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The Role of Gut Microbiota-derived Tryptophan Metabolites in *Mycobacterium tuberculosis* Infection: A Mini-Review

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Abstract

The gut microbiota has a major contribution in human physiology and influences disease pathogenesis, including in tuberculosis (TB) lung infection. Gut-lung axis has demonstrated the interplay of these two organs, mediated by metabolites produced by the gut microbes or derived from host molecules transformation. Tryptophan (Trp) is one of the essential aromatic amino acids catabolized as kynurenine, serotonin (5-hydroxytryptamine), and indole derivatives, including indole propionic acid (IPA), via 3 pathways. The latter was microbiota-derived Trp catabolism, which has known to have an immunomodulatory role, as ligands for Aryl hydrocarbon Receptor (AhR). Intriguingly, *Mycobacterium tuberculosis* required Trp as a nitrogen source, especially in CD4+ T cells-generated stress, to survive in the phagosome of macrophage and to cause disease. Recently, IPA is identified as a new anti-mycobacterial compound, which is specific and has broad spectrum of anti-mycobacterial activity. The structural similarity of this gut microbiota-derived metabolite and Trp allows IPA to inhibit the TrpE anthranilate synthase in Trp biosynthesis pathway in Mtb. In this review, we summarize findings from recent work by focusing on the role of Trp metabolites in host cells in TB infection. A better understanding of this chemical signal could potentially serve as a novel strategy for managing this chronic inflammatory disease.

Keywords: Tryptophan; Indole; Kynurenine; Tuberculosis

Background

Tuberculosis (TB) is still a global public health concern since the last few decades. World Health Organization (WHO) reported 10 million new cases of TB and 1.5 million deaths caused by TB infection in 2020, making it the second-placed single infectious pathogen after SARS-CoV-2 (WHO, 2021). Vaccine efficacy, delay in disease detection, co-infection with HIV or other comorbid, long-term treatment duration, and drug resistance emergence are significant challenges in disease management, especially in developing countries where TB is endemic field (Padayatchi *et al.*, 2019; WHO, 2021). To overcome these problems, the "End TB Strategy" were declared to define a priority of "early TB diagnosis and systematic screening of contacts and high-risk groups" (WHO, 2021).

Disease is transmitted when the bacteria *Mycobacterium tuberculosis* spread via person-to-person aerosol transmission. It is inhaled into the lower respiratory tract and engulfed by alveolar macrophages, dendritic cells and neutrophils (Bussi and Gutierrez, 2019). Then the phagosomes containing bacteria will undergo maturation, by phagocytic vacuole acidification and lysosomal fusion. However, this intracellular pathogen prevents this process and survives within the non-acidified phagosome. One of the essential mechanisms is the capability of Mtb to synthesize tryptophan (Trp) (Mwadumba, Henry C; Russel, David G; Nyirenda, H Mukanthu, 2004; Shaun Lott, 2020).

Tryptophan (Trp) is an amino acid used by many bacteria for its metabolism. They sometimes use host nutrients as sources of energy, and one of the essential nutrients in their metabolism is nitrogen. Amino acid is the source of nitrogen most crucial organic, and it has been known to help Mtb growth in intracellular. Several amino acids that contributed to providing nitrogen for Mtb growth are aspartate, glutamate, asparagine, and glutamine, which are found in human macrophages. They are actively transported from the human cell's cytoplasm into the Mtb (Gouzy, 2014). Other amino acids, including tryptophan (Trp) are synthesized by the mycobacterium itself, in the course of alveolar macrophage infection (Shin, Ji Hyun; Yang, Ji-Young; Jeon, Bo-Yong, 2011). These amino acids are contributed to the Mtb survival mechanism and replication (Borah *et al.*, 2019). Alanine, lysine, glutamine, and asparagine are found significantly low in TB patients as they are catabolized quickly as nitrogen sources (Albors-Vaquer *et al.*, 2020).

A high-resolution metabolomic profile study with an unbiased approach to metabolic analysis revealed that the Trp pathway is highly regulated in diverse spectrums of TB infection. The study discovered an increase of (IDO) activity, an enzyme that catalyzes Trp catabolism into kynurenine, not only in active TB disease but also in latent TB infection (LTBI). It further validates this disease mechanism complexity (Suzuki *et al.*, 2012).

Tryptophan (Trp) is also the biochemical precursor of metabolites that influence mammalian physiology, including functions in gastrointestinal, immunity, metabolism, and the nervous system. Amino acids are an important source of energy and nitrogen for cells involved in host immunity, including lymphocytes, fibroblasts, and enterocytes. This has a significant impact on both innate and adaptive host immunological responses (Ren *et al.*, 2019). These cells act to combat Mtb and release nitric oxide, which has potent anti-mycobacterial activity, and thus can cause Mtb clearance (Weiner *et al.*, 2018).

In the gastrointestinal tract, Trp will be metabolized by host cells (including kynurenine and serotonergic pathway) and by symbiotic gut microbiota (bacterial pathway). The gut microbiota as *Lactobacillus reuteri, Clostridium sporogenes, and Peptostreptococci* is taking part in gut Indole Propionic Acid (IPA) formation from ingested Trp, while others catabolize Trp into other indole derivates (Wikoff *et al.*, 2009; Rothhammer, Veit; Mascanfroni, Ivan D; Bunse, 2016; Roager and Licht, 2018). Specific gut microbiota uses this amino acid for their own necessity, simultaneously synthesizing active metabolites as mentioned that may affect the host's homeostasis.

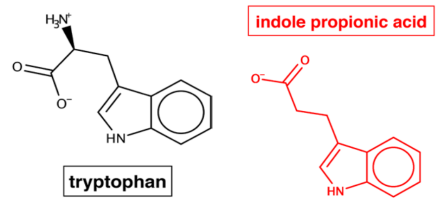

Figure 1. Similar Structure of Tryptophan and its metabolite, Indole Propionic Acid, allowing IPA acts as Trp's binding site of TrpE in blocking Trp biosynthesis in Mtb

Changes of Trp metabolism have been linked to several neurological, metabolic, psychiatric, intestinal and infectious diseases such as tuberculosis, clearing the way to evolve a new compound that targets its mechanism. Recently, the gut microbiota-derived Trp metabolite, indole propionic acid (IPA) inhibits the growth of Mtb in vitro and in a mouse model of infection (Dodd, Dylan; Spitzer, Matthew H; Van Treyren, William, 2017; Negatu *et al.*, 2020). Tryptophan deamination analog IPA has a similar structural makeup to Trp (Figure 1). As Trp biosynthesis pathway in Mtb is controlled via a negative feedback loop where the final product (Trp) performs as allosteric inhibitor of the initial metabolite conversion by anthranilate synthase TrpE, IPA may imitate Trp as allosteric inhibitor and inhibits synthesis of Trp (JM;, Bashiri G.; Johnston; Evans GL, 2015). This high light the interaction of Mtb tryptophan metabolism and host gut-

microbiota tryptophan metabolite in controlling Mtb infection.

Here we summarize the recent evidence of the gut microbiota-derived tryptophan metabolite's role in tuberculosis, the tryptophan itself in this disease and its potential applications as host-directed therapy or a new anti-tubercular compound.

Discussion

Tryptophan Biosynthesis in *Mycobacterium tuberculosis*

Mycobacterium tuberculosis is capable in synthesis it's on Trp during infection, as revealed when auxotrophic knockout strains were studied to discover the vaccine candidate's potential (Wellington, S; Nag, Partha P; Mischalka, Karolina, 2017). An Mtb strain with a mutation in Trp gene (Rv2192c) contributes to Trp biosynthesis and does not cause disease in the animal model. Therefore, it points out that Trp biosynthesis is critical for TB disease manifestation. The Trp auxotrophic strain of Mtb with trpD gene knockout was found avirulent, even in severe, combined immune-deficient (SCID) mice, with less adaptive immunity function. These mice are able to clear auxotrophic Mtb from their lungs and survive TB infection. This reveals that suitable inhibitors of Trp biosynthesis may work as effective anti-tubercular, specifically in the infection initiation (Roager and Licht, 2018).

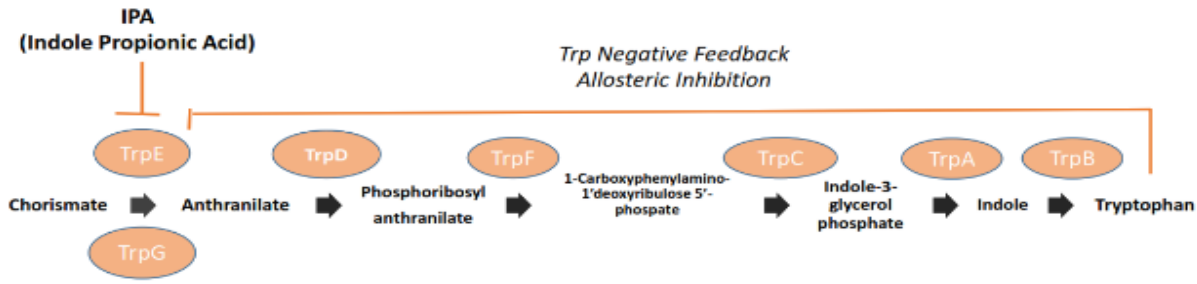

Figure 2. The Tryptophan Biosynthesis Pathway in Mycobacterium tuberculosis

The biosynthesis of bacterial Trp consists of six catalytic steps, beginning from the chorismite as a key metabolic intermediate (Figure 2) (Parker, 2017). The seven enzymes and the encoding genes are represented by the letters A–G, based on the *Escherichia coli* gene order. The open reading frames (ORFs) encoding these enzymes were discovered by sequence comparison when the full of Mtb genome sequence was established in 1998. However, since ORF of Mtb is not presented in a single operon as in *E. coli*, biochemical confirmation was also needed to know which ORFs encode the contributing enzymes (Parker, 2017).

The chorismite conversion to anthranilate-by-anthranilate synthase (AS) is the initial step in Trp biosynthesis. This enzyme is a functional heterodimer consisted of 2 different enzymes, AS-I (TrpE) and AS-II (TrpG). The first enzyme act by catabolizing anthranilate production from chorismate and ammonia, while AS-II (TrpG), a glutamine amidotransferase (GAT) serves the required ammonia by transforming glutamine to glutamate (Parker, 2017).

The second step is the production of phosphoribosyl-anthranilate (PRA), by transferring a 50-phospho-ribose unit from phosphoribosyl pyrophosphate (PRPP) onto the amino group of anthranilates by enzyme anthranilate phosphoribosyltransferase (AnPRT; TrpD). Then PRA isomerase (PRAI; TrpF) opened the PRA ribose ring resulting in the isomer 1-carboxy-phenyl-amino-deoxy-ribulose 50-phosphate formation (Parker, 2017). Indole-3-glycerol phosphate synthase (IGPS; TrpC) catalyzes a ring closure reaction by forming the characteristic system of indole heterocyclic ring. The last step is Trp production by cleavage of indole ring from the glycerol phosphate backbone by the heterotetrameric enzyme tryptophan

synthase (TrpAB), and indole moiety with serine condensation (Parker, 2017).

This biosynthesis pathway was regulated by feedback inhibition of Trp binding to the TrpE protein site in the initial step (Parker, 2017).

Tryptophan Catabolism Pathway in Host

Tryptophan is an essential aromatic amino acid for host homeostasis through complex metabolism processes (figure 1) and biological actions. Once it is ingested, the Trp will undergo catabolism in 3 different pathways.

a. Kynurenine Pathway

Around 95% of Trp catabolism undergoes via this pathway. The enzyme tryptophan 2,3-dioxygenase (TDO) in liver oxidize Trp into N-formylkynurenine (NFK) (Melhem and Taleb, 2021). The enzyme activity is controlled by Trp plasma level and steroids, such as cortisol. It selectively works and binds to Trp specifically. Indoleamine 2, 3-dioxygenase 1 (IDO) and indoleamine 2, 3-dioxygenase 2 (IDO2) are enzymes that catalyze Trp catabolism located in extrahepatic tissues and also have other ligands. In normal conditions, both are significantly less active than TDO and thus, most of KP occurred in the liver. Nevertheless, a study revealed that inflammation conditions may increase the formation of extrahepatic kynurenine (Kyn). Apart from this, NFK was transformed into Kyn by formidase, and it was further converted by enzymes into Kyn derivatives, such as anthranilic acid, kynurenic acid and quinolinic acid. In the last step of KP, quinolinic acid was transformed into nicotinamide adenine dinucleotide (NAD) (Badawy, 2017; Kanova and Kohout, 2021; Melhem and Taleb, 2021).

b. Serotonergic Pathway

Serotonergic pathway catabolizes only a small part (1–2%) of consumed Trp. Tryptophan hydroxylase 1 and 2 (TPH1 and TPH2) are important enzymes that contributed in this pathway, transforming Trp into an active intermediate metabolic, 5-hydroxytryptamine (serotonin, 5-HT), in the gut (by TPH1) and in the brain (by TPH2) (Kanova and Kohout, 2021). This metabolite is further converted into melatonin. Serotonin has an important role in the central nervous system as neurotransmitter, regulates physiological functions, and as a signaling molecule for platelets in the hemostasis process. Melatonin, one of serotonin metabolites, acts as an anti-inflammatory and controls the circadian rhythm (Fernstrom, 2016; Jones *et al.*, 2020; Kanova and Kohout, 2021).

c. Gut Microbiota Pathway

A small fraction of ingested Trp in the intestine lumen will be used by gut microbiota, to help in bacterial growth and function, simultaneously generating biologically active metabolites that affect host homeostasis. The symbiotic gut microbiota directly transforms Trp into its derivatives, including indole, skatole, indole-3-acetic acid (IAA), IPA, and indole-3-aldehyde (IAld) (Figure 3) (Konopelski, Piotr; Ufnal, 2018; Melhem and Taleb, 2021).

Indole derivatives were catabolized from Trp by multiple genera and species of gut microbiota. Bacteria such as *Escherichia coli, Clostridium spp.* and *Bacteroides spp.* utilize tryptophanase to catabolize tryptophan into indole (Roager and Licht, 2018). Furthermore, main bacteria producing IAA by decarboxylase and tryptophanase are *Bacteroides* such as *Bacteroides ovatus, B. eggerthii, B. thetaiotaomicron, and B. fragilis*, as well as *Clostridium, Bifidobacterium* and *Eubacterium* genus (Roager and Licht, 2018; Melhem and Taleb, 2021; Pappolla *et al.*, 2021). Some of *Lactobacilli* can also producing IAld using aromatic amino acid aminotransferase (Parthasarathy *et al.*, 2018; Pappolla *et al.*, 2021).

Gut microbiota that contributes to IPA formation includes *Lactobacillus reuteri, Clostridium sporogenes* as well as some *Peptostreptococci*. (Wikoff *et al.*, 2009; Rothhammer, Veit; Mascanfroni, Ivan D; Bunse, 2016; Roager and Licht, 2018). Production of IPA is mainly regulated by tryptophan aminotransferase (TAA, aromatic amino acid aminotransferase, ArAT) (Agus, Planchais and Sokol, 2018;

Roager and Licht, 2018), and it is also revealed that bacterial tryptophanase allows gut IPA production (Melhem and Taleb, 2021).

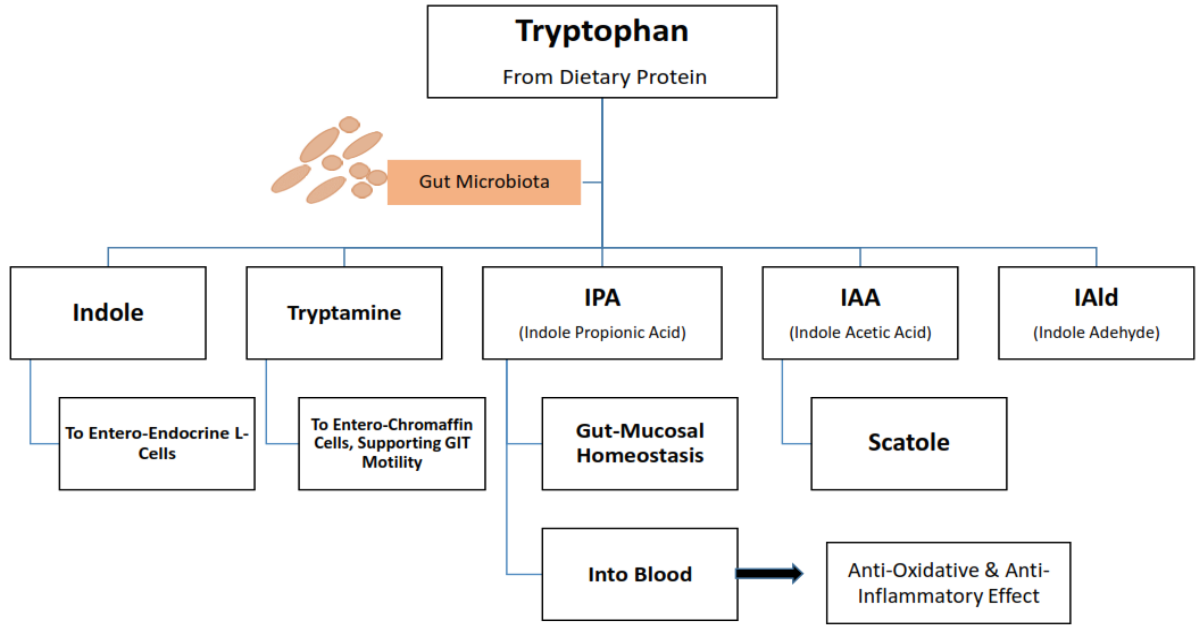

Figure 3. Gut Microbiota-Derived Metabolites and its Action on Host Physiology

Potential Use of Tryptophan Metabolites in Tuberculosis

The Mtb needs Trp to survive in alveolar macrophage phagosome and to cause disease manifestation. In response to infection, the innate immune system via IFN-γ will deplete cellular tryptophan to prevent microbial growth. This impact is a crucial part in developing inhibitors of Trp biosynthesis as new anti-tubercular. Interferon-γ (IFN-γ) activates an isoform of the host enzyme indoleamine 2,3-dioxygenase (IDO-1) that transforms Trp into N-formylkynurenine (NFK), which is then metabolized to kynurenine, in the kynurenine pathway, the major Trp catabolism pathway in mammals (Badawy, 2017; Shaun Lott, 2020), and when activated by IFN-γ strongly, it will deplete all detectable Trp in the lung tissue-specific manner (Badawy, 2017; Agus, Planchais and Sokol, 2018).

Blocking to the Mtb Trp biosynthetic will result in IDO-1 increase activity and it might cause Mtb cell death through Trp starvation, as occurred in *F. novicida*. However, as Mtb is capable to synthesize Trp, increased IDO-1 activity has minimal straight impact on Mtb replication capability leading to disease manifestation. Indeed, measuring IDO-1 activity by the ratio of Trp and kynurenine has been used as bacteria death predictor in Mtb infection (Suzuki *et al.*, 2012). It is likely due to the immunomodulatory effects of kynurenine which increase the infection severity, as it is identified as a strong negative regulator of inflammation and T-cell activity. Immune cells like dendritic cells expressing IDO-1 generate kynurenine that prevents the active T-cells proliferation and causes the expansion of the T-reg cells, resulting in an immune tolerance that leads to chronic Mtb infection (Zelante, Teresa; Fallarino, Francesco; Paolo, Bistoni, 2009; Suzuki *et al.*, 2012).

Bacteria's capability to synthesize Trp also might explain the insufficiency of the paramount number of CD4 T cells in the host immune response to eliminate the bacteria from TB patients. Self-production of Trp makes Mtb survive the host CD4-generated stress, thus preventing starvation and death. Losing or blocking of the Trp biosynthetic causes Mtb to become hypersusceptible to IFN-γ-mediated killing within alveolar macrophages, both in vitro

and during infection in animal models (Zhang *et al.*, 2013).

Several intracellular pathogens are sensitive to Trp depletion, including *Chlamydophila psittaci*, *Chlamydia trachomatis*, *Streptococcus agalactiae* and *Leishmania donovani*, which are all natural auxotrophs for Trp biosynthesis (Peng and Monack, 2010). In mycobacteria, Trp biosynthesis is not regulated transcriptionally as many other bacteria. They constitutively express the genes of Trp biosynthesis, even in the existence of exogenous tryptophan (Parish, 2003). However, Trp could inhibit its own production via allosteric feedback inhibition of anthranilate synthase TrpE). It is estimated that Trp concentration of 200nM, 1.5 μM or 6.3 μM will inhibit 50% of this enzyme (Zhang *et al.*, 2013; Negatu, DA; Yamada, Yoshiyuki; Xi, Yu, 2019). If sufficient Trp is remaining to block its biosynthesis, then the detailed blocking mechanism by exogenous parts in vivo is still unclear.

There is an increase of Trp catabolism in TB patients, showing by higher IDO-1 in TB patients, lower Trp level, and higher kynurenine level in both serum (Suzuki *et al.*, 2012) and pleural fluid (Suzuki, Y. ; Miwa, S. ; Akamatsu, 2013). Hence, to examine whether IDO-1 could be potential as TB host-directed therapy, a study used D-1-methyl-tryptophan as IDO inhibitor in TB animal model. The result showed that IDO-1 blocking decreased the bacterial burden and disease severity and increased CD4+ memory T cell proliferation. Besides, this also causes granulomas remodeling, providing greater access for CD4+ and CD8+ T cells to get into the necrotic area in the center of granuloma which is rich of bacteria, thus significantly enhancing immune-mediated Mtb cell death (Gautam *et al.*, 2018).

One of Trp metabolites that contributed in TB which is mediated by gut microbiota is indole propionic acid (IPA). This small molecule is chemically tractable and is known to target Trp biosynthesis in vitro and in vivo. In an identification study to discover new drug for drug-resistant Mtb strain and non-tuberculous mycobacteria (NTM) strain, screening of a library of rule-of-3 (R03) compliant compounds for whole cell actives resulted in indole propionic acid (IPA) identification (Negatu *et al.*, 2020). This molecule has anti-mycobacterial effect against multi-drug resistant Mtb (MDR-TB) and non-tuberculous mycobacteria (NTM), including *Mycobacterium avium* in vitro and in vivo. (Negatu *et al.*, 2020). IPA displays a selective but broad spectrum anti-mycobacterial activity, as it showed no effect against Gram-negative or -positive bacteria (Negatu, DA; Yamada, Yoshiyuki; Xi, Yu, 2019; Negatu *et al.*, 2020).

The IPA mechanism in blocking Trp biosynthesis was demonstrated by structural modeling, metabolic, genetic, and biochemical analyses. It showed that IPA inhibits Trp biosynthesis by binding to TrpE (the allosteric Trp binding site) and blocking this enzyme's action (Negatu, DA; Yamada, Yoshiyuki; Xi, Yu, 2019) (Figure 2). Thus, IPA performs by separating Mtb controlling feedback mechanism. The IPA is quite similar to tryptophan structurally as allosteric inhibitor, shutting down Trp production regardless of intracellular tryptophan levels.

Inhibition of an amino acid biosynthetic pathway is a new anti-microbial action. Many antimicrobials block macromolecular synthesis such as protein (e.g., streptomycin), RNA (e.g., rifamycins), or peptidoglycan synthesis (e.g., beta-lactams) (Clardy, Jon; Fischbach, Michael A; Currie, 2009). There are only a few synthetic anti-microbial affects on bacterial metabolism. A classic example is trimethoprim, a dihydrofolate reductase inhibitor, which acts by inhibiting folate biosynthesis. Pyrazinamide, an aspartate decarboxylase degrader, acts by blocking coenzyme A synthesis in Mtb and widely used in TB therapy (Gopal *et al.*, 2020).

Gut microbiota-derived Trp metabolite also might be the potential as host-directed therapy (HDT) for TB disease, as they are strong activators of the Aryl hydrocarbon Receptor (AhR), an important receptor in the human immune response (Gutiérrez-Vázquez and Quintana, 2018; Nicolas and Chang, 2019). Once activated by Trp metabolites, AhR will translocate

from the cytoplasm into the cell nucleus and binds to the AhR nuclear translocator (ARNT), controlling the expression of many immune cells genes, including genes for hyper-inflammation suppression, such as IFN-1, TGF-β and IL-10, because one of the key mechanisms in TB pathogenesis is hyper-inflammation (Yisireyili *et al.*, 2017).

Interestingly, this microbiota-produced metabolite can be detected in human plasma (control and TB patients) and also animal models. This emphasizes the gut-lung microbiome axis theory that the gut microbiota might affect TB disease pathogenesis. Understanding this will enable to investigate of IPA to be used as a disease progression biomarker and microbiota-based therapy. Furthermore, IPA also shows anti-inflammatory and anti-oxidant activities. This augments the hope of IPA as a new drug compound that has both anti-mycobacterial and host-directed therapy features, by the reason of that TB illness and death case are caused by the hyper-inflammation condition and tissue damage (Agus, Planchais and Sokol, 2018; Negatu, DA; Yamada, Yoshiyuki; Xi, Yu, 2019; Melhem and Taleb, 2021).

Conclusion

There is a number of studies showing that Mtb requires tryptophan biosynthesis to survive host immune response-generated stress mediated by IFN-γ and replicate in the non-acidified phagosome of alveolar macrophage. The discovery of tryptophan metabolite's role in TB, including tryptophan and kynurenine ratio showing IDO-1 activity as a disease biomarker, and gut microbiota-derived tryptophan, IPA, which has anti-mycobacterial activity, in MDR-strain and NTM lung disease strain, has raised the possibility of IPA potency as a therapeutic option and host-directed drug for TB treatment. This also confirms that gut microbiota affects disease progression. Further study is needed to explore the Trp biosynthesis mechanism as an important target for the effective anti-mycobacterial compound in multiple host microenvironments ranges that occurred during Mtb infection, to obtain the in vivo concentration of host Trp, and the bacterial uptake rate of Trp. Another challenge is designing new anti-TB drugs targeting Mtb Trp biosynthesis, as it potentially interferes with host Trp metabolism, including gut microbiota.

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