

The Role of Kynurenines Produced by Indolamine-2,3-Dioxygenase 1 in Sepsis

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Key Messages

- In sepsis, the depletion of tryptophan and the generation of kynurenine (KYN) contribute to development of sepsis-associated immunosuppression.
- The KYN pathway is mainly controlled through indolamine-2,3-dioxygenase 1 (IDO1), which is the first and rate-limiting step of this KYN pathway and is induced, e.g., by interferon- γ .
- The activity of IDO1 and activation of the kynurenic pathway can be measured by the KYN/tryptophan ratio. Data show that this ratio is linked with clinical outcomes in sepsis.
- The immunosuppressive effects of IDO1 on the immune system are mainly mediated through alterations of T-cell functions.
- KYN affects endothelial cells during inflammation leading to systemic hypotension and endothelial dysfunction.
- The inhibition of IDO1 is a potential therapeutic target.

Keywords

Tryptophan · Indolamine-2,3-dioxygenase 1 · Sepsis · Sepsis-associated immunosuppression · Kynurenine · Kynurenine pathway · Indolamine-2,3-dioxygenase 1 activation

Abstract

Background: The enzyme indolamine-2,3-dioxygenase 1 (IDO1) is the rate-limiting enzyme of the kynurenine (KYN) pathway and metabolizes the essential amino acid tryptophan to KYNs. The depletion of tryptophan and the generation of KYNs were shown to be involved in the global down-regulation of the immune system during the later stages of sepsis, also referred to as sepsis-associated immunosuppression. **Summary:** The generation of KYNs by IDO1 leads to a depletion of effector T cells, including increased rate of apo-

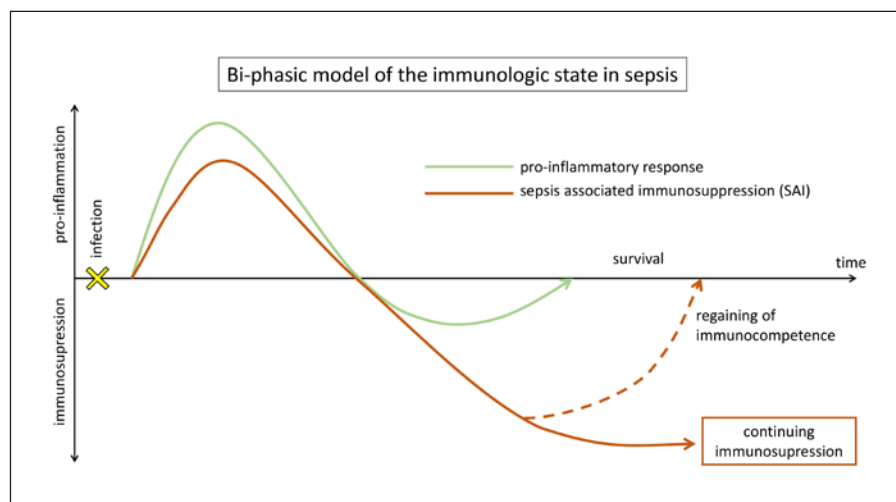
ptosis, decreased ability of T-cell proliferation and activation, and the generation of FoxP3⁺ regulatory T cells. Furthermore, KYN was shown a potent vasorelaxant during inflammation-induced hypotension. Experimental studies in murine sepsis models and in humans show promising data for using the activation of IDO1 both as a prognostic marker and potential drug target in sepsis.

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Introduction

Sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection [1] and one of the top three reasons for death on intensive care units (ICUs) [2]. Nevertheless, treatment for patients with sepsis is still mostly limited to supportive (intensive) care [3].

Fig. 1. Course of patients with versus without SAI (adapted from Pfortmueller et al. [4]). Patients with a pronounced proinflammatory response with a fast recovery to immune homeostasis and survival. Patients with SAI enter a state of persisting SAI with reactivation of primary pathogens, secondary infections, and increased mortality [4]. SAI, sepsis-associated immunosuppression.



During the last decades, the concept of differing immunologic phases of sepsis got widely accepted [4]. In septic critically ill patients, the hyperinflammatory phase is often followed by a secondary phase, in which many patients will enter a state of sustained systemic immunosuppression also referred to as sepsis-associated immunosuppression (SAI) (Fig. 1) [4].

SAI is characterized by the downregulation of monocytic human leukocyte antigen-DR (mHLA-DR), increased apoptosis of lymphocytes and dendritic cells (DC), and increase of immunosuppressive cells, including regulatory T cells (T_{reg}) [5]. Some authors assume that most deaths in sepsis are related to the inability to eradicate the primary infection or generation of secondary infections, including nosocomial infections during SAI [4, 6–8]. Not every patient with sepsis has the same course of the disease. It thus seems of crucial importance to adequately characterize patients (personalized medicine) who will go into a state of persistent immunosuppression as the individual response of septic patients makes it unlikely to treat all patients with the same immunomodulatory procedure [7]. In the last decade, the expression of mHLA-DR was observed to reflect a global state of immunosuppression and thus the global immune competence of the patient.

An important mechanism for SAI development might be activation of the immune regulatory enzyme indoleamine-2,3-dioxygenase 1 (IDO1). IDO1 metabolizes the essential amino acid tryptophan (tryptophan) to kynurenine (KYN) and is thereby the first and rate-limiting enzyme of the KYN pathway [9]. IDO1 activation leads to changes in T-cell populations and other immune cells, including B cells, monocytes, macrophages, DC, natural

killer cells (NK cells), and neutrophils [5, 10]. Furthermore, KYN affects endothelial cells during inflammation leading to systemic hypotension and endothelial dysfunction [11]. In general, IDO1 activity (1) is increased during sepsis, (2) correlates with severity, including the lethal outcome of sepsis, and (3) remains significantly higher compared to healthy controls for at least 14 days [5].

This review aimed to provide an overview of the current knowledge regarding the relation between tryptophan depletion via IDO1, the activation of the KYN pathway, and the resulting immunologic effects. The potential prospects of KYN pathway catabolites as biomarkers in sepsis will be identified, and different therapeutical approaches will be discussed.

Tryptophan and the KYN Pathway

Tryptophan levels are mostly (95%) [9] regulated through tryptophan-2,3-dioxygenase (TDO, 99%) and indoleamine-2,3-dioxygenase 1 (IDO1, about 1%). TDO is able to metabolize tryptophan to KYN and thereby induce the degradation of tryptophan by tryptophan hydroxylase, mostly leading to the production of serotonin products (serotonin pathway) [9].

During systemic or local inflammation IDO1 is strongly induced by the proinflammatory cytokine interferon- γ (IFN- γ). Upon activation, IDO1 is the major enzyme of tryptophan metabolism (99%) (Fig. 2). Due to the early release of IFN- γ , IDO1 is also activated at an early stage of sepsis. Other activators include interferon- α , interleukin-1 β , tumor necrosis factor- α , IL-2, IL-6, and drugs (e.g., dexamethasone) [9, 12].

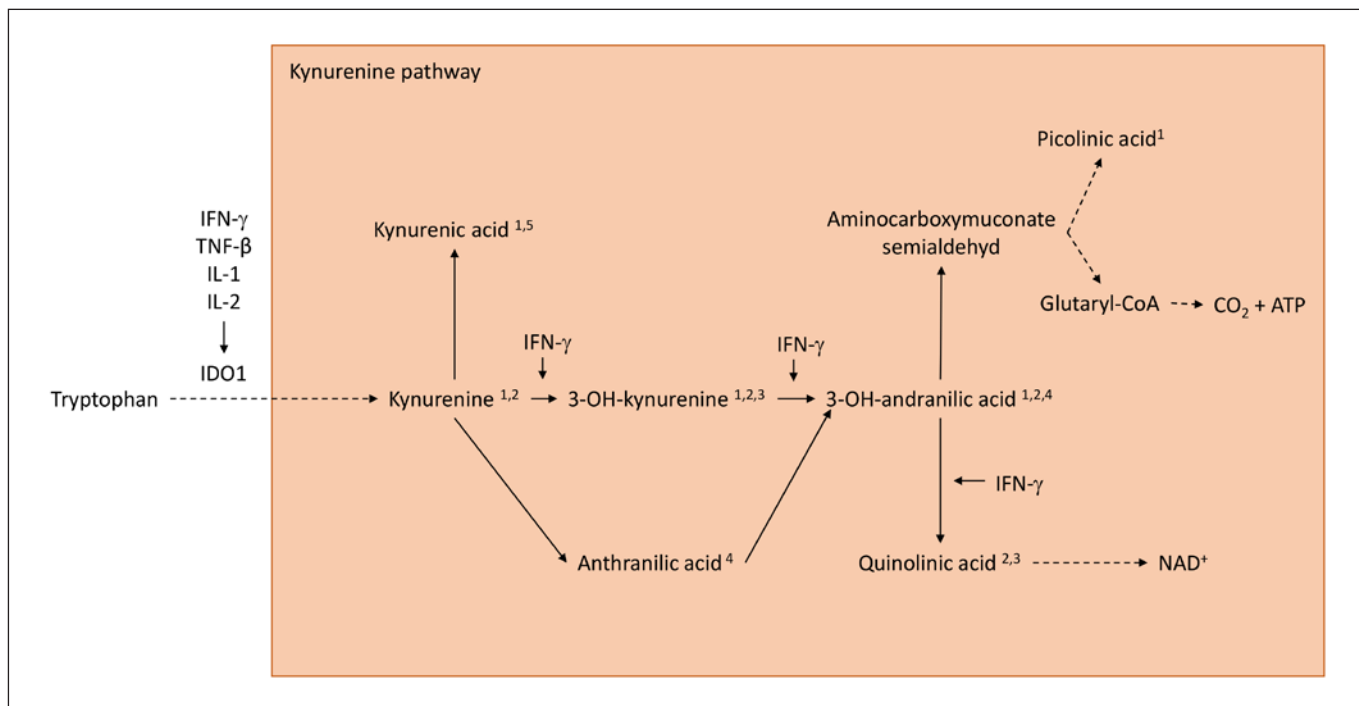


Fig. 2. The KYN pathway during inflammation and its activators (IFN- γ , TNF- α , IL-1, IL-2) (adapted from Wirthgen and Hoeflich [12]). Biological properties of the respective catabolites: ¹Immunosuppressive, ²production of radicals, ³neurotoxic, ⁴antioxidative properties, ⁵neuroprotective. IFN- γ , interferon γ ; TNF- α , tumor necrosis factor α ; IL-x, interleukin x.

IDO1 can deplete tryptophan very effectively at the local site of activation. Inhibitors of IDO1 include IL-4, IL-10, transforming growth factor- β , and nitric oxide [9].

The Effect of the KYN Pathway on Cells of the Immune System

Persistent IDO1 activation is a component of SAI in sepsis [5]. In this clinical context, the key effect of IDO1 activation may be a diminished T-cell response.

During inflammation, IFN- γ is considered the most important IDO1 activator [10]. Primarily, IDO1 activation is a local phenomenon, activated at the site of inflammation [13–15]. However, this local process can overspill to the systemic circulation as observed during sepsis.

In the murine cecal ligation and perfusion (CLP) models, neutrophils and mononuclear cells (characterized by cluster of differentiation 11b [CD11b] and CD11c expression) show increased IDO1-mRNA after CLP and are the most important producers of KYN in the peritoneal cavity. The number of CD11b⁺ cells is increased in both IDO1^{+/+} and IDO1^{-/-} mice after CLP, whereby IDO1^{-/-}

mice show a stronger increase in CD11b⁺ and CD11c⁺ cells compared to IDO1^{+/+} mice. The activation of IDO1 inhibits the further recruitment of other CD11b⁺ cells toward the focus of the infection by the inhibition of cytokine signaling. As IDO1^{-/-} mice cannot activate the KYN pathway, the recruitment of CD11b⁺ cells is not inhibited and so they show a stronger increase of these cells in the peritoneal cavity than IDO1^{+/+} mice [16].

The AhR-IL-6-STAT3 Loop

Once IDO1 is activated and hence the production of KYN, the aryl hydrocarbon receptor (AhR)-IL-6-signal transducer and activator of transcription 3 (STAT3) loop (Fig. 3) can maintain a constant activation of IDO1 activity. AhR is an intracellular transcription factor. It can form a complex with KYN. This KYN-AhR complex can induce the transcription of IL-6 mRNA. The release of IL-6 stimulates the transcription factor STAT3 in an autocrine manner. STAT3 is again a transcription factor for further IDO1 transcription. This loop enables a self-sufficient positive feedback loop that helps to maintain IDO1 activation on a high level [12]. It was also shown that patients who died from sepsis have constantly high IL-6 lev-

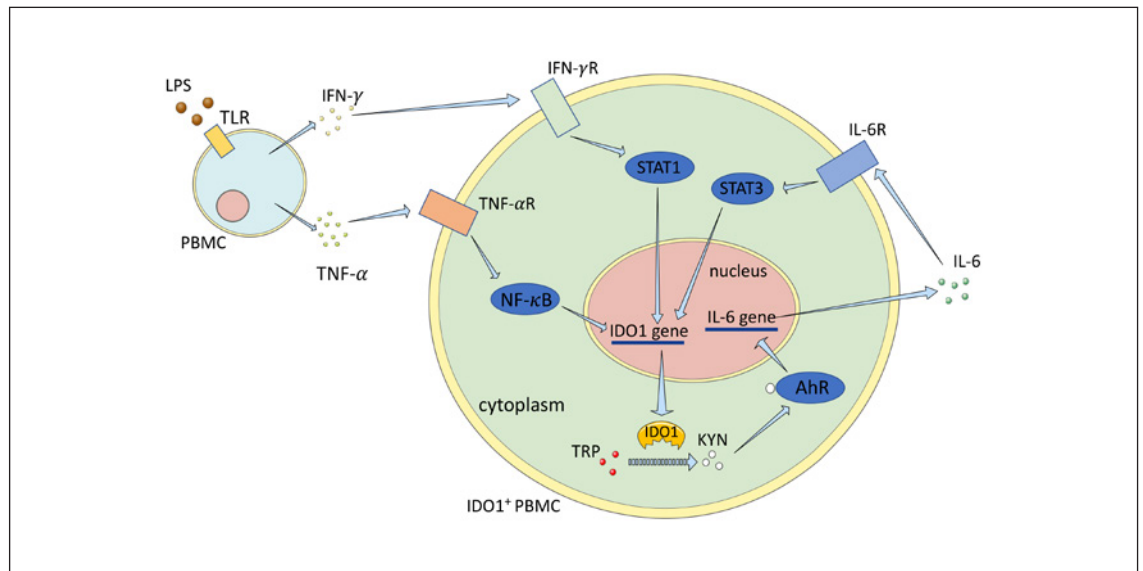


Fig. 3. Activation of IDO1 and AhR-IL-6-STAT3 loop. The transcription of IDO1 is induced by paracrine cytokines like IFN- γ or TNF- α and different intracellular transcription factors like NF- κ B, STAT1, and STAT3. When a PBMC is activated by LPSs through its TLR, it releases IFN- γ and TNF- α . Thereby, the AhR-IL-6-STAT3 loop is activated in IDO1⁺ PBMC. STAT1 (after signal transduction through IFN- γ receptor) and NF- κ B (after signal transduction through TNF- α receptor) activate the transcription of IDO1-mRNA. After the initial production of KYN, KYN forms a transcription-complex with AhR which leads to the transcription

of IL-6-mRNA. IL-6 activates further IDO1-mRNA transcription in the PBMC in through autocrine STAT3 signaling. In that way, IDO1 is able to maintain its own activity with the AhR-IL-6-STAT3 loop. PBMC, peripheral blood mononuclear cell; KYN, kynurenine; IFN- γ , interferon γ ; TNF- α , tumor necrosis factor α ; IL-6, interleukin 6; NF- κ B, nuclear factor κ -light-chain-enhancer of activated B cells; STATx, signal transducer and activator of transcription x; TLR, Toll-like receptor; AhR, aryl hydrocarbon receptor; LPS, lipopolysaccharide.

els. This could also be a contributor to the start or maintenance of the AhR-IL-6-STAT3 loop [12].

T Cells

A key effect of tryptophan degradation on the immune system is altered T-cell proliferation and function. Effector T cells are inhibited, and the population of T_{reg} is expanded.

Increased IDO1 activity correlates with inhibition of function and proliferation of CD4⁺ and CD8⁺ T cells and is associated with T-cell apoptosis. The IDO1 activity correlates with a reduced CD4⁺ T-cell and CD8⁺ T-cell count as well as the total T-cell count, reduced NK cells and a decreased lymphocyte count [10]. T-cells are affected in at least three ways:

Effects by Tryptophan Depletion

Depletion of tryptophan leads to an arrest of the T cells in the G₁ phase [17, 18]. During inflammation, IFN- γ induces IDO1 activity as well as the tryptophanyl-transfer RNA synthetase (WRS), an enzyme that is needed for loading tryptophan on its specific tRNA. The induction

of WRS by IFN- γ should help the cells to cope with the decreased tryptophan levels during inflammation. Interestingly, T cells lack the IFN- γ inducible WRS. This contributes to the high sensitivity of T cells for tryptophan depletion, leading to the inhibition of T-cell proliferation [13, 19]. Once arrested in the cell cycle, T cells are prone to apoptosis [20].

Effects by Tryptophan Catabolites

Tryptophan catabolites have several effects on T cells. KYNs can downregulate T-cell receptor in CD8⁺ T cells. This leads to the loss of their cytotoxicity [21]. Furthermore, the activation of AhR by KYN mediates cytostatic and cytotoxic effects in CD8⁺ T cells [22]. Further, KYNs are toxic for murine CD4⁺ helper T cells type 1 (T_H1 cells). Apoptosis is directly induced through the Fas/caspase 8 and Fas/cytochrome c pathways. Murine T_H2 cells are, however, not sensitive for KYN-induced apoptosis [20]. KYNs promote an antiproliferative, apoptotic state in human T cells [20], which cannot recover, once arrested in their cell cycle by KYNs [23]. Other data show that activated T cells are more sensitive for KYN-mediated effects

than naive T cells [23]. This finding appears reasonable for IDO1 activation and could theoretically protect from deleterious inflammation-induced effects.

Effects Caused by Expansion of Specific T-Cell Populations

IDO1 activation induces expansion of T_{reg} . Different immunogenic cell types can induce the generation of $Foxp3^+ T_{reg}$. It was shown in mice that stimulating plasmacytoid DCs (pDCs) with CpG oligodeoxynucleotides results in the formation of $CD4^+ CD25^+ Foxp3^+ T_{reg}$. When toll-like receptor-9 is stimulated with CpG oligodeoxynucleotides in pDCs, the expression of IDO1-mRNA along with the expression of mHLA-DR and B7 increases. Those pDCs show a high potential to induce T_{reg} from naive $CD4^+ CD25^-$ T cells. This process is cell-cell contact-dependent. Blocking IDO1 via a specific inhibitor (1-methyl-tryptophan, 1MT) inhibits T_{reg} expansion, while under simultaneous administration of 1MT and KYN, the T_{reg} population expansion persists. In this pathway, IDO1 activity and KYN are keys for the formation of T_{reg} [20].

Co-culturing murine hepatic stellate cells (HSCs) with lipopolysaccharides (LPSs) induces IDO1 in HSC. Thereby, $CD4^+ CD25^+ Foxp3^+ T_{reg}$ were induced, and non- T_{reg} were stimulated to undergo apoptosis. Inhibition of IDO1, as well as of AhR signaling, was able to reverse these effects. IDO1 thus stabilizes the expression of *Foxp3* and thereby leads to sustained immunosuppression. T_{reg} cells themselves have the potential to upregulate IDO1 in HSC when cocultured independent of HSC (being LPS pre-stimulated or not). In that way, T_{reg} are able to maintain a self-sufficient environment [24].

The streptococcal pyogenic endotoxin A (SPEA) is a superantigen of *Streptococcus pyogenes*. SPEA activates immunosuppressive effects in human monocytes including the activation of IDO1 that leads to the generation of T_{reg} when monocytes and $CD4^+$ T cells are cocultured. SPEA-treated monocytes lead to the apoptosis of $CD4^+ Foxp3^-$ T cells and increased the proportion of $CD4^+ Foxp3^+ T_{reg}$. KYN blockade decreases the count of $CD4^+ Foxp3^+ T_{reg}$ [25].

Additional Immune Cell Types

KYNs can induce apoptosis in B cells and NK cells [22, 23]. In monocytes, KYN induces AhR signaling leading to further induction of IDO1 (via the AhR-IL-6-STAT3 loop) [26]. In an in vitro study with human monocytes, the treatment with GM-CSF can partially restore immune competence in monocytes from patients suffering from sepsis, alongside with a decrease of IDO1 activity [5, 27].

Further, KYNs decrease proliferation and induce apoptosis in NK cells [22, 23]. Apoptosis is partly mediated through the radical oxygen species pathway, as well as through caspase 3 and cytochrome c pathways [28]. Antioxidants such as N-acetylcysteine lower the effects of KYNs on NK cells [28]. Human DCs are a major producer of KYNs during inflammation leading to immunosuppression [29]. Interestingly, KYNs do not induce changes in proliferation or rate of apoptosis in DCs [21, 23]. DCs are key players in KYN-mediated immunosuppression through both KYN production and unresponsiveness for cytostatic and cytotoxic effects. IDO⁺ DCs can inhibit the T-cell response to an antigen presented by nearby IDO⁻ antigen presenting cells (APCs). This leads to a dominant bystander immunosuppression. Due to the dominance of IDO⁺ DCs, a small number of IDO⁺ DCs can suppress an immune response on an antigen, even when many IDO⁻ APCs are presenting it [30–33]. In brief, IDO⁺ DCs are not only just producers of KYNs (to which they are themselves unresponsive) but they are also able to suppress antigen presenting by immunocompetent APCs, leading to a stable immunosuppression.

No reports are available on the effects of IDO1 activation or products of the KYN pathway on neutrophils homeostasis. Nevertheless, IDO1 activation may affect neutrophil function. Migration of neutrophils is crucial in sepsis and is mediated through different chemokine signals including C-X-C motive ligand (CXCL) 1 and CXCL2. Macrophages, epithelial cells, and neutrophils produce CXCL1 and CXCL2 after contact with endotoxins or other proinflammatory cytokines. The activation of IDO1 lowers the local chemokine concentration and thereby leads to reduced migration of neutrophils to the infection site. Neutrophils are considered important to contain infections to a local level [16].

KYN as a Vasorelaxant during Systemic Inflammation

During systemic inflammation, endothelial cells are key KYN producers, which may be of particular importance in endothelial cells of the vessels with resistance functions [11, 34]. KYN mediates vasodilatation through activation of adenylate cyclase and soluble guanylate cyclase pathway, contributing to decreased blood pressure during systemic inflammation [18, 34]. However, substantial IDO1 activation by inflammatory IFN- γ release is required for induction of KYN-induced hypotension. This may indicate that KYN may exclusively contribute

to hypotension during inflammation when IFN- γ is sufficiently released. Hypotension can be reversed by IDO1 inhibition with 1MT [34].

Increased IDO1 activity also induces changes in nitric oxide synthetase activation during sepsis augmenting misregulation of microvascular reactivity. The impact of KYN as a vasorelaxant is thus amplified [10]. Data show that the activation of IDO1 in mice correlates with hypotension and the need for inotropes in patients during septic shock. Inhibition of IDO1 with 1MT in mice helped to stabilize blood pressures and to improve outcomes [11]. These findings lead to new potential treatments of septic shock (e.g., using 1-MT) as IDO1 is a strong driver of hypotension during systemic euvolemic inflammation.

Further, elevated KYN levels are associated with increased endothelial dysfunction [35]. Loss of the endothelial glycocalyx and increased vascular permeability are crucial in the pathophysiology of sepsis and are associated with increased edema production [36].

KYN Pathway Catabolites as Markers of Immunosuppression

Immunosuppression is mostly overlooked in daily ICU treatment and is typically not followed up using appropriate biomarkers [4]. Because of this, it seems of crucial importance to have adequate prognostic indicators to detect and track the different states of the disease and to stratify respective patients. Measuring the IDO1 activity may be a prognostic indicator.

In a pilot study with 18 septic patients, a positive correlation was shown between a high IDO1 activity and nonsurvival. The nonsurvivor group shows a higher IDO1 activity at any time during the study (day 1–13 after admission to the hospital) [37]. Also nonsurviving patients with multiple traumas had increased IDO1 activity, KYN, and neopterin levels when compared to survivors [38].

In a study in 132 septic patients, it was shown that nonsurvivors had increased IDO1 activity from day 1–2 (after positive blood cultures) and day 2–4. In contrast, survivors had decreased IDO1 activity in respective time intervals. The maximum IDO1 activity measured between day 1 and day 4 was significantly higher in nonsurvivors and about 3 times higher when compared to healthy controls [39]. Generally, sepsis patients showed elevated IDO1 activity for 14 days compared with health controls [5]. Assessment of IDO1 activity should be done early after positive blood sampling as high IDO1 activity after day 5 may not be bacteremia related [39].

Other data show a correlation between IDO1 activity and nonsurvival up to 14 days [40]. Meier and coworkers [41] investigated the correlation between the outcome and singular IDO1 activity measurement at admission to the hospital in over 250 patients with community acquired pneumonia. The data show significant correlations between IDO1 activity and adverse short-term outcomes (death or ICU admission within 30 days) after first admission. Further, a strong correlation with CRP and procalcitonin levels was noted [41].

Additional data by Zeden and coworkers [42] identified the QA/tryptophan ratio as the marker with best sensitivity/specificity even before sepsis was established in respective patients. At a QA/tryptophan cutoff of ≥ 18.2 , a 73.3% sensitivity and an 86% specificity for later sepsis were shown [42].

Tryptophan uptake and/or resorption rates can lead to changes in tryptophan levels [42]. The findings in the literature are partially inconsistent. For example, tryptophan levels in trauma patients were not reported to significantly differ [38], whereas they were reported to inversely correlate with SOFA and APACHE II scores in septic patients [10].

KYN levels may also have prognostic value. An increase of plasma KYN from day 1 to day 7 was associated with nonsurvival after 28 and 90 days. KYN levels of 28-day nonsurvivor were almost doubled compared to survivor [35]. These data are supported by Meier and coworkers [41] where IDO1 activity at admission correlates with 30-day mortality or admission to an ICU in the same period. Elevated KYN is also associated with endothelial dysfunction and can act as a marker for the state of the endothelial reactivity and potential threat of a septic hypotensive shock [35].

Kidney Injury and Renal Excretion of KYNs

KYNs are partly cleared by renal filtration, as shown by Schefold and coworkers [43]. Thus, loss of renal excretion, e.g., during sepsis-induced kidney injury is associated with increased KYN levels [43]. Further, increased urinary excretion of KYNs is associated with nonrecovery from acute kidney injury in critical illness [44].

Although data in critical illness are conflicting, data reveal that patients with continuous renal replacement therapy have higher KYN levels than sepsis patients not treated with renal replacement therapy [42]. Further, KYN levels correlate with plasma creatinine levels [10].

Inhibition of the Kynurenic Pathway and Its Therapeutic Potential

The activation of IDO1 and the generation of KYNs has manifold effects on the immune system and on vascular regulation during sepsis. In different experiments, inhibition of IDO1 with 1MT was shown to prevent or even reverse respective effects. To this point, large-scale clinical data in sepsis is unavailable.

KYN-dependent vasorelaxation can also be reversed or inhibited by IDO1 blockage with 1MT [34]. The KYN pathway can be also with INCB023843, a specific IDO1 inhibitor. In a study on small lung cancer, inhibition of IDO1 with INCB023843 restored the sensibility of anti-programmed cell death protein (anti-PD1) or cytotoxic T-lymphocyte-associated protein 4 blockage therapy [45].

Like 1MT, Epcadostat shows an acceptable side effect profile and is a candidate for clinical trials in sepsis patients [46]. Nevertheless, phase III studies on Epcadostat in cancer patients showed no improvement in long term survival in this specific pathology [47].

Besides direct blocking of IDO1, there are other therapeutic approaches to reduce the effects of KYN pathway activation. For example, GM-CSF restores monocyte function and reduces IDO1 activity in severe sepsis/septic shock patients with SAI [27]. This supports the notion that systemic immunosuppression (as in SAI) is associated with increased systemic IDO1 expression. This may indicate that systemic interventions aiming to reduce IDO1 activity could indeed be of clinical benefit in SAI patients.

Discussion

It appears that IDO1 activation contributes significantly to SAI. The literature supports the importance of IDO1 in sustained immunosuppression during sepsis [5, 20, 23, 25].

IDO1 activation can be measured by assessment of IDO1 activity, i.e., (estimated) KYN/TRP ratio [5]. IDO1 activity is elevated in patients with sepsis as early as day 1 after positive blood cultures and is related to respective severity and outcome, including secondary infections [10, 37, 39, 40]. Nevertheless, IDO1 activity of patients with fatal outcomes shows a wide range. Thus, further stratification of these patients is needed to elevate the prognostic value of the IDO1 activity [37]. Although IDO1 activation has an impact on a variety of innate im-

mune cells, especially NK cells [28], the main effects on the immune system appears to be mediated through effects on T-cell functions [5, 10, 20, 21, 23–25]. In this perspective, it seems reasonable that main impacts of activation of IDO1 will occur later, i.e., in SAI. Nevertheless, further investigations are required to better understand the role of IDO, particularly in the different phases of sepsis.

Specificity of IDO1 Activity

An advantage of the IDO1 activity as an indicator of disease progression is the lack of pleiotropy of the measured molecules. During inflammation, KYN is produced almost exclusively by IDO1 [9].

Inhibition of IDO1

1MT is a potent inhibitor of IDO1 in murine sepsis models, especially when applied early. In an LPS-induced sepsis model in mice 1MT-pretreated mice, decreased IDO1 activation was noted [48]. Until now, controlled human studies on 1MT in sepsis are unavailable. Future efforts should be made to investigate 1MT or other IDO1 inhibitors as potential adjunct treatment in human critical illness [5, 16].

1MT is already used in phase II trials in cancer patients. The rather mild spectrum of side effects during these trials may pave the way for clinical trials with 1MT in patients with sepsis [49, 50]. Compared to other therapeutic approaches in the treatment of sepsis, the inhibition of IDO1 has the advantage of specificity. IDO1 is only activated during inflammation [9].

Vasorelaxant

Data show that KYN is a key vasorelaxant and inducer of endothelial dysfunction during inflammation [10, 11, 18, 34–36]. Administration of 1MT may be beneficial and should be considered in future research.

Conclusions

Severe infections pose a key challenge in intensive care medicine. During the last decades, most approaches have failed to significantly improve clinical outcomes. The activation of the KYN pathway plays a significant role in several aspects of SAI and inflammation-induced hypotension/shock. Depletion of tryptophan and generation of KYNs leads to changes in T-cell populations. CD4⁺ and CD8⁺ T cells are mostly inhibited with a resulting increased likelihood of apoptosis [20, 22]. Furthermore,

KYN alters different monocytic immune cells including monocytes, macrophages, NK cells, and DCs, increasing their ability to induce Foxp3⁺ T_{reg} [20, 24, 25]. 1MT is a potent inhibitor of IDO1 [20]. Further research is needed to assess whether IDO1 inhibition (e.g., by 1MT) would be beneficial in the treatment of critically ill patients with sepsis.

Conflict of Interest Statement

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Author Contributions

Simon Lerch searched the literature and drafted the manuscript. Joerg C. Schefold and Thibaud Spinetti developed the research strategy, revised the manuscript for important intellectual content, and cowrote the manuscript. All the authors have seen, reviewed, and approved the final version of the manuscript. This manuscript is part of the medical thesis of the first author (Simon Lerch) performed at the University of Bern, Bern, Switzerland.

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