 2010; Badawy...
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Fig. 1. Activation of the IDO-KYN-AhR pathway. Inflamming stimulates the expression of IDO1 which catabolizes L-tryptophan to kynurenine (KYN) and its metabolites. A depletion of L-tryptophan inhibits protein synthesis as well as the synthesis of serotonin and melatonin. KYN and its metabolite, kynurenic acid, are the activating ligands of aryl hydrocarbon receptor (AhR). AhR signaling stimulates immunosuppressive cells through the induction of immunosuppressive factors, e.g., FoxP3, IL-10, and TGF-β. Finally, the AhR factor stimulates the expression of IDO1, thus establishing a positive feedback loop in the regulation of the IDO1-KYN-AhR pathway.

Fig. 2. The kynurenine pathway and its enzymatic regulation. The IDO1 enzyme generates kynurenine (KYN) from L-tryptophan. KYN can be metabolized to kynurenic acid through the activation of kynurenine aminotransferase (KAT). KYN as well as kynurenic acid (KYNA) are activating ligands of AhR. AhR signaling stimulates immunosuppressive cells through the induction of immunosuppressive factors, e.g., FoxP3, IL-10, and TGF-β. Finally, the AhR factor stimulates the expression of IDO1, thus establishing a positive feedback loop in the regulation of the IDO1-KYN-AhR pathway.

Over 95% of free L-Trp can be catabolized via the KYN pathway in inflammatory states. Increased activity of IDO1 in neuroinflammation leads to a deficiency of serotonin synthesis which can subsequently trigger psychiatric disorders (Catenà-Dell’Osso et al., 2013; Jeon and Kim, 2017). Moreover, a depletion of L-Trp in chronic inflammation might reduce protein synthesis and promote atrophy in the host tissue. The IDO1 enzyme is a heme-containing dioxygenase which catalyzes the cleavage of the pyrrole ring of L-Trp through the oxidation of the iron-bound O2 (Sugimoto et al., 2006). IDO1 is the first and rate-limiting enzyme in the KYN pathway (Badawy et al., 2017) (Section 3.2.1) (Fig. 2). The expression of the IDO1 gene can be induced by several inflammatory factors via the activation of the NF-κB and JAK-STAT signaling pathways (Sections 3.1 and 5). IDO1 protein is expressed in many tissues although its expression is enriched in immune cells, e.g., monocytes and macrophages (Human Protein Atlas). IDO1 enzyme is present in the cytosol where it is involved in the activation of the KYN pathway which subsequently stimulates the suppressive properties of immune cells (Sections 3.2 and 5). Interestingly, IDO1 protein can also be located in early endosomes where it acts as a signaling platform mediating immunosuppressive signals in immune cells (Section 4). This moonlighting function of IDO1 is not dependent on its catalytic activity but is mediated through its two immunoreceptor tyrosine-based inhibitory motifs (ITIM). The depletion of L-Trp and the subsequent accumulation of KYN metabolites through the activation of IDO1 disturb tissue homeostasis and promote inflammatory pathologies (Sections 5 and 7).

There are two other dioxygenases, i.e., IDO2 and tryptophan 2,3-dioxygenase (TDO), which also catalyze the oxidation of L-Trp and thus increase the production of KYN (Badawy, 2017; Pallotta et al., 2021). The IDO2 enzyme possesses a lower catalytic activity and it has more restricted expression pattern than IDO1. Lee et al. (2014) demonstrated that human IDO2 was a negative regulator of the function of IDO1 enzyme in co-expression experiments with human HEK293 cells. They reported that the expression of IDO2 suppressed the catalytic activity of IDO1 by competing for the available heme protein required for the activation of IDO1. Accordingly, TDO is mainly expressed in the liver where it degrades L-Trp from dietary sources, thus maintaining a stable level of L-Trp in the circulation (Badawy, 2017; Pallotta et al., 2021). In fact, TDO is the major enzyme converting L-Trp amino acids to KYN in normal physiological conditions. The activity of TDO has been increased by certain hormones, e.g., glucocorticoids, its cofactor heme protein, and an increased level of L-Trp amino acids through substrate stabilization (Badawy, 2017). In contrast to TDO, the expression of IDO1 is increased in inflammatory conditions (Section 3.1) although the expression of TDO can be increased in some pathological conditions. For instance, Wu et al. (2013) demonstrated that the expression of TDO was robustly increased in the brains of transgenic Alzheimer’s mice and human patients. The increased activation of TDO also enhanced the accumulation of KYN and its metabolites within the brain. Subsequently, Breda et al. (2016) exploited the Drosophila models of neurodegenerative diseases and they found evidence that the inhibition of TDO significantly alleviated neurodegeneration in the flies and also extended their lifespan. Both studies indicated that an enhanced catabolism of L-Trp increased the levels of KYN and its metabolites in affected brains. It is known that the excessive production of KYN has many pathological consequences (Sections 3 and 5).

3. Regulation of immunosuppression via the IDO1-KYN-AhR pathway

There is substantial evidence that the activation of the IDO1 gene induces immunosuppression in several chronic inflammatory conditions, e.g., in autoimmune diseases, bacterial and viral infections, and many cancers (Schmidt and Schultze, 2014; Wang et al., 2014; Munn and Mellor, 2016; Pallotta et al., 2021). The IDO1 enzyme stimulates the KYN pathway which subsequently activates aryl hydrocarbon receptors (AhR), thus promoting an immunosuppressive state in the inflammatory microenvironment (Sections 3.2 and 5) (Fig. 1). It is known that inflammatory cytokines stimulate the expression of IDO1 protein which indicates that the inflammatory response can trigger an anti-inflammatory response mediated via the activation of
IDO1-KYN-AhR signaling (Sections 3.1 and 3.2). It seems plausible that the activation of the IDO1-KYN-AhR pathway in chronic inflammatory conditions, e.g., in the aging process (Section 6), might prevent the occurrence of excessive inflammation, thus maintaining a chronic low-grade inflammatory state.

3.1. The expression of IDO1

Dai and Gupta (1990a) cloned the human IDO1 gene based on its inducibility by interferon-γ (IFN-γ) treatment. They also revealed that the promoter region of the IDO1 gene contained a specific IFN-γ-responsive promoter segment, called the interferon-stimulated response element (ISRE) (Dai and Gupta, 1990b). Subsequent studies have revealed that the promoter of the IDO1 gene has other binding sites for several transcription factors, e.g., NF-κB, C/EBP, GAS, and STAT3 sequences (Du et al., 2000; Robinson et al., 2005; Yu et al., 2014; Mboogue et al., 2015). There is robust evidence that many cytokines stimulate the transcription of the IDO1 gene through the activation of the NF-κB and JAK-STAT3 signaling pathways (Yu et al., 2014; Baumgartner et al., 2019). For instance, Yu et al. (2014) demonstrated that the cytokine (IL-1β, GM-CSF, IL-6, and IL-10)-induced activation of STAT3 factor stimulates the transcription of the IDO1 gene via the non-canonical NF-κB signaling involving the binding of the RelB/p52 dimers to the promoter of the IDO1 gene in human MDSCs. Interestingly, Mezrich et al. (2010) demonstrated that KYN activated the AhR factor and subsequently induced the expression of IDO1 protein in mouse dendritic cells. AhR signaling also mediated the expression of IDO1 protein in human dendritic cells (DC) (Vogel et al., 2008, 2013), indicating that there exists a positive feedback loop between IDO1 and AhR activation (Fig. 1). In human tumors, IDO1 protein also sustained its own expression in an autocrine loop through the AhR/IL-6/STAT3 pathway (Litzenburger et al., 2014). There is convincing evidence indicating that the promoter of the human IDO1 gene is under epigenetic regulation. Hypomethylation of the IDO1 promoter enhanced the expression of IDO1 protein in cancer cells and this was associated with a poor prognosis in cancer patients (Noonepalle et al., 2017; Kiyozumi et al., 2019). Xue et al. (2012) demonstrated that the IFN-κ gene as well as zebularin, an inhibitor of DNA methyltransferase, increased the transcription of the IDO1 gene in human monocyctic THP-1 cells. An analysis of the methylation status of the IDO1 promoter region indicated that the CpG sites were hypermethylated in control cells, whereas both IFN-κ and zebularine treatments significantly reduced the number of the methylated CpG sites, especially those close to the ISRE1 and GAS1/GAS2 sites. The combination of IFN-κ and zebularin clearly increased both the demethylation and the transcription of the IDO1 gene in human THP1 cells. Rovira Gonzalez et al. (2016) reported that the priming of human bone marrow-derived mesenchymal stromal cells (MSC) with IFN-γ for 24 h reduced the trimethylation of H3K9 sites, whereas their acetylation level significantly increased at the IDO1 promoter. The enhanced acetylation of the promoter was associated with increased IDO1 expression. They also reported that the expression of IDO1 declined within two days after the removal of IFN-γ treatment. However, upon a re-exposure to IFN-γ after the freeze-thawing of the cells, the primed human MSCs reached the maximum IDO1 expression much faster than during the priming phase. This means that cytokine exposure had induced the licensing of the IDO1 promoter for pro-inflammatory cytokines through the chromatin remodeling. The permissive chromatin state of the IDO1 gene enhances the expression of IDO1, thus promoting counteracting immunosuppression. In addition, it seems that the epigenetic readers of acetylated lysines in histones, i.e., the bromodomain and extra-terminal domain proteins (BET), are involved in the transactivation of the IDO1 gene. For instance, Tian et al. (2019) demonstrated that the inhibitors of BET readers significantly reduced the IFN-γ-induced transcription of the IDO1 gene and inhibited the production of KYN in human cell lines. It seems that BET proteins might be involved in the long-term activation of the IDO1 gene in immunosuppressive cells.

It is known that the compounds with pathogen-associated molecular patterns (PAMP), e.g., many bacterial and viral structures, activate the expression of IDO1 through the Toll-like receptors (TLR), especially TLR4 and TLR9 (Opitz et al., 2009; Ciobra et al., 2010; Bahraoui et al., 2020). Opitz et al. (2009) demonstrated that lipopolysaccharide (LPS) treatment induced the expression of IDO1 and increased the production of KYN through the activation of TLR3 and TLR4 in human MSCs. Several endogenous TLR ligands, many of which are danger-associated molecular patterns (DAMP), can also stimulate the TLR-mediated signaling (Yu et al., 2010) and thus they are potential inducers of the expression of IDO1 enzyme. For instance, high mobility group box 1 (HMGB1), an inducer of TLR4, stimulated the expression of IDO1 in mouse hippocampus (Wang et al., 2019). Salazar et al. (2017) demonstrated that LPS-conditioning stimulated the expression of IDO1 and AhR in human DCs. They also reported that the LPS-conditioned DCs (endotoxin-tolerant cells) displayed many immunosuppressive properties, e.g., an increase in the expression of IL-10. It is known that LPS is a potent agonist for TLR4 signaling (Yu et al., 2008). Salazar et al. (2017) also reported that LPS treatment stimulated the non-canonical NF-κB pathway inducing RelB signaling in endotoxin-tolerant human DCs. There are also observations indicating that LPS exposure was able to induce immunosuppressive responses in sepsis and the cancer-associated endotoxin tolerance through the IDO1-KYN-AhR signaling pathway (Wirtzgen and Hoeflich, 2015). It seems that the activation of TLRs stimulates IDO1-KYN-AhR signaling which consequently triggers endotoxic tolerance involving the augmentation of immunosuppressive properties.

The activation of inducible cyclooxygenase-2 (COX-2)/prostaglandin E2 (PGE2) pathway is a common feature of chronic inflammation. Interestingly, several investigators have claimed that PGE2 has an important role in the generation of immune suppression in inflammatory conditions (Obermaier et al., 2011; Trabaneli et al., 2015; Hennequart et al., 2017; Tomic et al., 2019). Trabaneli et al. (2015) demonstrated that PGE2 induced the expression and also activated the IDO1 enzyme in human monocyte-derived DCs. Subsequently, IDO1 stimulated the KYN pathway and enhanced immunosuppression by stimulating the generation of Tregs. Obermaier et al. (2011) revealed that the COX-2/PGE2 pathway induced the differentiation of human DCs to monocyctic MDSCs. They also reported that PGE2 enhanced the differentiation of MDSCs in the human cancer environment. Hennequart et al. (2017) reported that COX-2/PGE2 signaling supported the constitutive expression of IDO1 in human melanoma and several cancer cell lines. They revealed that the PI3K/mTOR and PKC/GSK3β signaling pathways were involved in the expression of IDO1 protein. Interestingly, Newson et al. (2017) demonstrated that PGE2 not only enhanced the resolution of inflammation but expelled an immunosuppressive post-resolution phase for weeks in mouse macrophages after zymosan-induced peritonitis. They also reported that the post-resolution immunosuppression increased the differentiation of MDSCs and inhibited the function of lymphocytes. Given that IFN-γ was driving the post-resolution synthesis of PGE2, it seems possible that immunosuppression was induced by the sustained expression of IDO1.

The expression level of IDO1 protein can also be regulated by controlling its turnover rate through proteasomal degradation. Orbona et al. (2006) demonstrated that the suppressor of cytokine signaling 3 (SOCS3) stimulated the proteasomal degradation of IDO1 protein in mouse DCs. They reported that SOCS3 promoted the phosphorylated tyrosine motifs in the ITIM domain of the IDO1 protein. Recently, Albini et al. (2017) specified that the signaling molecules SHP1/2 interacted with the ITIM1 site (Section 4), whereas SOCS3 protein bound to the ITIM2 domain. Subsequently, the IDO/SOCS3 complex was ubiquitinated and degraded in proteasomes (Orbona et al., 2008). Pallotta et al. (2010) confirmed these observations and they also reported that IL-6 cytokine was able to convert tolerogenic, IDO-competent mouse DCs into active immunogenic cells through the
induction of SOCS3 protein. It is known that the SOCS3 protein controls many immune functions since it can induce a negative feedback response to the immune outcome mediated by several cytokines and hormones (Carow and Rottenberg, 2014). Given that AhR stimulates the expression of SOCS3 (Wada et al., 2016), it seems that the activation of AhR signaling not only increases the expression of IDO1 (see above) but it can also enhance the turnover of IDO1 protein in a context-dependent manner.

3.2. The IDO1-KYN-AhR signaling pathway

The activation of IDO1 enzyme triggers the KYN pathway generating a number of active tryptophan metabolites which have significant effects, e.g., on immune regulation, energy metabolism, neuronal activity, and hormonal responses (Badawy, 2017; Wirthgen et al., 2018; Savitz, 2020). For instance, KYNA, the first metabolite formed in the pathway, and its downstream metabolite, kynurenic acid (KYNA), are endogenous activators of the AhR factor which is a potent inducer of immunosuppression (Section 3.2.2) (Fig. 2). The KYN pathway has a crucial role in energy metabolism since nicotinamide adenine dinucleotide (NAD) is synthesized from quinolinic acid (QUIN), a downstream metabolite of KYN (McReynolds et al., 2017; Castro-Portuguez and Sutphin, 2020) (Fig. 2). However, the KYN pathway generates metabolites which have both toxic and protective effects, e.g., in brain pathology. Since the metabolites of KYN can be secreted to circulation, this means that the overproduction of KYN and its metabolites in some organs can have detrimental effects on remote tissues in the body. For instance, it is known that KYN metabolites generated by gut microbiota not only affect intestinal immunity but also the homeostasis of the brain and thus they are capable of inducing many neurologic and psychiatric disorders (Kennedy et al., 2017; Gao et al., 2018).

3.2.1. The KYN pathway

The IDO1 enzyme catalyzes the conversion of L-Trp into KYN which consequently can be enzymatically processed to several metabolites, e.g., KYNA, 3-hydroxykynurenine (3-HK), 3-hydroxyanthranilic acid, and finally to quinolinic and picolinic acids (Fig. 2). There are several review articles describing in detail the molecular pathways and enzymes involved in the processing of KYN (Badawy, 2017; Wirthgen et al., 2018; Marszalek-Grabska et al., 2021). The KYN aminotransferases (KAT) converts KYNA to KYN which has several neuroprotective effects, e.g., it inhibits glutamate neurotransmission (Carpenedo et al., 2001). Moreover, KYNA has anti-inflammatory and immunosuppressive properties which can be attributed to its capacity to activate the signaling of immunosuppressive AhR factor (DiNatale et al., 2010; Wirthgen et al., 2018) (Fig. 2). For instance, KYNA alleviated the LPS-induced pro-inflammatory responses in human HUVEC cells and THP-1 monocytes (Lee et al., 2019). In addition, KYNA was able to scavenge oxygen free radicals and attenuates ROS production in chemical and biological assays (Lugo-Huitron et al., 2011). It seems that the KAT-driven KYNA synthesis represent the protective/survival branch of the KYN pathway under diverse pathological conditions (Wirthgen et al., 2018; Mor et al., 2021).

Kynurenine 3-monooxygenase (KMO) is the rate-limiting enzyme for the catalysis of KYN, thus representing a major catabolic route for L-Trp degradation (Parrott and O’Connor, 2015; Smith et al., 2016) (Fig. 2). The activation of KMO produces many neurotoxic compounds, such as 3-HK and QUIN (Okuda et al., 1998; Lugo-Huitron et al., 2019). For instance, QUIN and 3-HK are the agonists of N-methyl-D-aspartate (NMDA) receptors and thus they can enhance brain excitotoxicity in inflammatory conditions, e.g., associated with ischemic insults and many neurodegenerative diseases (Loveless et al., 2017; Savitz, 2020). In addition, KYNA, an antagonist to NMDA receptors, can disturb the developmental processes in human brain (Bagasrawala et al., 2016). Given that the activation of KMO generates toxic responses in a context-dependent manner, the inhibition of KMO has been a promising drug target for many diseases, especially neurodegenerative diseases and psychiatric disorders (Parrott and O’Connor, 2015; Smith et al., 2016). For instance, Garrison et al. (2018) demonstrated that LPS exposure robustly increased the expression of IDO1 and KMO in mouse BV2 microglia. Accordingly, the inhibition of KMO significantly reduced the level of the LPS-induced pro-inflammatory response in both mouse BV2 and primary microglia. Furthermore, Giorgini et al. (2013) demonstrated that the knockout of KMO induced a clear increase in the levels of KYN and KYNA in mouse brain, liver, and plasma, whereas the concentrations of 3-HK and QUIN were significantly reduced. This indicates that the inhibition of KMO can induce an accumulation of KYN and KYNA not only in tissues but most probably also in immune cells. Given that KYN and KYNA are potent activators of AhR factors (Fig. 2), this might increase immunosuppression and protect tissues from acute inflammatory insults. Zheng et al. (2019) revealed that the inflammation occurring after a renal ischemia-reperfusion injury was significantly reduced in the KMO knockout mice as compared to their wild-type counterparts. It seems that the beneficial effects of KYN and KYNA can be partly attributed to the anti-inflammatory/immunosuppressive effects induced by the activation of AhR.

3.2.2. AhR signaling promotes immunosuppression

In their seminal study, Mezirich et al. (2010) demonstrated that KYN but not 3-HK or QUIN activated the AhR factor in mouse CD4 T, DC, and hepatoma cells. Interestingly, they reported that KYN induced an AhR-dependent differentiation of Treg cells through the stimulation of the expression of the Foxp3 gene, a master gene of immunosuppressive Tregs. They also reported that TGF-β upregulated the expression of AhR in mouse CD4 T cells. This implies that the AhR factor can be involved in the TGF-β-mediated Treg differentiation. DiNatale et al. (2010) demonstrated that KYNA also was a potent endogenous inducer of AhR in mouse HepG2 cells and human primary hepatocytes. They also revealed that KYNA was able to occupy the ligand-binding pocket of the AhR protein. Currently, it is known that there are a number of endogenous agonists for AhR factor, originating either from L-Trp or other sources (Torti et al., 2021). Rannug et al. (1995) demonstrated that UV irradiation of L-Trp amino acids in vitro produced the photo-oxidized derivative 6-formylindolo [3,2-b] carbazole (FICZ) which was a high affinity agonist to the AhR receptor. Subsequently, Fritsche et al. (2007) demonstrated that UVB radiation induced the FICZ-mediated activation of AhR transcription in human keratinocytes. It seems that the photo-oxidation of L-Trp to FICZ can have a significant role in the photoaging process in the skin. Recently, Sadik et al. (2020) demonstrated that interleukin-4-induced 1 enzyme (IL4I1), also known as L-amino acid oxidase, catalyzed L-Trp amino acid to indole-3-aldehyde and KYNA which consequently activated the AhR-mediated transcription. These studies indicated that there exist the L-Trp-dependent, but IDO1-independent, endogenous activation mechanisms of AhR-mediated transcription.

AhR factor is a multifunctional transcription factor which after ligand binding translocates into the nucleus where it forms a heterodimer with AhR nuclear translocator (ARNT) protein. Subsequently, the AhR/ARNT complex binds to the specific dioxin/xenobiotic responsive element (DRE/XRE) and controls the expression of a diverse set of genes, e.g., those involved in chemical and microbial defence, cell proliferation and development, as well as many functions of the immune system (Stockinger et al., 2014; Gutierrez-Vazquez and Quintana, 2018; Rotherhammer and Quintana, 2019). There is substantial evidence that the AhR factor and the RBP component form dimers which can bind both to the DRE and the NF-κB consensus elements and subsequently transactivate gene expression (Vogel et al., 2007; Vogel and Matsumura, 2009). However, the co-operation of AhR and RBP proteins seems to be ligand-dependent (Ishihara et al., 2019) and probably, also a context-dependent process, as has been commonly observed in other aspects of AhR-driven regulation. Given that the RBP factor is a potent regulator of epigenetic landscape, e.g., in endotoxin tolerance (Chen
et al., 2009; Gupta et al., 2019), it seems possible that the AhR factor modifies the functions of RelB-regulated genes in the control of immune responses. For instance, the activation of AhR increased the nuclear accumulation of RelB protein and augmented its DNA-binding activity in mouse bone-marrow DCs and consequently enhanced their maturation (Vogel et al., 2013). Moreover, AhR factor co-operates with several other transcription factors, e.g., STAT3 and NRF2, in the regulation of immune responses (Liu et al., 2017a; Lin et al., 2021).

Currently, there is substantial evidence that the IDO1-induced immunosuppression can be mediated through the AhR signaling promoted by KYN/KYNA (Fig. 1). For instance, the activation of AhR by both KYN and TCDD, stimulated the differentiation of T cells to the immunosuppressive, FoxP3-positive Tregs (Quintana et al., 2008; Ganddhi et al., 2010; Mezrich et al., 2010). Gagliani et al. (2015) revealed that TGF-β signaling and the activation of AhR signaling induced the transdifferentiation of pro-inflammatory Th17 cells into Tregs which promoted the resolution of inflammation in two mouse inflammatory models. Accordingly, Campesato et al. (2020) demonstrated that the blockade of AhR signaling inhibited the IDO/IDO-induced immunosuppression in mouse tumor models. They revealed that the KYN-AhR-mediated signaling was able to increase the activation of Tregs which subsequently promoted the immunosuppressive activity of M2 macrophages and tumor-associated macrophages (TAM). It is known that the activation of AhR signaling enhanced the polarization of macrophages towards the anti-inflammatory M2 phenotype (Yang et al., 2020). Holmgard et al. (2015) reported that the tumor-expressed IDO induced the recruitment of immunosuppressive MDCs into tumor sites and activated them in a Treg-dependent manner. Moreover, Neamah et al. (2019) demonstrated that an injection of TCDD into mouse peritoneal cavity induced the activation of AhR and triggered a robust expression of several chemokines which promoted the differentiation of MDCs in mouse bone marrow (BM). Consequently, MDCs were mobilized from BM to the peritoneal cavity. The recruited MDCs suppressed the proliferation of T cells and repressed inflammatory response. Recently, Piper et al. (2019) reported that the activation of AhR signaling induced the differentiation of mouse B cells into the IL-10-producing, immunosuppressive Breg cells. They also identified a putative AhR binding site in the promoter of the IL-10 gene. It is known that the activation of AhR signaling could stimulate the expression and secretion of immunosuppressive cytokines, e.g., IL-10 (Ganddhi et al., 2010; Zhu et al., 2018; Piper et al., 2019). There is clear evidence that AhR signaling stimulated the generation of tolerogenic DCs (tolDC) which subsequently enhanced the differentiation of Tregs (Bruhs et al., 2015; Takenaka and Quintana, 2017; Barroso et al., 2021). The therapeutic induction of tolDCs might have beneficial effects in autoimmune diseases and allergy.

The activation of AhR signaling also induced the expression of several immune checkpoint proteins, both in immune and cancer cells (Rad Pour et al., 2019; Amobi-McCloud et al., 2021; Kenison et al., 2021). For instance, the AhR-mediated signaling enhanced the expression of PD-1, PD-L1, CTLA4, Lag3, and CD39; all being recognized immune checkpoint proteins. Rad Pour et al. (2019) demonstrated that the co-culture of human CD4 T cells with melanoma cells induced the expression of IDO1 and stimulated the production of KYN and KYNA in CD4 T cells. Subsequently, the increased expression of AhR, PD-L1, and CTLA4, common exhaustion markers of T cells, impaired the function of effector CD4 T cells. Interestingly, Liu et al. (2018) demonstrated that in the inflammatory microenvironment present in mouse tumors, the secretion of KYN was robustly increased and it was transferred into the invading CD8 T cells via the SLCA7A8 and PAT4 transporters. In CD8 T cells, KYNA activated AhR signaling which consequently upregulated the expression of KYNA transporter and PD-1 checkpoint protein. These observations have also been verified in human cancer patients. In conclusion, the activation of IDO1 enzyme, either in non-immune or immune cells, can trigger KYNA production which promotes the immunosuppressive activities of immune cells infiltrating into inflamed host tissues.

4. IDO1 acts as a signaling platform enhancing immunosuppression

The IDO1 protein is not only a catalytic enzyme but it can also act as a non-enzymatic signaling platform via its phosphorylation domains, i.e., the ITIM1 and ITIM2 motifs as well as the YENM sequence (Pallotta et al., 2021). The catalytic IDO1 is mostly located in the cytosol, whereas the signaling IDO1 protein has been localized to the early endosomes (EE) which are active subcellular signaling locations (Sadowski et al., 2009). Iacono et al. (2020) reported that the treatment of plasmacytoid DCs (pDC) with TGF-β robustly increased the relocation of IDO1 proteins from the cytosol to the EE. They demonstrated that the YENM phosphorylation domain of IDO1 protein was required for its transfer from the cytosol to the EE in mouse pDCs. They revealed that IDO1 protein interacted with the p85 subunit of class IA phosphoinositide 3-kinase (PI3K) via the YENM domain. Subsequently, the p85 subunit recruited the catalytic p110 unit, commonly the p110β or δ subunit in human immune cells (Human Protein Atlas). These observations indicated that the binding of PI3K to IDO1 protein anchored the IDO1 complex to the EE where it acts as a signaling platform capable of driving immunosuppressive processes (Fig. 3). Iacono et al. (2020) reported that the activation of PI3K p110 subunit was required for the signaling of IDO1 protein, e.g., the induction of the IDO1 and TGF-β genes, which consequently induced immunosuppressive properties in pDCs. This implies that PI3K not only targets the IDO1 protein to the EE but might also be involved in the IDO1/PI3K-mediated immunosuppressive signaling. Aksoy et al. (2012) reported that PI3K p110δ also regulated the endosomal compartmentalization of TLR4 protein and subsequently it
conferred protection against endotoxic shock in mouse DCs. There is convincing evidence that the activation of PI3K p110δ promoted immunosuppression as well as human T cell senescence and immunodeficiency (Lucas et al., 2014; Chellappa et al., 2019). Currently, the role of signaling IDO1 protein in these responses remains to be clarified.

Pallotta et al. (2011) observed that TGF-β treatment conferred a long-term, IDO1-dependent immune tolerance in mouse pDCs. They demonstrated that TGF-β stimulated the Fyn kinase-dependent phosphorylation of the ITIM domains of IDO1 protein. TGF-β exposure induced the binding of SHP-1, a tyrosine-protein phosphatase, to the phosphorylated ITIM sequences (Fig. 3). Consequently, SHP-1 stimulated the non-canonical, p52/RelB-dependent NF-κB signaling. They also reported that TGF-β treatment of pDCs induced an IDO1-dependent, but its catalytic activity-independent, immunosuppressive effects, e.g., an increase in the expression of the IDO1 and TGF-β genes. Albini et al. (2017) identified that the SHP-1 protein interacted with the ITIM motif. They also revealed that the antigen-specific immunosuppressive properties of pDCs were mediated through the ITIM1 domain of the IDO1 protein in mouse. There are observations indicating that the activation of SHP-1 stimulated IKKα which induced the non-canonical NF-κB signaling through the p52/RelB pathway (Pallotta et al., 2011; Mbongue et al., 2015) (Fig. 3). For instance, Yu et al. (2014) demonstrated that RelB/p52 dimers were able to bind to the promoter of the IDO1 gene and increase the expression of IDO1 protein in human MDSCs. It is known that SHP-1 has diverse effects in immune cells, mostly enhancing immunosuppressive functions (Dong et al., 1999; Zhang et al., 2000). For instance, Myers et al. (2020) demonstrated that the inducible deletion of Ptpn6 gene, a gene coding for SHP-1 protein, induced hyperactivation of immune cells and simultaneously provoked a robust anti-tumor immune response in mouse macrophages. The RelB protein is an interesting transcription factor since it can bind several transcription factors, e.g., AhR factor, and induce endothelin receptor (Section 3.2.2) (Fig. 3). Moreover, RelB factor possesses many immunosuppressive properties, e.g., a capacity to converge naïve T cells into immunosuppressive Tregs (Lutz, 2016; Grinberg-Bleyer et al., 2018). Currently, it is not known whether the RelB factor stimulated by non-catalytic IDO1 signaling co-operates with the AhR factor in the generation of immunosuppressive responses.

5. Chronic inflammation stimulates immunosuppression via IDO1-KYN-AhR signaling

Many immune cells are auxotrophic for certain amino acids, mostly L-Trp and L-Arg, which means that they are unable to synthesize those amino acids. Immunosuppressive cells exploit this deficiency and deplete the inflamed microenvironment from these amino acids, thus suppressing the proliferation of pro-inflammatory cells and enhancing the resolution of inflammation (Grohmann et al., 2017). There is substantial evidence that chronic inflammation is associated with the activation of L-Trp catabolism and increased production of KYN metabolites, e.g., in bacterial and viral infections (Tattevin et al., 2010; Schmidt and Schulzit, 2014), cardiovascular diseases (Liu et al., 2017b), chronic kidney disease (Pawlak et al., 2002), autoimmune diseases (Mbongue et al., 2015), and many tumors (Munn and Mellor, 2016; Lanser et al., 2020). Psychological stress can also stimulate the IDO1-dependent L-Trp degradation and induce immunosuppression in mice and humans (Klaiek et al., 2010). The IDO1-induced breakdown of L-Trp also reduced the synthesis of serotonin and it is known that many neuroinflammatory diseases are associated with brain inflammation (Dantzer et al., 2011; Jeon and Kim, 2017). Given that chronic inflammation increases the degradation of L-Trp, an enhanced dietary supply of L-Trp might have beneficial effects in chronic inflammatory conditions. There are observations indicating that an increased dietary supply of L-Trp alleviated experimentally-induced inflammation in rodents (Del Angel-Meza et al., 2011; Islam et al., 2017), whereas an L-Trp-deficient diet increased systemic inflammation in aged mice (Yusufu et al., 2021).

In particular, the role of dietary L-Trp is important in the immune homeostasis in the gut. Nikolaus et al. (2017) reported that inflammatory bowel disease (IBD) was associated with a significant downregulation of the serum L-Trp concentration. Correspondingly, the serum concentrations of KYN and its metabolites, especially QUIN, as well as inflammatory C-reactive protein (CRP) were robustly increased in IBD patients. There is clear evidence that the metabolites of L-Trp, produced by colon epithelium and microbiota, activate AhR signaling which promotes immune tolerance, e.g., via the differentiation of Tregs (Ding et al., 2020; Pernomian et al., 2020). Several investigators have claimed that L-Trp metabolites produced by the microbiota of inflammatory gut can affect brain and augment depression (Waclawiakova and El Aydi, 2018; Roth et al., 2021). Currently, it is not known whether the microbiota-produced L-Trp metabolites, e.g., KYN and KYNA, can evoke immunosuppressive effects in remote target tissues via the circulation.

The KYN pathway has been activated in several diseases involving chronic inflammation, e.g., KYN signaling aggravates human atherosclerotic pathology (Baumgartner et al., 2021). The activation of AhR signaling promotes the development of atherosclerosis, partly through the control of foam cell formation (Vogel et al., 2004; Wang et al., 2020). The KYN pathway has a crucial role in the pathogenesis of many neurodegenerative diseases as well as that of neuropsychiatric disorders (Lovelace et al., 2017; Muneer, 2020). However, it seems that the neurotoxic effects of KYN metabolites, e.g., those of QUIN, are driving pathological processes rather than that of AhR-mediated immunosuppressive responses (Jago-Huitron et al., 2013; Mor et al., 2021). In community-dwelling patients, an increased KYN-to-L-Trp ratio significantly correlated with poorer cognitive performance in these individuals (Solvang et al., 2019). Recent studies have also revealed that neuro-pathic pain is caused by the activation of the KYN pathway in chronic inflammatory conditions (Jovanovic et al., 2020; Tanaka et al., 2021). Huang et al. (2016) demonstrated that viral infections enhanced mouse pain hypersensitivity by stimulating KYN production in the IDO-positive DCs. QUIN is an interesting KYN metabolite since its concentration robustly increases in chronic inflammation and it has both toxic and beneficial effects, e.g., it is a substrate for the de novo synthesis of NAD+ (Fig. 2). Currently, it is not known whether its role is to replenish the reduced content of NAD+ during chronic inflammation (Moffett et al., 2020). It has also been claimed that QUIN might be immunosuppressant since it can induce the apoptosis of thymocytes and Th1 cells at physiological concentrations (Fallarino et al., 2002; Badawy, 2018). Nonetheless, it seems that KYN/KYNA are the major inducers of the AhR-mediated immunosuppression in inflammatory conditions.

The evolutionarily conserved AhR factor is robustly expressed in several immune cells and it has different immunomodulatory functions (Gutierrez-Vazquez and Quintana, 2018; Rothhammer and Quintana, 2019; Torti et al., 2021). The expression of AhR is commonly upregulated in chronic inflammatory diseases, e.g., atherosclerosis (Zhu et al., 2019), IBD (Pernomian et al., 2020), psoriasis (Kim et al., 2020), and viral infections (Torti et al., 2021). As described in Section 3.2.2., the activation of AhR signaling induces immunosuppressive responses in chronic inflammatory diseases by promoting the recruitment and differentiation of immunosuppressive cells. In addition, there are observations indicating that the AhR factor repressed the function of NLRP3 inflammasomes by inhibiting the expression of NLRP3 protein (Hua et al., 2014). Subsequently, the secretion of IL-1β was decreased and the severity of alum-induced peritonitis inhibited in mice. AhR signaling was also reported to maintain immunosuppressive responses in IBD by inhibiting the function of NLRP3 inflammasomes (Ngui et al., 2020). AhR signaling also suppressed inflammatory responses in mouse epididymal y6 T cells (Merches et al., 2020). Interestingly, Wada et al. (2016) reported that the SOCS 3 gene was a novel target of the AhR factor and that the activation of AhR signaling induced the expression of SOCS3 protein in mouse liver. SOCS3 protein is a potent suppressor of cytokine signaling and a crucial inhibitor of chronic inflammation (Carow and Rottenberg, 2014). Accordingly, the deletion of the AhR gene in mouse liver,
enhanced hepatic inflammation and provoked steatosis in animals fed with a high fat diet (HFD) (Wada et al., 2016). Given that AhR signaling triggers anti-inflammatory/immunosuppressive effects in diverse conditions, the activation of AhR has been an important therapeutic target in drug discovery projects (Cheong and Sun, 2018; Hui and Dai, 2020). Many natural products are agonists of the AhR factor and thus they are potent activators of AhR signaling. For instance, berberine, curcumin, indole-3-carbinol, and tetrandrine were demonstrated to stimulate AhR signaling and attenuated inflammation in different models (Hui and Dai, 2020). IDO1 could also be a significant therapeutic target in cancer and inflammatory diseases although currently it seems that there are problems with efficacy and side effects (Günther et al., 2019).

6. Aging is associated with the activation of IDO1-KYN-AhR signaling

There is convincing evidence that the catabolism of L-Trp increases with aging through the KYN pathway. This is based on the observations that the plasma concentration of L-Trp decreases, whereas concurrently the ratio of KYN/L-Trp significantly increases (Frick et al., 2004; Pertoarau et al., 2006; Capuron et al., 2011; van der Goes and Nollen, 2013; da Silva et al., 2021). Accordingly, a decline in the L-Trp level with aging impairs the synthesis of serotonin and melatonin, enhancing neuropsychiatric disorders in aged people (Section 2). de Bie et al. (2016) reported that the level of L-Trp decreased in the cerebrospinal fluid (CSF) of women with aging, whereas the concentrations of KYN, QUIN, and picolinic acid were increased. There are only a few studies which have examined on the age-related changes in the metabolites of L-Trp in different tissues. Braidy et al. (2011) demonstrated that the level of free L-Trp decreased with aging in rat brain, liver and kidney. Simultaneously, there was an increase in the level of KYN in brain and kidney as well as those of QUIN and picolinic acids in rat brain and liver. They also revealed that the activity of IDO increased with aging in brain but not in liver and kidney, whereas the activities of TDO decreased in all three tissues. Interestingly, Marttila et al. (2011) demonstrated that the age-related increase in the KYN/L-Trp ratio in human plasma was not associated with the transcription level of IDO1 or IDO2 genes in peripheral blood mononuclear cells (PBMC). Currently, the cellular source of IDO1 enzyme in tissue samples and thus the location of L-Trp catabolism needs to be clarified although it is recognized that IDO1 expression is enriched in myeloid cells, especially in monocytes (Human Protein Atlas).

The age-related activation of the KYN pathway may be attributed to an enhanced inflammaging process since similar changes have been observed in many inflammatory diseases (Section 5). There are several studies indicating that the frailty of elderly people is associated with a robust activation of the KYN pathway (Valdiglesias et al., 2018; Jang et al., 2020; Westbrook et al., 2020). Ramos-Chavez et al. (2018) reported that low plasma levels of L-Trp and increased KYN concentrations were associated with cognitive impairment in nondemented women over 50 years of age. KYN signaling is a promising drug target in humans since it has been claimed to act as a trigger for many health problems associated with chronic inflammatory diseases (Platten et al., 2019). There are many studies performed with L-Trp-deficient diets, although in aged mice it is known that these diets can induce dysbiosis in gut microbiota and increase systemic inflammation (Yusufu et al., 2021). Experimental studies with the deletion of the Tdo-2 gene revealed that the genetic inhibition of L-Trp degradation improved protein homeostasis and delayed the aging process in C. elegans model (van der Goot et al., 2012). In addition, a Drosophila mutant, deficient of Tdo-2 gene, also displayed an extended lifespan (Oxenkrag, 2010). These observations might be linked to improved healthspan through the reduction of L-Trp catabolism.

The role of the AhR signaling in the regulation of the aging process has been recently reviewed in detail by Brinkmann et al. (2020) and Kaiser et al. (2020). The AhR factor is widely expressed in human tissues (Human Protein Atlas) indicating that AhR factor also has important non-immune functions, e.g., in the developmental processes. The expression of AhR factor increases with aging, e.g., in astrocytes of human hippocampus (Ramos-Garcia et al., 2020). It is not surprising that the loss of the AhR gene is associated with many health problems and shortens lifespan, both in invertebrate and mouse models (reviewed by Brinkmann et al., 2020). Interestingly, Andersson et al. (2002) demonstrated that a constitutive low-level activity of the AhR gene significantly reduced the lifespan of mice and induced tumors, especially in stomach. Eckers et al. (2016) revealed that the overexpression of the AhR gene in mice reduced the activation of endothelial nitric oxide synthase (eNOS) and consequently decreased the production of NO. This process led to a dysfunction of endothelial cells and increased vascular stiffness. An increase in vascular stiffness is a common age-related alteration encountered in humans. In C. elegans, the abr-1 mutants displayed an enhanced eNOS activity, augmented resistance to heat shock, and significantly extended mean lifespan as compared to their wildtype counterparts (Eckers et al., 2016). These studies indicate that the AhR factor exerts harmful effects in terms not only of vascular but also organismal aging. Huang et al. (2015) reported that the expression of AhR gene was significantly increased in the peripheral blood of patients with coronary artery disease (CAD). They also identified a polymorphic site in the AhR gene which was a risk factor for CAD. There are also observations that the sustained activation of AhR signaling in skin increased premature cellular aging and enhanced the development of skin tumors (Vogeley et al., 2019). It is known that the activation of AhR factor promotes cellular senescence through the inhibition of autophagy (Kim et al., 2020; Kondrikov et al., 2020). Moreover, the KYN-induced osteoclastogenesis was mediated by the activation of AhR signaling (Eisa et al., 2020). ROS, well-known enhancers of cellular senescence and the aging process, are also able to evoke AhR signaling (Smirnova et al., 2016; Kubli et al., 2019) and subsequently might promote the aging process.

7. IDO1-KYN-AhR signaling is a double-edged sword

Signaling through the IDO1-KYN-AhR pathway is stringently regulated since the pathway can induce both beneficial and harmful effects in a context-dependent manner. It is not only the expression level of IDO1 (Section 3.1) but also the activity of the IDO1 enzyme that is strictly controlled in cells. IDO1 protein is typically present in cells as an inactive apo-form. IDO1 protein is a heme-containing dioxygenase which incorporates oxygen and its presence stimulates the catalytic activity of IDO1. The iron-binding heme protein has an important role in the heme-responsive sensor proteins, such as hemoglobin and myoglobin (Shimizu et al., 2019). Evolutionarily, it seems that myoglobin evolved from IDO (Suzuki et al., 1998). Given that the heme protein is synthesized from succinyl-CoA, this connects the content of heme to the activity of energy metabolism. There is clear evidence that heme synthesis declines with aging (Atamna et al., 2002) which is probably attributed to an increase in the expression of heme oxygenase-1 (HO-1), an enzyme which can catalyze heme protein (Schipper et al., 2019). The catalytic activity of IDO1 is also controlled by the oxygen supply, i.e., enzymatic activity is reduced in tumor sites and inflamed tissues (Schmidt et al., 2013). Intriguingly, IDO1 is also involved in immunosuppressive moonlighting through its ITIM motifs in an oxygen-independent manner (Section 4). Given that this signaling platform function is associated with epigenetic regulation, indicating that IDO1 might control persistent inflammatory changes. The activation of IDO1 has a crucial role in the activation of immunosuppressive cells in the resolution phase of acute inflammation (Section 5). However, the catabolism of L-Trp with the purpose to suppress the proliferation of pro-inflammatory cells has counteracting effects, such as the reduced synthesis of serotonin and melatonin (Section 2). The long-term deprivation of L-Trp also disturbs protein synthesis in neighboring cells within inflamed tissues causing degenerative changes in host tissues.
Inflammatory conditions significantly increase the expression and activity of IDO1, thus enhancing the production of KYN and its metabolites (Section 5). The KYN pathway is typically a double-edged sword since the KYN pathway generates metabolites which can exert either favorable or unfavorable responses. Normally, KYN, KYN, and picolinic acids have anti-inflammatory and neuroprotective properties, whereas 3-HK and QUIN evoke many harmful effects. For instance, QUIN has been associated with neurotoxicity and inflammatory responses (Lugo-Huiron et al., 2013), although its further processing generates NAD, an important energy metabolic coenzyme (Castro-Portuguez and Surphin, 2020) (Fig. 2). NAD can also be produced from nicotinic acid and nicotinamide riboside through the salvage pathway. The level of NAD declines with aging and thus the regulation mechanisms of NAD biosynthesis are promising anti-aging drug targets (Imai and Guarente, 2014; Covarrubias et al., 2021). Minhas et al. (2019) demonstrated that NAD is mostly synthesized from KYN in mouse and human macrophages. The blockade of this pathway impaired mitochondrial respiration, phagocytosis, and resolution of inflammation. They also reported that the LPS-induced inflammatory insult suppressed the KYN-induced NAD synthesis by decreasing the expression of quinolate phosphoribosyl transferase (QPRt), the first QUIN-processing enzyme. Minhas et al. (2019) also revealed that macrophages sampled from aged people displayed a decline in the expression of QPRt and a low concentration of NAD but in contrast, the levels of KYN metabolites were significantly increased. This clearly indicates that the enzymes driving the KYN pathway have a critical role in outcome responses. However, Zhang et al. (2019) demonstrated that the induction of IDO1 with a high dose of LPS switched the generation NAD from the salvage pathway to the IDO1-dependent, QUIN-mediated de novo NAD biosynthesis in human THP-1 and PBMC cells. An increase in the nuclear level of NAD stimulated the epigenetic SIRT1/ReLB-directed inflammatory tolerance. This indicates that IDO1 is also able to promote immunosuppression by increasing the biosynthesis of NAD.

The AhR factor controls the transcription of multiple genes, either directly or in co-operation with other transcription factors. Accordingly, the AhR factor regulates a diverse set of dissimilar functions, e.g., reproduction, cellular development, energy metabolism, chemical and microbial defence, and inflammation/immunity (Bock, 2019; Rothhammer and Quintana, 2019). For instance, the AhR factor plays a significant role in mammalian hematopoiesis, e.g., it controls the differentiation of hematopoietic stem cells and progenitor cells (Lindsey and Papoutsakis, 2012; Angelos et al., 2017; Angelos and Kaufman, 2018). On the other hand, the AhR factor is able to promote cellular senescence and the aging process (Section 6). Thus, the AhR factor is a good example of the genes which display an antagonistic pleiotropy, i.e., a gene which has very different functions in early development and later in the lifespan (Austad and Hoffman, 2018; Kyriazis, 2020). This characteristic of AhR is most probably attributable to its crosstalk and co-operation with other transcription factors, some of which control the epigenetic landscape, such as ReLB (Section 3.2.2). Interestingly, the AhR factor is able to display both pro- and anti-inflammatory/immunosuppressive activities in a context-dependent manner. For instance, some environmental toxins, e.g., polycyclic aromatic hydrocarbons (PAH) and diesel exhaust particles, act as triggers for pro-inflammatory responses (Brinckmann et al., 2018; O’Driscoll et al., 2018). However, the AhR factor has a major role in the activation of immunosuppressive network in the resolution phase of inflammatory conditions (Section 5). Immunosuppressive cells, e.g., MDSC, Treg, and M2 macrophages, secrete anti-inflammatory cytokines and reactive oxygen and nitrogen species as well as stimulating amino acid catabolism. These processes enhance the resolution of inflammation in the acute phase but they have harmful effects in persistent inflammatory states, such as in the aging process. For instance, anti-inflammatory cytokines impaire autophagy, induce cellular and immune senescence, remodel the extracellular matrix, enhance osteoporosis and vascular diseases, and augment tissue atrophy (Quan and Fisher, 2015; Wu et al., 2016; MacFarlane et al., 2017; Kondrikov et al., 2020). The activation of the AhR factor is able to produce all these changes either directly or indirectly by activating the immunosuppressive network, thus promoting the aging process and age-related diseases.

8. Conclusions

Several inflammatory mediators stimulate the expression of IDO1 enzyme which consequently activates the KYN pathway. The metabolites of the KYN pathway can induce diverse immune, metabolic, and hormonal responses, either beneficial or harmful effects (Badawy, 2017; Savitz, 2020). The KYN pathway is activated in many chronic diseases, especially in those involving persistent inflammation. Currently it is not known whether the activation of the KYN pathway is a driving force or a compensating inhibitory mechanism in chronic inflammatory conditions (Wirthgen et al., 2018; Baumgartner et al., 2019; Joisten et al., 2021). Given that KYN metabolites have many opposite functions, thus the regulation of the enzymes controlling the dynamics of the KYN pathway has a key role in outcome responses. For instance, the inhibition of KMO increases the accumulation of KYN and KYNA, well-known activators of immunosuppressive AhR factor (Figs. 1 and 2). IDO1-KYN-AhR signaling has a beneficial counteracting role in acute inflammation enhancing the resolution of inflammatory condition, whereas in the chronic inflammatory states the persistence of the IDO1-KYN-AhR signaling has harmful effects not only on the host cells of inflamed tissues but also on the cells of the immune system, probably promoting immunosenescence (Section 7). There is substantial evidence that the aging process involving a chronic low-grade inflammation is also associated with the activation of IDO1-KYN-AhR signaling (Brinkmann et al., 2020; Kaiser et al., 2020). It seems that a persistent mild inflammatory state maintains an increased activation of the IDO1-mediated signaling with aging. It is known that IDO1 is a major inducer of immunosuppressive state in many cancers and other chronic inflammatory conditions. There is convincing evidence that aging is associated with an increased immunosuppressive activity, e.g., involving expanded numbers of MDSCs and Tregs (Lages et al., 2008; Verschoor et al., 2013; Ruhland et al., 2016; Flores et al., 2017; Salminen, 2020). Immunosuppression induced by chronic inflammation impairs tissue homeostasis by secreting anti-inflammatory cytokines, e.g., TGF-β and IL-10, reactive oxygen and nitrogen species (ROS/RNS), as well as KYN metabolites generated by the activation of the IDO1-KYN pathway (reviewed by Salminen, 2021). Moreover, a long-term decrease of L-Trp level by IDO1 activation disturbs serotonin synthesis predisposing to psychiatric disorders and inhibits protein synthesis promoting tissue atrophy. Both conditions appear during the aging process.

Declaration of Competing Interest

None.

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References

Akroyd, E., Taboubi, S., Torres, D., Delbaeue, S., Iachani, A., Whitehead, M.A., Pearce, W. P., Berenjeno, I.M., Nock, G., Filloux, A., Beyaert, R., Flamand, V., Vanhaesebroeck, B., 2012. The p110δ isoform of the kinase PI3K controls the subcellular compartmentalization of TLR4 signaling and protects from endotoxic shock. Nat. Immunol. 13, 1045–1054. https://doi.org/10.1038/ni.2426.
Albini, E., Rosini, V., Gargaro, M., Mondanelli, G., Bellomonna, M.L., Pallotta, M.T., Volpi, C., Fallarino, F., Macchiariulo, A., Antognelli, C., Bianchi, R., Vacca, C., Puccetti, P., Grohmann, U., Otobona, C., 2017. Distinct roles of immunoreceptor tyrosine-based motifs in immunosuppressive indoleamine 2,3-dioxynegenase I. J. Cell. Mol. Med. 21, 165–176. https://doi.org/10.1111/jcmm.12954.
Huang, L., Ou, R., Rabelo de Souza, G., Cunha, T.M., Lemos, H., Mohamed, E., Li, L., Grinberg-Bleyer, Y., Caron, R., Seeley, J.J., De Silva, N.S., Schindler, C.W., Hayden, M.S., Gao, J., Xu, K., Liu, H., Liu, G., Bai, M., Peng, C., Li, T., Yin, Y., 2018. Impact of the gut microbiota on intestinal immunity mediated by tryptophan metabolism. Ageing Research Reviews 75 (2022), 1-10.

Gagliani, N., Amezcua Vesely, M.C., Iseppon, A., Brockmann, L., Xu, H., Palm, N.W., de Eynde, B.J., 2017. Constitutive IDO1 expression in human tumors is driven by TGF-β signaling. J. Immunol. 208, 1540-1548. https://doi.org/10.4049/jimmunol.1900656.

Lin, X., Tawch, S., Wong, H.T., Roy, S., Gaudino, S., Castillo, P., Elsegeiny, W., Lee, Y.K., Lee, H.B., Shin, D.M., Kang, M.J., Yi, E.C., Noh, S., Lee, J., Lee, C., Min, C.K., Lee, T., Park, H.S., Jeong, J.H., Jung, T.W., 2019. Kynurenic acid attenuates pro-inflammatory reactions in lipopolysaccharide-stimulated endothelial cells through aryl hydrocarbon receptor in mice. Mol. Med. 25, 946-954. https://doi.org/10.1016/j.molmed.2021.07.006.

Kiyozumi, Y., Baba, Y., Okadome, K., Yagi, T., Ogata, Y., Eto, K., Hiyoshi, Y., Ishimoto, T., Iwatsuki, M., Iwagami, S., Miyamoto, Y., Yoshida, N., Watanabe, M., Baba, H., 2019. Indoleamine 2,3-dioxigenase 1 promoter hypomethylation is associated with poor prognosis in patients with esophageal cancer. Cancer Sci. 110, 1863-1871. https://doi.org/10.1111/cas.14028.

Kondrikov, D., Elamani, A., Bragg, R.T., Mobley, T., Barrett, T., Elisa, N., Kondrikova, G., Schoenfeld, P., Agueroz, A., Shi, X.M., Fulzele, S., Lawrence, M.M., Hamrick, M., Isales, C., Hill, W., 2020. Kynurenine inhibits autophagy and promotes senescence in aged bone marrow mesenchymal stem cells through the aryl hydrocarbon receptor pathway. Exp. Gerontol. 130, 225-234. https://doi.org/10.1016/j.exger.2020.101573.

Kryazhimskiy, M., 2020. Ageing throughout history: the evolution of human lifespan. J. Mol. Med. 28, 87-95. https://doi.org/10.1007/s00109-020-01770-0.

Lages, C.S., Suffia, I., Veilas, P.A., Huang, B., Warshaw, G., Hildeman, D.A., Belkaid, Y., Chougnet, C., 2008. Functional regulatory T cells accumulate in aged hosts and promote chronic infectious disease reactivation. J. Immunol. 181, 1853-1858. https://doi.org/10.4049/jimmunol.181.3.1853.

Larsen, L., Klink, P., Egger, E.M., Willersbach, W., Fuchs, D., Weiss, G., Kurz, K., 2020. Inflammation-induced tryptophan breakdown is related with anemia, fatigue, and depression in cancer. Front. Immunol. 11, 249. https://doi.org/10.3389/fimmu.2020.00249.

Lee, Y.K., Lee, H.B., Shin, D.M., Kang, M.J., Yi, E.C., Noh, S., Lee, J., Lee, C., Min, C.K., Choi, E.H., 2014. Heme-binding-mediated negative regulation of the tryptophan-metabolizing enzyme indoleamine 2,3-dioxigenase 1 (IDO1) by DOX. Exp. Mol. Med. 46, e412 https://doi.org/10.1038/EMM.2014.69.

Lin, T., Tawch, S., Wang, H.Y., Roy, S., Gaudino, S., Casati, F., Epelejnov, W., Watanabe, N., Ouy, S., Chen, K., McInnes, N., Melville, P., Syritsyna, O., Coyle, P., Good, M., Awasthi, A., Kolls, J.K., Kumar, P., 2021. Nrf2 in host cells and in host macrophages does not protect mice from fungal infection. Nature 599, 106-110. https://doi.org/10.1038/s41586-021-03542-x.

Liu, I., Li, Y., Wang, X., Deng, B., Striffler, M., Wilson, K., Nakamura, E., Liu, J., Chen, C., 2015. Aryl hydrocarbon receptor negatively regulates tryptophan metabolism activity by inhibiting NLRP3 transcription. Nat. Commun. 5, 5738. https://doi.org/10.1038/ncomms6753.

Mansour, A.M., Elgar, J.E., Hajimiragha, H., Schroeder, P., Klotz, L.O., Rannug, A., Gunther-Vazquez, C., Quintana, F.J., 2018. Regulation of the immune response by the aryl hydrocarbon receptor. Immunity 48, 19-33. https://doi.org/10.1016/j.immuni.2017.12.012.

Hamrick, M.W., Kim, B.J., 2020. The association of circulating kynurenine, a kynurenine pathway metabolite, and the PPARδ in inflammatory diseases. J. Mol. Med. 98, 597-608. https://doi.org/10.1007/s00109-020-01770-0.
Wu, W., Nicolazzo, J.A., Wen, L., Chung, R., Stankovic, R., Bao, S.S., Lim, C.K., Brew, B.J., Callen, K.M., Guillemain, G.J., 2013. Expression of tryptophan 2,3-dioxygenase and production of kynurenine pathway metabolites in triple transgenic mice and human Alzheimer’s disease brain. PLoS One 8, e59749. https://doi.org/10.1371/journal.pone.0059749.