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REVIEW

The Kynurenine/Tryptophan Ratio as a Promising Metabolomic Biomarker for Diagnosing the Spectrum of Tuberculosis Infection and Disease

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Abstract: The metabolic system and immunology used to be seen as distinct fields of study. Recent developments in our understanding of how the immune system operates in health and disease have connected these fields to complex systems. An effective technique for identifying probable abnormalities of metabolic homeostasis brought on by disease is metabolomics, which is defined as the thorough study of small molecule metabolic intermediates within a biological system that collectively make up the metabolome. A prognostic metabolic biomarker with adequate prognostic accuracy for tuberculosis progression has recently been created. The rate-limiting host enzyme for the conversion of tryptophan to kynurenine, indoleamine 2,3-dioxygenase (IDO), is greatly elevated in the lungs of tuberculosis disease patients. Targeted study on tryptophan in tuberculosis disease indicates that such decreases may also resembled this upregulation. Although tuberculosis diagnosis has improved with the use of interferon release assay and tuberculosis nucleic acid amplification, tuberculosis control is made difficult by the lack of a biomarker to diagnose active tuberculosis disease. We hope that the reader of this work can develop an understanding of the advantages of metabolomics testing, particularly as a sort of testing that can be used for both diagnosing and monitoring a patient's response to treatment for tuberculosis.

Keywords: biomarker, K/T ratio, metabolomic study, tuberculosis spectrum

Introduction

Metabolomics was originally part of the science of biology and was introduced there. After going through improvements in both analytical and bioinformatic terms, metabolomics is now a popular and widely recognized method and is even used for diagnostic approaches, such as in the clinical or biomedical fields. Metabolomics measurement is part of a biological system that is often related to a person's physiological processes, where these processes are closely related to the initial process of disease. This approach allows metabolomics as a research method to assist in the diagnosis or prognosis of various body disorders caused by organisms, or it can be used to look for certain biomarkers as markers of a disease.[1–3]

Metabolomics has been recognized as a highly effective assessment technique in recent years, particularly for examining diverse disorders. Liquid chromatography (LC), gas chromatography (GC), nuclear magnetic resonance (NMR) spectroscopy, capillary electrophoresis, and mass spectrometry are just several examples of separation methods used in metabolomics. Some of those techniques are combined, such as tandem mass spectrometry (MS/MS), which uses ultra-high performance liquid chromatography (UHPLC) for recognizing smaller compounds across a larger range.[4–7]

Target and nontarget are two types of metabolomics categories. Clinical laboratory tests such as the detection of amino acids or the analysis of very long-chain fatty acids are examples of the use of targeted metabolomics. For medical research, commonly used samples may be plasma, cerebrospinal fluid (CSF), or urine samples.[8–11] In this review, we will

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discuss several studies related to targeted metabolomics, namely kynurenine and tryptophan, and their changes during infection, especially in tuberculosis.

The keywords "kynurenine/tryptophan ratio" and "TB" were combined to discover publications in online databases like PubMed, ScienceDirect, Scopus, and Clinical Key. Full-text English articles published within the last ten years met the inclusion requirements. After extensive research, the exclusion criteria were literature reviews, the research subjects are human and papers that had no direct relevance to our purpose. Six papers were objectively picked as the most essential for this review topic after searches were done with the phrases "tuberculosis' and either 'kynurenine/tryptophan ratio" either "IDO activity" or "metabolomic".

Tryptophan Metabolism

One of the essential amino acids that we get from our daily protein intake is tryptophan. There are 20 types of amino acids that make up proteins, one of which is a relatively small amount, namely tryptophan, which can be found in the proteins that make up plasma. A distinctive feature of this amino acid is the extremely low amount found in the body, but it is known to be involved in a wide variety of physiological functions throughout. Tryptophan is known to be a precursor for the synthesis of serotonin as well as niacin. With various physiological conditions in a person and low levels of tryptophan, of course, it can lead to an increase in the situation of unbalanced tryptophan homeostasis.[12–14] The role of tryptophan in physiological and pathological conditions is certainly unique and extraordinary.

In cells such as fat cells, macrophages, antigen-presenting cells, fibroblasts, and placental trophoblasts tryptophan degradation can be detected. Inflammatory cytokines will be released through activated immune cells, stimulating the expression and activity of an enzyme called Indoleamine Dioxygenase (IDO). Tryptophan degradation can be induced by the immune system, such as interferon α and β, as well as tumor necrosis factor a, but interferon gamma plays an important role. In a recent study, it was stated that dendritic cells (DC) can also express IDO. Among DCs, there is a position to categorize SSIs into certain subsets, either constitutively or after induction.[14–16]

From several theories and studies that have been carried out, there is a theory that tryptophan metabolism via the kynurenine pathway has a role in regulating the immune response to maintain autoimmunity.[17–19] An essential amino acid called tryptophan is utilized to make proteins and gives rise to a number of bioactive substances with crucial physiological roles, including serotonin, tryptamine, indoles, kynurenines, and nicotinamide adenine dinucleotide (NAD+).[20] Tryptophan cannot be synthesized by humans by any of the biochemical pathways. The process of absorption of tryptophan by erythrocytes occurs in the intestine; the hepatic portal system transports tryptophan into the liver; less than 1% of ingested tryptophan is used for protein synthesis; and 95% is metabolized via the kynurenine pathway in the liver.[21,22] The rest of the tryptophan is utilized by peripheral tissue cells, including vascular endothelial cells, fibroblasts, and cells of innate immunity acquired by secretion in the bloodstream.

In experimentally developed viral, bacterial, or parasite inside the cell or inflammation, plasma tryptophan levels have been shown to decrease or to raise kynurenine-tryptophan levels.[23] When the immune system is chronically activated, as in autoimmune disorders,[18,24] inflammatory diseases,[2,25] cancer,[14,26] and major trauma, tryptophan use has been reported to increase. The increase of metabolic intermediates including kynurenine and quinolinic acid in almost all of these investigations suggests tryptophan breakdown pathway participation. A high level of IDO raises the possibility that IDO plays a role in the degradation of tryptophan when taken as an entire substance.[14,16,19,24]

Kynurenine

Kynurenine (KYN) is a direct precursor of kynurenic acid, anthranilic acid, 3-hydroxykynurenine (3HK), and tryptophan metabolites, as well as various downstream metabolites formed along the kynurenine pathway. More than 95% of tryptophan degradation in mammals occurs in this pathway.

The main pathway of tryptophan metabolism is the kynurenine pathway. Initially, tryptophan is converted to N-formylkynurenine via indoleamine 2.3-dioxygenase (IDO) and tryptophan 2.3- dioxygenase (TDO), and then to kynurenine (Kyn) via N-formylkynurenine formamidase (FAM).[20,27] TDO mediates tryptophan under normal conditions. TDO is a determinant of the amount of extrahepatic tryptophan and is induced by tryptophan, estrogen, and glucocorticoids. In abnormal conditions where there is an excessive increase in cortisol concentrations and the presence of

inflammation, TDO expression is suppressed in the liver, while IDO1 expression occurs in cells of the immune system as part of negative feedback, which aims to control the inflammatory response.[20,22]

Metabolomic, Immune Systems, and Tuberculosis

Tuberculosis diagnosis and biomarkers are popular and widely discussed types of research. Tuberculosis endemic areas have their own complex problems, so an appropriate and validated method has not been found to become a specific biomarker. One of the widely studied and proposed biomarkers is the enzymatic activity of indoleamine 2, 3-dioxygenase (IDO). IDO is a cytosolic interferon γ– induced enzyme that catalyzes the degradation of tryptophan (Trp) to kynurenine (Kyn).[14,15,19,28] T cell proliferation and function are suppressed by IDO, by degrading tryptophan and producing immunomodulatory metabolites, which lead to immune suppression and tolerance. Physiological functions, such as pregnancy, modulate the pathogenesis of various pathological conditions, such as cancer and infectious diseases, that can be regulated by IDO.[16,23]

Two purposes, microbial amino acid deprivation and immunological tolerance, may be served by the IDO-induced removal of tryptophan through host immune activation. A strategy for preventing the spread of bacteria, viruses, and parasites would be the local tryptophan depletion brought on by IDO activation in macrophages.[12] By depleting tryptophan via IDO, interferon-stimulated lung cells can stop the growth of bacteria in in vitro models of T. gondii and S. aureus infections.[20,29] According to this claim, host tryptophan modification in the parasites' microenvironment inhibits microbial production, giving the host a competitive edge.[30] As a result, in immunocompetent cells, tryptophan depletion was once thought to represent a defense mechanism brought on by immunological activation. However, the increased consumption of tryptophan during long-term immune activation from non-pathogenic sources suggests that IDO has a wider range of actions.[26]

During pregnancy, IDO plays a protective role by preventing rejection of the fetus by maternal T lymphocyte cells, so it is known that IDO can regulate T cell activity.[31,32] T-cell proliferation by IDO is carried out through different mechanisms. The first mechanism, prevention of lymphocyte proliferation by tryptophan depletion in the cell environment by IDO-expressing macrophages, inhibits the G1 phase of the cellular cycle of activated T cells.[33] In addition, catabolites such as kynurenine, 3-hydroxyanthranilic acid, and quinolinic acid can induce apoptosis by conferring cytotoxic properties on T cells.[34] In addition to macrophages, DCs also express IDO, which is associated with the acquisition of a regulatory phenotype, leading to immune tolerance. This leads to the induction of the maturation of T cells so that they become regulatory T cells or activate resting memory T cells that have a regulatory phenotype. In the absence of tryptophan, IDO is still able to initiate tolerogenesis via DC due to downstream enzymes of the kynurenine pathway.[35]

IDO is essentially expressed in many immune system cells, including regulatory B cells, eosinophils, neutrophils, macrophages, monocytes, DCs, and a number T-cell subsets.[14,26] Antigen-presenting cells (APCs), such as DCs and monocyte-derived macrophages, as well as other components of the innate immune system (NK cells, eosinophils, and neutrophils), are all affected in a variety of ways by the activation of IDO expression and activity.

APC is an IDO-expressing cell, APC that is activated by M. tuberculosis infection causes increased IDO activity which will result in tryptophan depletion and upregulation of kynurenine as its metabolite, kynurenine formed will affect naive CD4 cells in response to the immune system (Figure 1).

Trp cleavage inhibits T-cell proliferation by substantially reducing the local tissue amino acid pool. Trp-deficient T cells are unable to synthesize sufficient protein to proliferate following antigen presentation by antigen-presenting cells (APCs). IDO1-based Trp depletion in CD4+ T cells activates the general control sensor amino acid non-depressible kinase 2 (GCN2K), which regulates the programs involved in transcription and translation which consider cell growth and the availability of amino acids into factor. IDO-1 can inhibit the enzymes responsible for CD4+ T cells' fatty acid production by promoting GCN2K. With T-cell activation, fatty acid production increases and is necessary to avoid growing cells from dying. In this way, IDO1-dependent GCN2K activation and the purification of the acid-leaf syncytia inhibit cell proliferation while making CD4+ differentiation the primary effector of cell differentiation. It has been demonstrated that TRP depletion and the primary TRP metabolites Kyn, 3-HKyn, and 3-HAA can prevent cytotoxin-

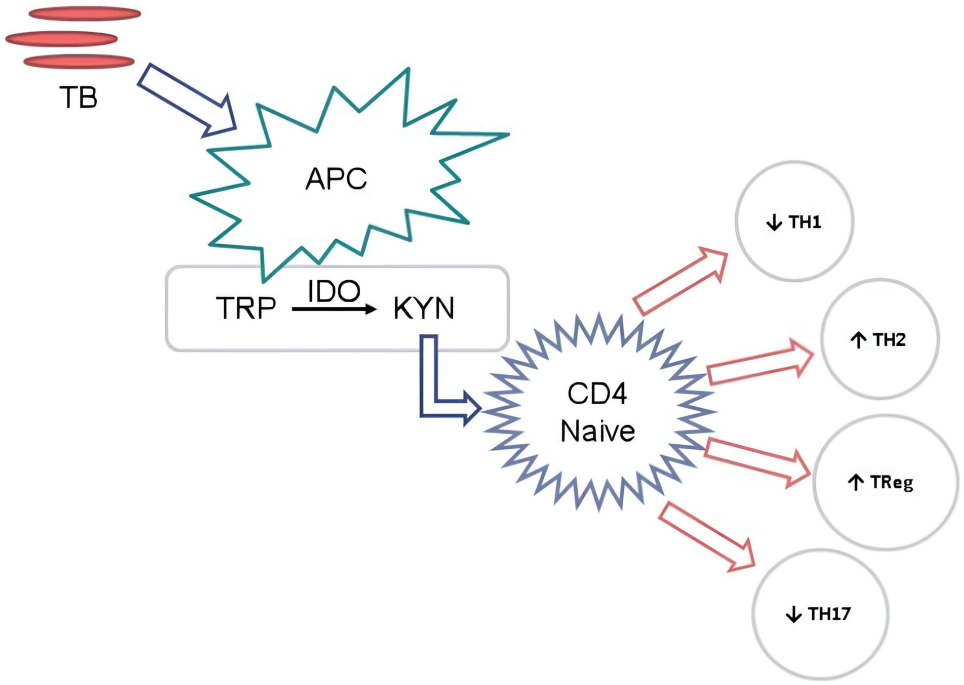

Figure 1 APC is an IDO-expressing cell, APC that is activated by M. tuberculosis infection causes increased IDO activity which will result in tryptophan depletion and upregulation of kynurenine as its metabolite, kynurenine formed will affect naive CD4 cells in response to the immune system.

induced TCR zeta complex chain downregulation in CD8+ T cells. Nowadays, the process by which CD4+ CD25-T cells develop a Treg phenotype involves GCN2K, the suppression of IL-2 production, and elevated IL-10 and TGF-β.[19]

Immunological tolerance and the regulation of the Th1/Th2 ratios are both significantly influenced by IDO-1. Dendritic cells express IDO-1, which inhibits the proliferation of human T cells and produces local immunity. Dendritic cell IDO-1 activity limits the growth of Th2 cells while inhibiting the production of cytotoxic T lymphocytes (CTLs), naive CD4+ and CD8+ T cells, and Th1 cells. Both Kyn and its downstream metabolites have an impact on the Th17/Treg system's equilibrium when this balance is out of whack and support immunosuppressive Tregs.[19]

Spectrum of Tuberculosis Infection

Due in part to a lack of understanding on the clinical pathogenic range of infections and diseases associated with tuberculosis (TB), it is the most common infectious cause of mortality worldwide. Researchers and health workers are currently struggling to eradicate tuberculosis; unfortunately, they are more focused on two types of TB, namely latent TB and active TB disease. Based on recent research, tuberculosis in humans changes from latent to active through several stages that cause changes in the metabolic spectrum of bacterial activity and an opposing immunological response. Between these two spectrums, there are several stages, including incipient and subclinical TB. If we can distinguish these various spectrums, it will certainly help us determine the right therapy and develop an appropriate way of diagnosing to prevent the development of latent tuberculosis germs to become active and prevent their spread.[36]

The TB clinical spectrum is a classification that describes the degradation of the severity of TB disease. The TB spectrum classification is based on the pathogenesis of TB disease, which is known through examination of clinical symptoms of TB, X-rays, and microscopic sputum examination. The clinical spectrum of TB is used as an operational basis for TB case management programs in the community.[23,36,37] In addition, this TB clinical spectrum classification can provide a basis for doctors to describe the severity of TB disease so that it can be used as a basis for providing appropriate treatment according to the level of TB infection, as can be seen in Table 1. Spectrum determination, especially in Latent TB, subclinical TB, and Active TB, requires further understanding, and research still needs to be carried out to determine the possibility of a change from latent TB to subclinical TB and even active TB in vulnerable

Table 1 Categorical States of Tuberculosis

	Spectrum of TB				
	Infection Eliminated		Latent TB Infection	Subclinical TB Disease	Active TB Disease
	With Innate Imune Response	With Acquired Immune Response			
TST	-	+	+	+	Usually positive
IGRA	-	+	+	+	Usually positive
Culture	-	+	+	Intermittently positive	Usually positive
Sputum Smear	-	-	-	Usually negative	+
Infectious	No	No	No	Sporadically	Yes
Spymptoms	None	None	None	Mild or none	Mild to serve
Preferred treatment	None	None	Preventive therapy	Multidrug therapy	Multidrug therapy

groups such as HIV patients. Based on this approach, several researchers have found a method to help provide an overview regarding the differences between latent TB and active TB, namely through a metabolomics approach, especially in terms of the kynurenine/tryptophan ratio as described in Table 2.

Research by Adu Gyamfi[38] in 2017 and Olsson[27] in 2022 showed similar results where there was an increase in Tryptophan levels in HIV co-infected TB patients, where in Adu Gyamfi's study it was expressed in the form of IDO activity which is a ratio of kynurenine/tryptophan, even IDO activity was found to be higher high in people who later turned into active TB, after TB treatment IDO activity decreased in line with the reduction in TB germs until the results resembled controls without TB, whereas in Olsson's study it was described based on each parameter such as tryptophan which increased in HIV co-infected TB patients compared to patients HIV without TB, while the kynurenine levels of the two groups were not much different, but the kynurenine/tryptophan ratio still showed a significant difference.

In another study by Shi,[14] IDO activity was measured in various TB comorbid conditions, ranging from DS-TB and MDR-TB to patients with lung cancer, and IDO activity was found to be higher in MDR-TB patients than other groups. This is in line with research by Collins,[23] who also examined the quinuronium/tryptophan ratio in various TB groups, including MDR-TB and DS-TB. The tryptophan pathway plays a crucial role in the host response to TB infection and disease along with chemotherapy-mediated bacterial clearance, according to metabolic pathway examinations. An increase in tryptophan catabolism to kynurenine, which was seen in both silent LTBI patients and those with active TB disease, was the main factor contributing to changes in tryptophan metabolism. They also demonstrate that rises tryptophan catabolism is reversible with effective treatment of active TB disease and LTBI at a rate of this closely reflects the way the body reacts to treatment. IDO-1 transcript levels are much higher in populations with LTBI and in those with active TB disease, suggesting that IDO-1 induction is a mechanism through which tryptophan catabolism is increased. These findings point to IDO-1-mediated catabolism of tryptophan is a metabolic process.

Pregnancy is one of the causes of increased tryptophan levels, so Adu Gyamfi[31] also conducted research on this matter. The patients studied were pregnant women with TB, and it was found that the Plasma K/T ratio was elevated in women with active TB at time of diagnosis compared to those without TB. This strengthens the hypothesis that IDO activity is directly proportional to the activation of TB germs. Adu Gyamfi[28] also conducted research to compare two methods for measuring IDO activity, including MS and ELISA, where these two tools showed results that were not significantly different but still gave results discovered that people with HIV with active tuberculosis had higher K/T ratios

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Table 2 Kynurenine/Tryptophan (IDO Activity) in TB

No	Author	Year	Study Design	Sample	Analytical Apparatus	Groups Compared (Size n)	Result and Conclusion	Kynurenine/ Tryptophan Ratio (IDO Activity)
1	Adu-Gyamfi et al[38]	2017	Cohorts	Plasma	UPLC-MS /MS	HIV-TB (32) HIV (70) HIV-Pneumonia (37)	IDO activity was noticeably higher in tuberculosis patients than in controls at the time of diagnosis (P 0.001). IDO activity was significantly higher in all patients who later got tuberculosis than in controls six months prior to their tuberculosis diagnosis (P 0.001). IDO activity in tuberculosis patients lowered to levels comparable to controls following 6 months of treatment.	TB active > After TB Treatment HIV-TB Active > HIV-Pneumonia > Controls
2	Shi et al[14]	2019	Cross sectional	Plasma	LC-MS/MS	DS-TB (18) MDR-TB(16) LC (6) HC (11)	Compared to DS-TB patients and LC patients, IDO activity was noticeably higher in MDR-TB patients. Plasma IDO activity's relevance in separating the MDRTB group from the DS-TB group.	MDR-TB > DS TB MDR TB > LC
3	Collins et al[23]	2020	Cohorts	Plasma	HRM	DS-TB (89), MDR-TB HIV (64), MDR TB (21), Control without active TB (57), refugees treated for LTBI (28), HHC (69), untreated LTBI (30), Uninfected Control (39)	plasma tryptophan downregulated, kynurenine/ tryptophan ratio and kynurenine upregulated	TB disease > Control without active TB MDR TB HIV and MDR TB > Control LTBI > Negative LTBI
4	Adu-Gyamfi et al[28]	2020	Case-control	Plasma	ELISA, MS	HIV negative-TB (25), HIV negative-LTBI(25) HIV-TB (20) HIV-LTBI (20)	K/T ratios were higher in patients with HIV having active TB disease than in HIV-uninfected patients with active TB, latent TB infection patients, and patients without TB.	HIV-TB > HIV-LTBI TB > LTBI
5	Adu-Gyamfi et al[31]	2021	Case-control	Plasma	ELISA	Pregnant Women TB Active (72) Pregnant women Negative TB (117)	Compared to women without TB, those with active TB at the time of diagnosis had a higher plasma K/T ratio.	Pregnant Women TB Active > Pregnant women Negative TB
6	Olsson et al[27]	2022	Case-control	Plasma	LC-MS/MS	HIV-TB (124) HIV (125)	While kynurenine levels were similar between these groups, tryptophan levels were lower in HIV+/TB+ than in HIV+/TB-, while the median kynurenine/ tryptophan ratio in HIV+/TB+ was considerably higher than in HIV+/TB-	HIV-TB > HIV

Abbreviations: IDO, Indoleamine Dioxygenase; TB, Tuberculosis; LTBI, Latent Tuberculosis Infection; HIV, Human Immunodeficiency Virus; DS-TB, Drug-Susceptible pulmonary TB; MDR-TB, Multi Drug Resistance TB; HC, Healthy Controls; LC, Lung Cancer; HHC, House Hold Contacts of Pulmonary Tuberculosis; MS, Mass Spectrometry; UPLC-MS, Ultra Performance Liquid Chromatography–Mass Spectrometry; LC-MS, Liquid Chromatography–Mass Spectrometry; HRM, a High-Resolution Metabolomics; ELISA, Enzyme Linked Immunosorbent Assay.

than HIV-uninfected individuals with active tuberculosis, who also had higher K/T ratios than those with latent tuberculosis or individuals without TB.

Discussion

Pulmonary TB patients are under the spotlight in various studies, especially because of an increase in kynurenine and a decrease in tryptophan or also known as an increase in IDO activity which can be measured by the kynurenine/tryptophan ratio.[23,39] The potential of the kynurenine/tryptophan ratio as a biomarker for the diagnosis of TB has actually been proposed by many researchers, of course the results have also been associated with the effect of treatment. Induction of the immunoregulatory enzyme indoleamine 2.3-dioxygenase (IDO-1) associated with tryptophan depletion in which tryptophan is broken down into its metabolite, kynurenine, thereby suppressing the immune response through changes in macrophage metabolism in response to tuberculosis germs, induction of T-cell energy and apoptosis.[16,24] In cases of multidrug-resistant TB, cavitary disease, and extrapulmonary TB, metabolic changes are also detected, as evidenced by low tryptophan levels.[14,23] Interestingly, tryptophan can return to normal within a certain time after TB treatment, which indicates that changes in tryptophan catabolism respond to treatment. The Kynurenine/Tryptophan (K/T) ratio and IDO-1 performance have been associated with TB diagnosis and response to treatment in other susceptible populations of concern, such as HIV- positive individuals.[28,32,40]

Indoleamine 2.3-dioxygenase 1 (IDO-1) is at the central of immune synapses that link innate and adaptive immune responses involving antigen-presenting cells (APCs) such as dendritic cells (DCs), macrophages (MPs) and lymphocytes, effector T cells (Teff), natural killer (NK) cells and regulatory T cells (Treg). Induction of Indoleamine 2.3-dioxygenase 1 (IDO1) in cells belonging to innate immunity causes a decrease in tryptophan levels, formation of kynurenine and its metabolites which are crucial regulators of adaptive immune system. Patients with active TB who had low tryptophan/kynurenine ratio (high IDO activity) progressed more slowly than those with low IDO activity.

Physiological differences in tuberculosis patients are influenced by the activity of bacteria in the body; of course, in susceptible groups, TB bacteria that were initially latent can become active. Metabolic changes are expected to be a special characteristic in determining the spectrum of TB because if there is a change in the activity of TB germs from latent to active, a different treatment is required. Decreased immunity in patients with HIV or other immune disorders can encourage the activation of TB germs, so that preventive therapy can no longer prevent TB disease, but appropriate TB drugs need to be given. It is hoped that a clearer diagnosis of various TB spectrums can reduce the incidence of TB, especially in tuberculosis-endemic countries.

Conclusion

Given these data, it is essential to recognize how amino acids or metabolomic changes contribute to immune cell characteristic following Mtb infection spectrum, interesting research can be done by evaluate at the different types of tuberculosis coinfection on amino acid levels especially the kynurenine/tryptophan ratio or even various types of amino acids, both essential and non-essential. Further research needs to be carried out to determine the usefulness of the kynurenine/tryptophan ratio, especially to establish it as a biomarker in various TB spectrums.

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Disclosure

The authors report no conflicts of interest in this work.

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