AHR and tryptophan metabolism: a collaborative dynamics of immune regulation

Jingjing Zhu[1,2,3] and Benoit Van den Eynde [1,2,3,4]

1. de Duve Institute, UCLouvain, Brussels B-1200, Belgium.

2. Ludwig Institute for Cancer Research, Brussels B-1200, Belgium.

3. WEL Research Institute, Brussels B-1200, Belgium.

4. Ludwig Institute for Cancer Research Nuffield Department of Clinical Medicine, University of Oxford, Oxfordshire, UK.

Editorial correspondence to: jingjng.zhu@uclouvain.be

Mailing address: Avenue Hippocrate, 75 B1.74.03 – B-1200 Brussels, BELGIUM
Phone number: 0032 2 764 75 72

A profound comprehension of the intricate regulatory mechanisms within the immune system is essential for navigating the complexities of cancer and immunotherapy. This commentary paper delves into the intricate interplay between tryptophan metabolism, the enzymes indoleamine 2,3-dioxygenase 1 (IDO1) and tryptophan-dioxygenase (TDO), and the aryl hydrocarbon receptor (AHR). These elements play pivotal roles in shaping immune responses, particularly in advanced-stage cancers, where their overexpression is associated with poor prognosis and immune suppression[1].

Studies examining the effects of immune suppression caused by IDO and TDO tended to focus separately on the outcomes of tryptophan deprivation and kynurenine production. The connection between IDO and AHR has long been associated with the metabolite kynurenine[2]. Recent research by Solvay et al. has revealed the complex ways in which AHR activation is influenced by both the lack of tryptophan and the production of kynurenine[3]. This interaction demonstrates the impressive complexity of the immune suppression orchestrated by the enzymes IDO and TDO. Specifically, it has been found that when tryptophan is in short supply, it can boost the expression of AHR and make it more responsive to triggers, especially making it more sensitive to relatively weak triggers like kynurenine. Importantly, this increased sensitivity has been demonstrated to favor the in vitro differentiation of regulatory T cells (Tregs).

The potentiation of AHR activation: a multifaceted collaboration

The process by which IDO and TDO enhance AHR activation is intricate and involves several crucial steps (Figure 1). This complex sequence of events includes multiple aspects. One of the key elements in this process is the increase in the production of AHR, a receptor that plays a central role in immune regulation. As AHR levels rise, it becomes more available

for interaction with activating molecules. Kynurenine needs a way to enter cells to exert its effects on the immune system. The increased expression of kynurenine transporter LAT1 ensures that more kynurenine can enter cells, making it readily available to participate in immune regulation. As tryptophan is depleted due to the action of IDO and TDO, there is less competition for cellular entry between tryptophan and kynurenine[4]. This reduction in competition allows kynurenine to enter cells more efficiently. Enzymes responsible for metabolizing kynurenine, including kynurenine formamidase (KFA) and kynurenine aminotransferase (KAT) are also upregulated. This means that once kynurenine enters the cell, it undergoes a series of transformations that are essential for its role in immune regulation.

Tryptophan deprivation is the driving force behind these processes. When tryptophan becomes scarce due to the actions of IDO and TDO, the stage is set for kynurenine, a metabolite of tryptophan, to enter cells, undergo the necessary metabolic changes, and subsequently activate AHR.

Understanding this intricate series of events is crucial for comprehending the adaptability and precision of immune suppression mechanisms orchestrated by IDO and TDO. By manipulating multiple factors simultaneously, these enzymes create an environment conducive to AHR activation, thereby influencing immune responses in a coordinated manner. This multi-step process not only underscores the complexity of AHR regulation but also highlights the potential for developing therapeutic interventions that specifically target these individual steps within the cascade.

In addition, it is important to recognize that the physiological consequences of tryptophan deprivation may extend far beyond our current understanding. For instance, the

increased AHR expression due to tryptophan deprivation could potentially enhance the AHR activation to other AHR ligands. Additionally, this deprivation might influence the cellular uptake of other amino acids that uses LAT1 for transportation[5]. It would be intriguing to conduct a detailed analysis of the cellular state when exposed to tryptophan deprivation and its potential impact on different immune suppressive mechanisms. More research might reveal a complex network of connections and outcomes in this situation.

Amino acid metabolism: a complex and context-dependent process

The insights into tryptophan metabolism and its impact on AHR activation provide valuable insights into the intricate network of amino acid metabolism and its pivotal role in immune regulation and cellular responses. Amino acids are not isolated entities; their metabolic pathways are intricately interconnected, exerting mutual influence.

The dynamic impact of tryptophan metabolism on AHR activation could imply the existence of analogous regulatory mechanisms for other amino acids. This complex interplay between amino acids and immune regulation has the potential to illuminate how different amino acids modulate immune responses.

Moreover, considering that tryptophan metabolism can adapt to environmental changes, such as limited tryptophan availability, it is conceivable that other amino acids and their metabolic pathways may possess a similar adaptive capacity in response to changing conditions. This adaptability could have profound implications for cellular functions that extend beyond immediate effects. In this context, the interplay between IDO/TDO, kynurenine, and AHR may serve as a model for comprehending the broader landscape of amino acid metabolism and its role in immune regulation.

Conclusion

In conclusion, this commentary underscores the multifaceted nature of immune response regulation and its potential for therapeutic development. The journey through the intricate interplay between tryptophan metabolism, IDO/TDO, and AHR reveals a complex cooperation for immune regulation. Understanding the multifaceted mechanisms by which tryptophan metabolism impacts AHR activation is critical for unravelling immune suppression and developing targeted interventions. Beyond this, it hints at broader connections in amino acid metabolism and its impact on immune regulation, offering a promising avenue for further exploration.

Reference:

1 Chen, X., Zang, Y., Li, D., Guo, J., Wang, Y., Lin, Y. *et al*. IDO, TDO, and AHR overexpression is associated with poor outcome in diffuse large B-cell lymphoma patients in the rituximab era. Medicine (Baltimore) 2020; 99, e19883.

2 Kaiser, H., Parker, E. & Hamrick, M. W. Kynurenine signaling through the aryl hydrocarbon receptor: Implications for aging and healthspan. Exp. Gerontol. 2020; 130, 110797.

3 Solvay, M., Holfelder, P., Klaessens, S., Pilotte, L., Stroobant, V., Lamy, J. *et al.* Tryptophan depletion sensitizes the AHR pathway by increasing AHR expression and GCN2/LAT1-mediated kynurenine uptake, and potentiates induction of regulatory T lymphocytes. J. Immunother. Cancer 2023; 11.

4 Sinclair, L. V., Neyens, D., Ramsay, G., Taylor, P. M. & Cantrell, D. A. Single cell analysis of kynurenine and System L amino acid transport in T cells. Nat. Commun. 2018; 9, 1981.

5 Scalise, M., Galluccio, M., Console, L., Pochini, L. & Indiveri, C. The Human SLC7A5 (LAT1): The Intriguing Histidine/Large Neutral Amino Acid Transporter and Its Relevance to Human Health. Front. Chem. 2018; 6, 243.

Figure Legend:

Figure 1: IDO/TDO-Enhanced AHR Activation. The potentiation of AHR activation by IDO/TDO is the result of a multifaceted process, encompassing several crucial steps. This intricate sequence includes the upregulation of AHR expression, the elevated expression of kynurenine transporters, the reduced competition with tryptophan for entry, and the increased expression of enzymes responsible for producing kynurenine metabolites. All of these processes, induced by tryptophan deprivation, collectively set the stage for the tryptophan catabolite kynurenine to enter, undergo metabolism, and subsequently activate AHR. Illustration created with BioRender.com.

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JZ originated and composed the manuscript, BJVdE provided revisions and valuable comments.

Conflict of Interest:

The author declares no conflict of interest.