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Human and gut microbiota synergy in a metabolically active superorganism: a cardiovascular perspective

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Despite significant advances in diagnosis and treatment over recent decades, cardiovascular disease (CVD) remains one of the leading causes of morbidity and mortality in Western countries. This persistent burden is partly due to the incomplete understanding of fundamental pathogenic mechanisms, which limits the effectiveness of current therapeutic interventions. In this context, recent evidence highlights the pivotal role of immuno-inflammatory activation by the gut microbiome in influencing cardiovascular disorders, potentially opening new therapeutic avenues. Indeed, while atherosclerosis has been established as a chronic inflammatory disease of the arterial wall, accumulating data suggest that immune system regulation and anti-inflammatory pathways mediated by gut microbiota metabolites play a crucial role in a range of CVDs, including heart failure, pericardial disease, arrhythmias, and cardiomyopathies. Of particular interest is the emerging understanding of how tryptophan metabolism—by both host and microbiota—converges on the Aryl hydrocarbon Receptor (AhR), a key regulator of immune homeostasis. This review seeks to enhance our understanding of the role of the immune system and inflammation in CVD, with a focus on how gut microbiome-derived tryptophan metabolites, such as indoles and their derivatives, contribute to cardioimmunopathology. By exploring these mechanisms, we aim to facilitate the development of novel, microbiome-centered strategies for combating CVD.

KEYWORDS

cardioimmunology, cardiovascular diseases, tryptophan, indole-3-aldehyde, Aryl hydrocarbon receptor

1 Introduction

Cardioimmunology is a field of study that focuses on the interactions between the cardiovascular system and the immune system (1–5). It explores how the immune system can impact various cardiovascular diseases, such as atherosclerosis, myocardial infarction, cardiomyopathies, arrhythmias and heart failure. Research in cardioimmunology aims to understand the complex mechanisms by which immune cells and molecules contribute to both the pathogenesis and resolution of cardiovascular diseases (CVD) (6). By uncovering these interactions, scientists hope to develop new

strategies for preventing and treating cardiovascular conditions through targeted immunomodulatory therapies (7).

Cardioimmunology, indeed, is a relatively new and rapidly growing field that focuses on the intersection of CVD and the immune system (8). It explores the complex interactions between the immune system and the cardiovascular system, as well as the role of inflammation in the development and progression of various cardiovascular conditions (9, 10). In the last decade, the systemic dimension has emerged as a predictor of CVD, alongside cardiomyopathies and arrhythmias. Immunomodulation in the local microenvironment, metabolism and mitochondria of the cardiac tissue are highly responsive to the environment (10–15). Experiments involving factors such as gut microbial composition (e.g., considering the host-microbiome dyad as a “superorganism”), the circadian clock (16) or hypoxia (17) have been shown to impact tissue function, leading to conditions such as cardiometabolic disorders, myocarditis, arrhythmias along with tissue remodeling notably with occurrence of fibrosis. Similarly, systemic inflammation, immune cells and oxidative stress also contribute to the pathogenesis of hypertension, which is a significant risk factor for CVD, through vascular inflammation and microvascular remodeling (18).

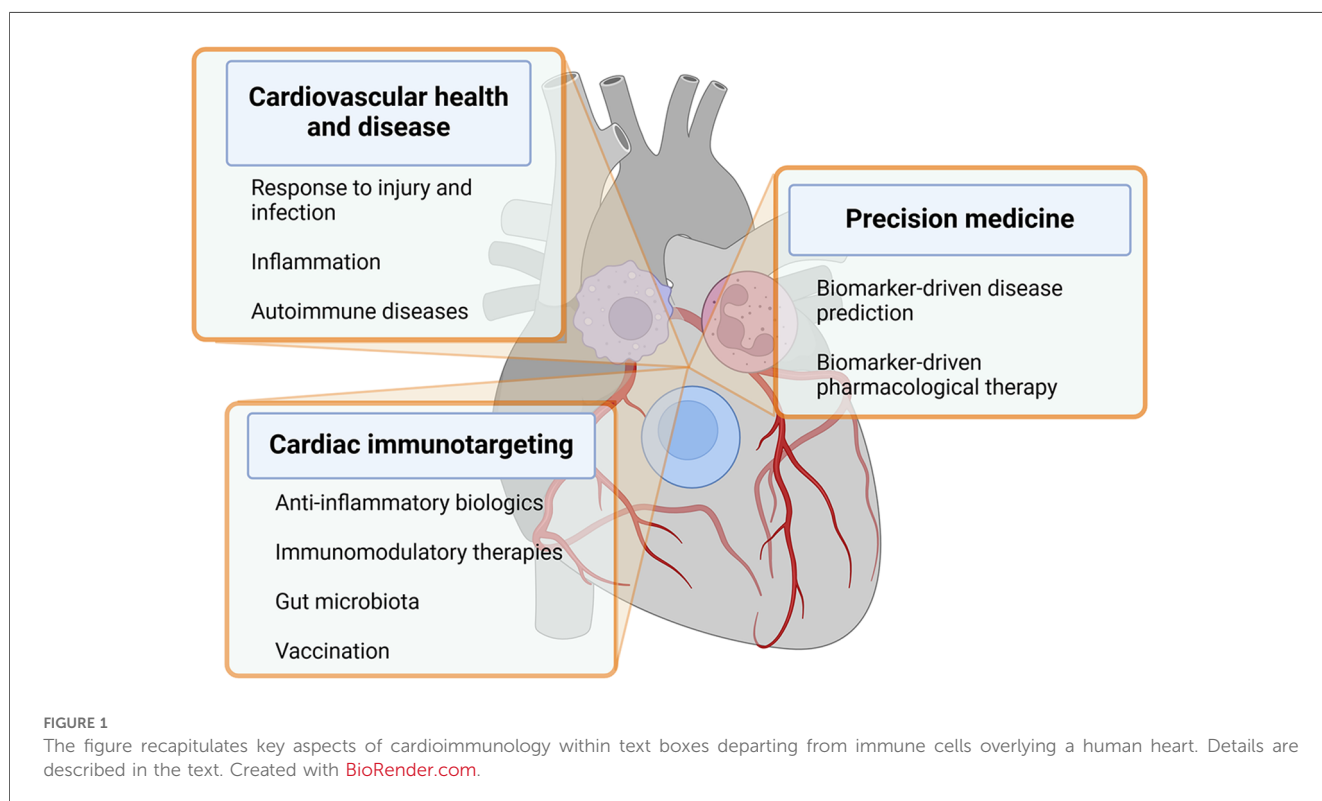
Mapping cell destinies, depleting and regenerating immune cells in experimental models of heart disease, along with analyzing the human heart at a cellular level, significantly enhance our comprehension of the intricate communication between immune and non-immune cells within the heart (19, 20). Although the immediate immune reaction is crucial for triggering inflammation and repairing tissue after damage, prolonged activation leads to harmful effects, influencing negative

changes in the heart’s structure and function. Identifying the precise roles of immune cells within the cardiac setting opens up novel avenues for adjusting immune responses to manage inflammation effectively in cases of heart diseases.

2 Key aspects of cardioimmunology

The heart incorporates immune cells as crucial cellular elements that engage in communication with resident cardiac cells in situations of homeostasis, cardiac injury, and remodeling (21, 22). These discoveries play a pivotal role in shaping and broadening the emerging domain of cardioimmunology. In this analysis, we examine the latest literature related to this subject and deliberate on the ongoing and prospective initiatives aimed at propelling this field ahead. Some of the crucial aspects of cardioimmunology are depicted in Figure 1 and listed below.

- Inflammation and cardiovascular disease:* Chronic inflammation is now recognized as a key driver of CVD, including atherosclerosis, cardiomyopathies, arrhythmias, heart failure, and myocarditis. Immune cells and inflammatory mediators play a crucial role in the development of these conditions (12, 23).
- Immune cells in cardiovascular health and disease:* Immune cells such as macrophages, T cells, and neutrophils play important roles in maintaining cardiovascular health and responding to injury or infection in the heart and blood vessels (22).
- Immunomodulatory therapies for CVD:* Researchers are exploring the potential of targeting the immune system to develop novel therapies for CVD (24). This includes



investigating the use of anti-inflammatory agents, immunomodulating drugs, and biologics to reduce inflammation and improve outcomes in patients with heart disease (25–27).

- (d) *Biomarkers of inflammation in CVD*: Biomarkers of inflammation, such as C-reactive protein and IL-6, are used to assess the level of inflammation in patients with CVD. Monitoring these biomarkers can help guide treatment decisions and predict outcomes (28).
- (e) *Cardiovascular complications of autoimmune diseases*: Some autoimmune diseases, such as rheumatoid arthritis and systemic lupus erythematosus, are associated with an increased risk of cardiovascular complications due to chronic inflammation and immune system dysregulation (29).
- (f) *Ongoing directions*: Current research in cardioimmunology aims to further elucidate the mechanisms underlying the crosstalk between the immune system and the cardiovascular system, identify new therapeutic targets, and develop personalized approaches to prevent and treat CVD based on immunological profiles (10). Paradigmatic in this context are the mechanistic studies linking autoimmunity and inflammation to the development of arrhythmia (Box 1).

Overall, cardioimmunology represents an exciting and promising area of research that has the potential to improve our understanding of CVD and lead to the development of innovative therapies to combat these conditions. In particular, some emerging areas of particular interest are represented by:

- (i) The role of the gut microbiota and products thereof. The gut microbiota plays a pivotal role in educating and modulating the immune system, influencing the balance between pro-inflammatory and anti-inflammatory responses. On the one hand, dysbiosis of the gut microbiota, characterized by alterations in microbial composition and function, has been linked to immune dysregulation and chronic low-grade inflammation, which are key drivers of atherosclerosis, hypertension, and other cardiovascular conditions. Understanding the interconnections between the cardiovascular and the gut microbiota opens avenues for developing novel therapeutic strategies (37, 38). On the other hand, the intricate crosstalk between the gut microbiota and the cardiovascular system underscores the importance of considering the gut as a key player in cardioimmunology (39). By elucidating the mechanisms by which the gut microbiota influences immune responses, inflammation, and metabolism in the context of cardiovascular health, researchers may uncover novel therapeutic targets and strategies for the prevention and management of several pathologic conditions, including CVD (39, 40).
- (ii) The potential role of anti-inflammatory biologics in CVD. The gut microbiota produces a myriad of bioactive metabolites and signaling molecules that can impact immune function and cardiovascular health. Short-chain fatty acids (SCFAs), produced through the fermentation of dietary fibers by gut bacteria, have been shown to exert immunomodulatory effects by regulating the differentiation and activity of immune cells, thereby influencing inflammation in the

BOX 1 The role of immunity and inflammation in arrhythmia development.

Arrhythmias associated with autoimmunity and inflammation occur through at least four mechanisms that disrupt electrical coupling:

- 1. Autoimmunity targeting ion channels and junctional molecules of the intercalated disc and lateral gap junctions.** The clinical manifestation involves the presence of autoantibodies against ion channels (Na⁺, Ca²⁺, K⁺) and junctional molecules (connexins and intercalated disc molecules). It has been proposed that these arrhythmias may respond to mild immunosuppressive treatment, which suppresses autoantibody production (30).
- 2. Direct effects of proinflammatory mediators and cytokines on channel function and gap junction coupling.** Molecules like histamine and prostaglandins, which increase cytosolic c-AMP/c-GMP, temporarily disrupt cell-to-cell junctions, leading to electrical uncoupling between cardiomyocytes at the intercalated disc level (31). Cytokines such as TNF- α , IL-1 β , and IL-6 can also affect both cardiomyocyte channels and gap junctions, thus influencing electrical activity and leading to cytokine-associated arrhythmias (32).
- 3. Immuno-mediated damage of excitable and conduction tissue,** resulting in blocks, bradycardias, and various types of tachyarrhythmia (33–35). Myocardial cell death and myocardiosclerosis following immuno-inflammation are frequent arrhythmic causes in myocarditis. Also, these arrhythmias may respond to mild immunosuppressive treatment, when allowing the repair of sublethally damaged tissue.
- 4. Arrhythmogenic cardiomyopathy,** a rare heart disease characterized by structural and electrical alterations, including abnormalities in intercalated discs and fibro-fatty replacement of ventricular myocardium. While familial genetic factors play a significant role in its pathogenesis, subsequent alterations in intercalated disc junctional complexes contribute to the clinical presentation, especially involving desmosome and tight junction components. Autoantibodies against tight junction and desmosome-associated molecular components have been described (36).

cardiovascular system (41). Beyond SCFAs, the gut microbiota generates a diverse array of metabolites, including trimethylamine N-oxide (TMAO), lipopolysaccharides (LPS), and bile acids (BAs), which have been implicated in the pathogenesis of CVD (42). On the one hand, the exploration of anti-inflammatory biologics in cardiovascular diseases, particularly anti-inflammatory and immunomodulatory indole derivatives, represents an exciting avenue for research and therapeutic development (43). While there is evidence suggesting their potential benefits, ongoing studies and further clinical trials are necessary to establish their role in specific

patient populations and to refine treatment strategies. On the other hand, chronic inflammation is a hallmark of many cardiovascular diseases, and the gut microbiota has been implicated in the regulation of inflammatory pathways that contribute to vascular dysfunction and atherogenesis. Through the activation of toll-like receptors and nucleotide-binding oligomerization domain-like receptors, gut-derived microbial products can trigger inflammatory cascades that promote the development of cardiovascular pathology. Some biologics that target inflammatory pathways, such as TNF- α inhibitors or IL-1 inhibitors (26, 27, 44), may have indirect heart-protective effects by reducing systemic inflammation, which is a risk factor for cardiovascular disease (45). Overall, targeting the gut microbiota represents a promising avenue for the development of novel therapeutic strategies in cardioimmunology. Approaches such as probiotics, prebiotics, postbiotics, and fecal microbiota transplantation offer the potential to modulate the gut microbiota composition and activity, thereby influencing immune responses and mitigating cardiovascular risk factors (46–48).

- (iii) Vaccination and cardiovascular health. Some research in cardioimmunology explores the impact of vaccinations on cardiovascular health. For instance, vaccines targeting infectious agents may not only prevent infections but also impact the risk of cardiovascular events associated with inflammation. In particular, vaccination plays a crucial role in maintaining overall health, including cardiovascular health. While vaccines primarily target specific infections, their impact can extend beyond preventing the targeted diseases. Here are some aspects of vaccination and cardiovascular health (49). A prototypic example is represented by influenza vaccine: Influenza infections can lead to respiratory complications, and severe cases may have cardiovascular implications. By preventing the flu, the vaccine helps reduce the risk of influenza-related cardiovascular events. Not secondarily, COVID-19, caused by the SARS-CoV-2 virus, has been associated with various cardiovascular complications. These include myocarditis, pericarditis, and an increased risk of blood clot formation. COVID-19 vaccination has been shown to be effective in preventing severe illness and complications, including those related to the cardiovascular system (50). Nevertheless, the very vaccine, owing to its formulation (i.e., mRNA in lipid nanoparticles) can exert direct effects on the cardiovascular system (51, 52). Relevant in this regard are experimental studies on autoimmune myocarditis. **Box 2** provides some information in this regard.

3 Human and gut microbiota synergy on tryptophan utilization

Both humans and gut microbiota feed on dietary Trp for proteogenesis and other functions that rely of the degradation of this essential amino acid. The phylogenesis of Trp catabolism across different organisms provides insights into the evolutionary advantages and diverse functions of this pathway (59). Trp

BOX 2 Autoimmune myocarditis in viral infection.

Autoimmune myocarditis is often indirectly linked to viral infections (53). One potential contributing factor is the release or exposure of cardiac myosin following viral-mediated myocyte damage, triggering autoimmune responses and myocardial inflammation (54, 55). Fulminant myocarditis spontaneously develops in $Pdcd1^{-/-}$ $Ctla4^{+/-}$ mice. Axelrod et al. (56) conducted single-cell sequencing and TCR sequencing of immune cells infiltrating these myocarditis tissues, revealing a significant increase in the number of $CD8^{+}$ T cells with clonal expansions. The removal of $CD8^{+}$ T cells prevented myocarditis development, while the removal of $CD4^{+}$ T cells did not alter myocarditis incidences. Adoptively transferring $CD8^{+}$ T cells from $Pdcd1^{-/-}$ $Ctla4^{+/-}$ mice to $Rag1^{-/-}$ mice led to myocarditis development after two months, emphasizing the pivotal role of $CD8^{+}$ T cells in fulminant myocarditis (56). Additionally, a recent study highlighted macrophage migration as a notable histopathological feature of myocarditis, suggesting that targeting macrophages could be a potential therapeutic approach for this disease (57). Treating mice with a nontoxic endogenous Aryl hydrocarbon Receptor (AhR) ligand, ITE [2-(1^H-indole-3[′]-carbonyl)-thiazole-4-carboxylic acid methyl ester] ameliorated cardiac function. It was hypothesized that activation of AhR by ITE in myocardial infarction mice would boost regulatory T-cell differentiation, modulate macrophage activity, and facilitate infarct healing (58).

catabolism is a highly conserved process that has evolved over time, and its existence across various organisms suggests its importance in adaptation and survival (60–62). Here are some key points regarding the phylogenesis of Trp catabolism: (a) *Universal presence*: Trp catabolism is found in a wide range of organisms, including bacteria, fungi, plants, and animals. This universality indicates that the pathway has been evolutionarily conserved and is fundamental to the biology of diverse life forms (60); (b) *Metabolic regulation*: The regulation of Trp catabolism has likely evolved as a mechanism for organisms to adapt to changing environmental conditions, nutrient availability, and immune responses (63). In many cases, the regulation of Trp catabolism is responsive to external stimuli, such as stress, infection, or inflammation, highlighting its role in the adaptive response to various challenges; (c) *Host-pathogen dynamics*: The evolutionary arms race between hosts and pathogens has likely shaped the development and diversification of Trp catabolism. Hosts may have evolved this pathway as a defense mechanism to limit nutrient availability for pathogens, while some pathogens have developed strategies to exploit or manipulate Trp metabolism for their benefit (64); (d) *Immunomodulation and tolerance*: The immunomodulatory effects of Trp catabolism, including the generation of metabolites with immunosuppressive properties, suggest that this pathway has evolved to play a role in

regulating the immune response (65). Tolerance induction, mediated by Trp catabolism, could have provided an evolutionary advantage by preventing excessive inflammation and immunopathology, contributing to the host's ability to coexist with commensal microorganisms; (e) *Nutrient sensing and energy metabolism*: Trp catabolism is not only involved in immune responses but is also linked to broader metabolic processes. The breakdown of Trp can provide precursors for the synthesis of other molecules, and its regulation may be tied to overall energy metabolism.

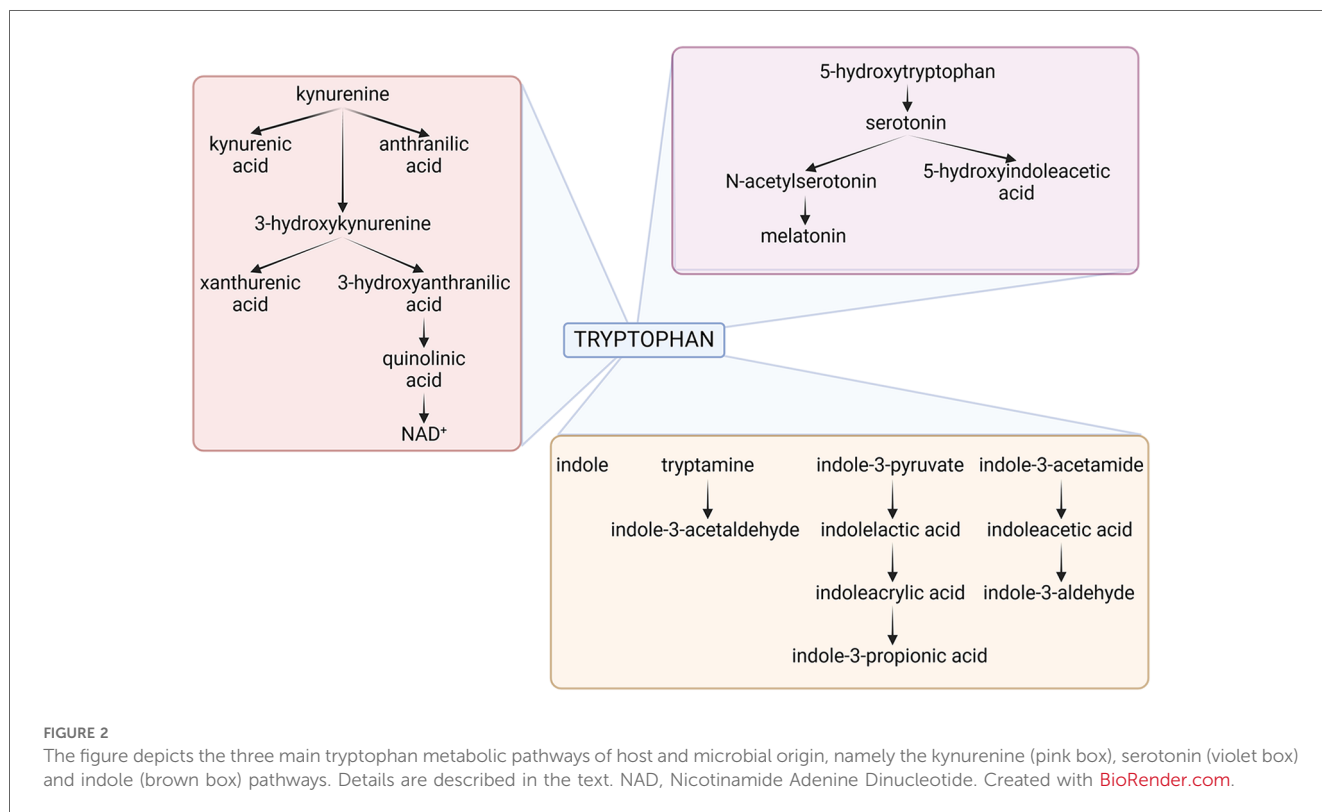
Therefore, as to the question of why an organism would want to destroy an essential amino acid like Trp, it is important to note that the goal is not necessarily the destruction of Trp but rather the modulation of its levels (63, 66–69). The evolutionary advantage lies in the ability to dynamically regulate Trp availability in response to specific environmental and physiological cues. By controlling Trp levels, organisms can influence their own metabolism, respond to stressors, and shape the host-microbe interaction in ways that promote survival and adaptation. It is interesting to note that bacteria that eat worms use NAD as a 'food signal' to open their mouths but, if NAD is unavailable, they stop reproducing and enter a developmental and reproductive arrest phase, mediated by serotonin, to survive (60, 70). In the context of host defense, limiting the availability of essential nutrients like Trp can be a strategic means of thwarting the growth and proliferation of pathogens (Figure 2).

Much like their hosts, bacteria can metabolize Trp along all three pathways, influencing the so-called "brain-gut-microbiota axis". *Bacteroides* spp., *Clostridium* spp., *Escherichia coli*, *Lactobacillus* spp., *Bifidobacterium* spp., *Akkermansia muciniphila*, *Faecalibacterium*

prausnitzii, *Prevotella* spp., *Ruminococcus* spp., all degrade Trp in the gut via the kynurenine pathway (71). There is some evidence that several of the same species may likewise induce serotonin in the gut. *Escherichia coli*, *Clostridium* spp., *Bacteroides* spp., *Akkermansia muciniphila*, *Clostridioides difficile*, *Enterococcus* spp., *Proteus* spp., *Citrobacter* spp., and *Klebsiella* spp. will instead produce a preponderance of indole or derivatives thereof (72). It follows that—if host and gut bacteria—both metabolize Trp there must be competition for the substrate, yet flexible balance for local and systemic homeostasis (69).

4 Tryptophan and the heart

Gut microbiota and microbiota-derived metabolites have been increasingly recognized for their potential impact on CVD, including hypertension, heart failure, myocardial infarction, arrhythmia, atherosclerosis, and myocarditis. Evidence from recent studies has shown that gut microbiota contributes to the development of myocarditis, an inflammatory disease that can result in myocardial damage and the emerging field of cardioimmunology (37, 73, 74). The metabolites produced by gut microbiota can affect the immune system and have an impact on cardiovascular health (10, 40). This is in line with the long-established notion that gut microbiota-dependent metabolites serve as a link connecting the dynamic balance between the host and the gut microbiota (75). In addition to microbial-derived SCFAs, BAs and TMAO, a number of host and microbial metabolites derived from the essential amino acid tryptophan (Trp) degradation has been implicated in cardiovascular diseases (10, 76).



The kynurenine pathway is a metabolic pathway that plays a crucial role in Trp degradation (77–82). This pathway is primarily associated with immune regulation and has been implicated in various physiological and pathological processes, including immune homeostasis and cardiovascular integrity (83). The pathway's contributions to immune homeostasis include (a) *Regulation of T-cell responses*: The kynurenine pathway is a key player in the modulation of immune responses. One of its main functions is the regulation of T cell activity. Specifically, the production of kynurenine metabolites can influence T cell differentiation and function (84); (b) *Immunosuppressive effects*: Certain metabolites of the kynurenine pathway, such as kynurenine itself, have immunosuppressive properties. They can inhibit the proliferation of T cells and promote the generation of regulatory T cells, which are crucial for maintaining immune tolerance and preventing autoimmune reactions (82). As regards the cardiovascular system, additional functions are: (c) *Regulation of vascular function*: Components of the kynurenine pathway, including kynurenine and its derivatives, have been implicated in vascular function by affecting, for instance, endothelial function and blood vessel integrity (85); (d) *Control of inflammation and atherosclerosis*. The immunomodulatory effects of the kynurenine pathway may influence the inflammatory processes associated with cardiovascular conditions (86–88). As a matter of fact, dysregulation of the kynurenine pathway has been implicated in cardiovascular diseases in which the kynurenine and the [Kyn]/[Trp]-ratio were associated with an increased risk of developing cardiovascular disease (10, 76) while higher Trp levels were associated with a tendency toward lower incident risk of mortality (76).

The serotonin pathway also plays an important role in the degradation of Trp with effects that go beyond its role as neurotransmitter in the central nervous system to include, among others, the regulation the immune and cardiovascular functions. In the periphery, serotonin is a major regulator of vasoreactivity, by directly inducing vasoconstriction in large arteries and veins and exerting a vasodilatory effect in arterioles via nitric oxide release and vascular smooth muscle relaxation (89). Aggregating platelets release serotonin that may contribute to the etiology of spasm in cerebral, digital and coronary vessels, and in the maintenance of the elevated peripheral resistance in arterial hypertension (90). Increased concentrations of serotonin were indeed associated with an increased risk of cardiovascular damage and disease (76, 91).

Finally, the impact of indoles, produced by bacterial degradation of Trp, has gained attention for their dual influence at the pathogen-host interface (84, 92–94). In cardiology, metabolites in the indole pathway did not show consistent associations with cardiovascular outcomes, although higher concentrations of some end products of the indole pathway have been reported to be associated with a lower risk of atherosclerosis (76, 95). For instance, the indole-3-aldehyde (3-IAld) metabolite was found to be lower, different from others, in patients with myocardial infarction (96). The section below delves into the manifold influence of indole metabolites on the host metabolism and immunity, specifically examining their systemic effects from the standpoint of cardioimmunology.

4.1 Indoles and systemic immunity

Indole is a heterocyclic organic compound with a bicyclic structure consisting of a six-membered benzene ring fused to a five-membered pyrrole ring. It is found in various natural products such as the amino acid tryptophan and the hormone serotonin. Indole derivatives have been studied in relation to their effects on the cardiovascular system (Box 3).

4.2 Indole and the aryl hydrocarbon receptor: the case of indole-3-aldehyde, 3-IAld

The Aryl hydrocarbon receptor (AhR) is a ligand-activated transcription factor that plays a crucial role in regulating various physiological processes, including immune responses,

BOX 3 Key points regarding indole and its derivatives on the cardiovascular system.

- Vasodilation:** Some studies have shown that certain indole derivatives exhibit vasodilatory effects, which can help relax blood vessels and lower blood pressure. For example, indole-3-acetic acid has been shown to induce vasodilation in experimental models (97).
- Anti-inflammatory effects:** Indole derivatives may possess anti-inflammatory properties that can be beneficial in cardiovascular health (98).
- Antioxidant activity:** Some indole derivatives have been found to have antioxidant activity, which can help reduce oxidative stress in the cardiovascular system. Oxidative stress is implicated in various cardiovascular diseases, and antioxidants can help neutralize harmful free radicals (99).
- Serotonin receptor modulation:** Indole derivatives play a role in regulating cardiovascular function through the modulation of serotonin receptors.
- Platelet aggregation:** Some indole derivatives may affect platelet function and aggregation, which are important in the formation of blood clots. Modulation of platelet activity by indole derivatives could have implications for cardiovascular health and thrombotic events (100).
- Cardioprotective effects:** Certain indole derivatives have been investigated for their potential cardioprotective effects. For example, indole-3-carbinol has been studied for its anti-inflammatory and antioxidant properties, which could contribute to protecting the heart from damage (101, 102).
- Potential therapeutic applications:** Indole derivatives are being explored for their potential therapeutic applications in CVD such as hypertension, atherosclerosis, and heart failure. Further research is needed to better understand the mechanisms of action and potential benefits of indole derivatives in cardiovascular health (103–105).

xenobiotic metabolism, and maintenance of cellular homeostasis (106–108). AhR is a member of the basic helix-loop-helix/Per-ARNT-Sim (bHLH-PAS) protein family and is primarily localized in the cytoplasm in its inactive state. AhR activation occurs when it binds to specific ligands, leading to its translocation into the nucleus, where it forms a complex with its partner, the AhR nuclear translocator. This complex then binds to specific DNA sequences known as xenobiotic response elements in the promoter regions of target genes, thereby regulating their expression.

The gut microbiota has been implicated in the production of AhR ligands (106–110). These ligands are often derived from dietary components and microbial metabolism. Indole derivatives are prominent examples of AhR ligands produced by gut microbiota through the breakdown of dietary tryptophan. Additionally, certain metabolites of tryptophan, such as kynurenine and kynurenic acid, can also activate AhR. The activation of AhR by these microbial-derived ligands has been associated with various immunomodulatory effects. AhR activation in immune cells can regulate the balance between pro-inflammatory and anti-inflammatory responses, impacting the development and function of immune cells. Furthermore, AhR activation in the gut has been linked to the maintenance of intestinal barrier integrity and the regulation of mucosal immune responses (111–113). The interaction between the gut microbiota and AhR highlights the intricate relationship between the microbiome, dietary factors, and host physiology, emphasizing the importance of these interactions in shaping immune and metabolic functions (114). As mentioned above, degradation of Trp by bacteria or enterocytes generates several AhR-binding molecules, mainly serotonin, tryptamine and indoles, including: indole, indole-3-propionic acid (IPA), indole-3-acetic acid (IAA), indole-3-aldehyde (3-IAld), indole-3-acetaldehyde (IAAld), indole-3-lactic acid (ILA), indole acrylic acid and others, including tryptamine and skatole (115). Thus, the co-evolution of microbial communities with mammalian hosts has led to interconnected metabolic pathways that intricately influence both physiological and pathological processes. Trp derivatives, arising from both host and microbial sources, exemplify this metabolic complexity. Among these derivatives, 3-IAld stands out as a metabolite produced by the gut microbiota (92, 116–119).

Initially recognized for its role as an agonist of the AhR, particularly in promoting epithelial barrier functions, this compound has now been implicated in a myriad of activities across various pathological conditions. Along this direction, our group has been involved for some time in turning microbial AhR agonists into therapeutic agents via drug delivery systems (116, 118). By deciphering how signaling molecules, such as 3-IAld, interact with AhR may pave the way for novel therapeutics in inflammatory human diseases, for the realization of which drug delivery platforms are instrumental. So far, three synthetic AhR agonists—laquinimod, tranilast and benvitimod—have been investigated in phase I–III clinical trials. The trials involved patients with autoimmune conditions, such as Crohn's disease, rheumatoid arthritis, asthma, atopic dermatitis or multiple sclerosis (120). However, to our knowledge, none of them was tested in patients

with cardiovascular diseases. A 3-IAld dry powder for inhalation was formulated and assessed for its effectiveness in comparison to oral and intranasal delivery methods in experimental lung inflammation (44). The resulting inhalable dry powder demonstrated: (i) suitability for pulmonary administration, (ii) favorable toxicological safety, and (iii) superior efficacy over alternative administration routes (oral and intranasal) in reducing inflammatory and disease scores. This research advocates for the utilization of 3-IAld inhalable dry powders as a promising and innovative therapeutic approach for targeting inflammation in pulmonary diseases and, likely, cardiopulmonary conditions (121, 122).

In conclusion, AhR plays a crucial role not only in detoxification but also in various physiological processes, particularly in maintaining vascular homeostasis. Despite its high expression in the endothelium, there is a lack of comprehensive understanding of AhR's function in this context. There is a definite need for consolidating existing knowledge regarding AhR's involvement in the endothelium and its implications for cardiovascular health (122). Whatever, modulating AhR signaling emerges as a potential therapeutic target for addressing vascular disorders whereby systemic low-grade inflammation reduces circulating endothelial progenitor cells (123). In this regard, it is of interest that while indoxyl sulfate promoted vascular inflammation, IPA and 3-IAld had protective effects (117).

5 Future perspectives and conclusions

Accumulated evidence substantiates the notion that a triad comprising microbiota, Trp, and AhR is a targeted axis in several cardiovascular conditions (Figure 3).

Presently, most treatments primarily address symptoms, focusing on enhancing compromised functionality. However, therapeutic options capable of influencing cellular degeneration or pathology remain elusive. Should a significant role of abnormal intestinal flora composition in specific phenotypes be confirmed, a promising therapeutic avenue could emerge by optimizing pharmacological therapy of CVD with Trp supplementation and/or medications altering the Trp metabolic pathways. Nevertheless, variations among individuals, coupled with the impact of comorbidities, dietary patterns, medications, infections, and lifestyle, can alter gut microbiota composition. Hence, future research demands meticulous investigation using a rigorous experimental framework, taking these factors into account (124). Indeed, despite the potential promise of precisely defined and tailored diets in influencing the microbiome and inflammation, their practical applicability in the general population remains questionable as it is the potential long-lasting benefits of fecal microbiota transplantation in CVD (125).

Additionally, the potential value of the measurement of Trp metabolites as screening and diagnostic tools for a broader population, indicate that mechanistic studies are required to understand the role of Trp metabolism in CVD with the goal to identify new diagnostic and therapeutic options.

Lastly, delving into research on microbiota, Trp catabolic pathways and AhR signaling has uncovered insights into the

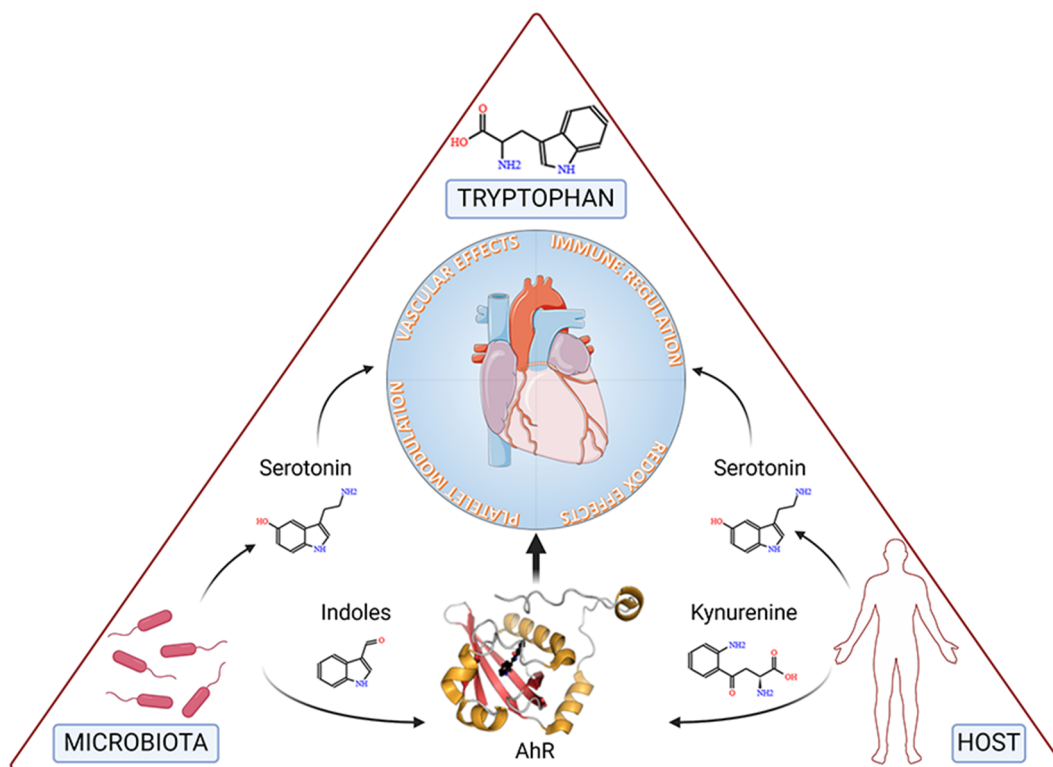


FIGURE 3

The figure depicts tryptophan, the microbiota and the host at the vertices of a triangle representing the triad involved in cardiovascular health and disease. Specifically, microbial- and host-dependent degradation of tryptophan results in the production of metabolites, including serotonin, indoles and kynurenine, the latter two working as ligands of the Aryl Hydrocarbon Receptor (AhR), ultimately affecting key functions of the cardiovascular system. Details are described in the text. Created with [BioRender.com](https://www.biorender.com).

mechanisms of intestinal distress (126, 127). Despite being underappreciated, a role for the intestinal barrier dysfunction in CVD has become evident in light of its occurrence in hypertension, coronary artery disease, atherosclerosis, heart failure, and myocardial infarction (128). Thus, testing indole derivatives as intestinal barrier-targeted compounds may lead to their potential new class of CVD therapeutics.

Author contributions

MR: Conceptualization, Writing – review & editing. MP: Writing – review & editing. CC: Writing – review & editing. SG: Writing – review & editing. MR: Writing – review & editing. EG: Conceptualization, Writing – review & editing. LR: Conceptualization, Funding acquisition, Writing – original draft, Writing – review & editing.

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Conflict of interest

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References

- Gergely TG, Drobní ZD, Kallikourdis M, Zhu H, Meijers WC, Neilan TG, et al. Immune checkpoints in cardiac physiology and pathology: therapeutic targets for heart failure. *Nat Rev Cardiol.* (2024) 21(7):443–62. doi: 10.1038/s41569-023-00986-9
- Thackeray JT, Lavine KJ, Liu Y. Imaging inflammation past, present, and future: focus on cardioimmunology. *J Nucl Med.* (2023) 64:39s–48. doi: 10.2967/jnumed.122.264865
- Thorp EB. Cardiac macrophages and emerging roles for their metabolism after myocardial infarction. *J Clin Invest.* (2023) 133:e171953. doi: 10.1172/JCI171953
- Saleh D, Jones RTL, Schroth SL, Thorp EB, Feinstein MJ. Emerging roles for dendritic cells in heart failure. *Biomolecules.* (2023) 13:1535. doi: 10.3390/biom13101535
- Zambrano MA, Alcaide P. Immune cells in cardiac injury repair and remodeling. *Curr Cardiol Rep.* (2023) 25:315–23. doi: 10.1007/s11886-023-01854-1
- Wong A, Hamidzada H, Epelman S. A cardioimmunologist's toolkit: genetic tools to dissect immune cells in cardiac disease. *Nat Rev Cardiol.* (2022) 19:395–413. doi: 10.1038/s41569-022-00701-0
- Galajda N, Meznerics FA, Mátrai P, Fehérvári P, Lengyel AS, Kolonics MV, et al. Reducing cardiovascular risk in immune-mediated inflammatory diseases: tumour necrosis factor inhibitors compared to conventional therapies-A systematic review and meta-analysis. *J Eur Acad Dermatol Venereol.* (2024) 38(6):1070–88. doi: 10.1111/jdv.19900
- Swirski FK, Nahrendorf M. Cardioimmunology: the immune system in cardiac homeostasis and disease. *Nat Rev Immunol.* (2018) 18:733–44. doi: 10.1038/s41577-018-0065-8
- Lazzerini PE, Hamilton RM, Boutjdir M. Editorial: cardioimmunology: inflammation and immunity in cardiovascular disease. *Front Cardiovasc Med.* (2019) 6:181. doi: 10.3389/fcvm.2019.00181
- Russo MA, Garaci E, Frustaci A, Fini M, Costantini C, Oikonomou V, et al. Host-microbe tryptophan partitioning in cardiovascular diseases. *Pharmacol Res.* (2023) 198:106994. doi: 10.1016/j.phrs.2023.106994
- Suffee N, Le Goff W, Chen J. Editorial: cardiometabolic diseases and inflammatory responses. *Front Immunol.* (2024) 15:1384022. doi: 10.3389/fimmu.2024.1384022
- Henein MY, Vancheri S, Longo G, Vancheri F. The role of inflammation in cardiovascular disease. *Int J Mol Sci.* (2022) 23:12906. doi: 10.3390/ijms232112906
- Fredman G, Serhan CN. Specialized pro-resolving mediators in vascular inflammation and atherosclerotic cardiovascular disease. *Nat Rev Cardiol.* (2024) doi: 10.1038/s41569-023-00984-x
- Toldo S, Abbate A. The role of the NLRP3 inflammasome and pyroptosis in cardiovascular diseases. *Nat Rev Cardiol.* (2024) 21:219–37. doi: 10.1038/s41569-023-00946-3
- Riksen NP, Bekkering S, Mulder WJM, Netea MG. Trained immunity in atherosclerotic cardiovascular disease. *Nat Rev Cardiol.* (2023) 20:799–811. doi: 10.1038/s41569-023-00894-y
- Crnko S, Du Pre BC, Sluijter JPG, Van Laake LW. Circadian rhythms and the molecular clock in cardiovascular biology and disease. *Nat Rev Cardiol.* (2019) 16:437–47. doi: 10.1038/s41569-019-0167-4
- Bilo G, Gatterer H, Torlasco C, Villafuerte FC, Parati G. Editorial: hypoxia in cardiovascular disease. *Front Cardiovasc Med.* (2022) 9:990013. doi: 10.3389/fcvm.2022.990013
- Guzik TJ, Nosalski R, Maffia P, Drummond GR. Immune and inflammatory mechanisms in hypertension. *Nat Rev Cardiol.* (2024) 21(6):396–416. doi: 10.1038/s41569-023-00964-1
- Simões FC, Riley PR. Immune cells in cardiac repair and regeneration. *Development.* (2022) 149:dev199906. doi: 10.1242/dev.199906
- Su X, Wang L, Ma N, Yang X, Liu C, Yang F, et al. Immune heterogeneity in cardiovascular diseases from a single-cell perspective. *Front Cardiovasc Med.* (2023) 10:1057870. doi: 10.3389/fcvm.2023.1057870
- Kologrivova I, Shtatolkinina M, Suslova T, Ryabov V. Cells of the immune system in cardiac remodeling: main players in resolution of inflammation and repair after myocardial infarction. *Front Immunol.* (2021) 12:664457. doi: 10.3389/fimmu.2021.664457
- Steffens S, Nahrendorf M, Madonna R. Immune cells in cardiac homeostasis and disease: emerging insights from novel technologies. *Eur Heart J.* (2022) 43:1533–41. doi: 10.1093/eurheartj/ehab842
- Attiq A, Afzal S, Ahmad W, Kandeel M. Hegemony of inflammation in atherosclerosis and coronary artery disease. *Eur J Pharmacol.* (2024) 966:176338. doi: 10.1016/j.ejphar.2024.176338
- Jyotsna F, Ikram J, Nageeta F, Komal F, Anjee F, Patel H, et al. Unlocking the potential of immunotherapy in cardiovascular disease: a comprehensive review of applications and future directions. *Cureus.* (2023) 15:e42790. doi: 10.7759/cureus.42790
- Booz GW, Altara R, Zouein FA. Editorial: immunomodulatory approaches in cardiovascular diseases. *Front Cardiovasc Med.* (2022) 9:873452. doi: 10.3389/fcvm.2022.873452
- Ridker PM, Everett BM, Thuren T, Macfadyen JG, Chang WH, Ballantyne C, et al. Antiinflammatory therapy with canakinumab for atherosclerotic disease. *N Engl J Med.* (2017) 377:1119–31. doi: 10.1056/NEJMoa1707914
- Thompson PL, Nidorf SM. Anti-inflammatory therapy with canakinumab for atherosclerotic disease: lessons from the cantos trial. *J Thorac Dis.* (2018) 10:695–8. doi: 10.21037/jtd.2018.01.119
- Liu Y, Guan S, Xu H, Zhang N, Huang M, Liu Z. Inflammation biomarkers are associated with the incidence of cardiovascular disease: a meta-analysis. *Front Cardiovasc Med.* (2023) 10:1175174. doi: 10.3389/fcvm.2023.1175174
- Mesa A, Giménez M, Perea V, Serés-Noriega T, Boswell L, Blanco J, et al. Severe hypoglycemia and hypoglycemia awareness are associated with preclinical atherosclerosis in patients with type 1 diabetes without an estimated high cardiovascular risk. *Diabetes Metab Res Rev.* (2024) 40:e3785. doi: 10.1002/dmrr.3785
- Frustaci A, Chimenti C, Pieroni M, Salvatori L, Morgante E, Sale P, et al. Cell death, proliferation and repair in human myocarditis responding to immunosuppressive therapy. *Mod Pathol.* (2006) 19:755–65. doi: 10.1038/modpathol.3800594
- Frustaci A, Caldaruolo M, Di Rienzo V, Russo MA, Gentiloni N. Antiarrhythmic effect of H-2 antihistamines. *Chest.* (1991) 99:262–3. doi: 10.1378/chest.99.1.262
- Lazzerini PE, Capecci PL, Laghi-Pasini F, Boutjdir M. Autoimmune channelopathies as a novel mechanism in cardiac arrhythmias. *Nat Rev Cardiol.* (2017) 14:521–35. doi: 10.1038/nrcardio.2017.61
- Frustaci A, Chimenti C, Bellocchi F, Morgante E, Russo MA, Maseri A. Histological substrate of atrial biopsies in patients with lone atrial fibrillation. *Circulation.* (1997) 96:1180–4. doi: 10.1161/01.CIR.96.4.1180
- Frustaci A, Priori SG, Pieroni M, Chimenti C, Napolitano C, Rivolta I, et al. Cardiac histological substrate in patients with clinical phenotype of brugada syndrome. *Circulation.* (2005) 112:3680–7. doi: 10.1161/CIRCULATIONAHA.105.520999
- Chimenti C, Russo MA, Carpi A, Frustaci A. Histological substrate of human atrial fibrillation. *Biomed Pharmacother.* (2010) 64:177–83. doi: 10.1016/j.biopha.2009.09.017
- Austin KM, Trembley MA, Chandler SF, Sanders SP, Saffitz JE, Abrams DJ, et al. Molecular mechanisms of arrhythmogenic cardiomyopathy. *Nat Rev Cardiol.* (2019) 16:519–37. doi: 10.1038/s41569-019-0200-7
- Rahman MM, Islam F, Or-Rashid MH, Mamun AA, Rahaman MS, Islam MM, et al. The gut microbiota (microbiome) in cardiovascular disease and its therapeutic regulation. *Front Cell Infect Microbiol.* (2022) 12:903570. doi: 10.3389/fcimb.2022.903570
- Rashid S, Sado AI, Afzal MS, Ahmed A, Almaalouli B, Waheed T, et al. Role of gut microbiota in cardiovascular diseases—a comprehensive review. *Ann Med Surg (Lond).* (2024) 86:1483–9. doi: 10.1097/MS9.0000000000001419
- Nesci A, Carnuccio C, Ruggieri V, D'alessandro A, Di Giorgio A, Santoro L, et al. Gut Microbiota and cardiovascular disease: evidence on the metabolic and inflammatory background of a Complex relationship. *Int J Mol Sci.* (2023) 24:9087. doi: 10.3390/ijms24109087
- Shi B, Li H, He X. Advancing lifelong precision medicine for cardiovascular diseases through gut microbiota modulation. *Gut Microbes.* (2024) 16:2323237. doi: 10.1080/19490976.2024.2323237
- Lu Y, Zhang Y, Zhao X, Shang C, Xiang M, Li L, et al. Microbiota-derived short-chain fatty acids: implications for cardiovascular and metabolic disease. *Front Cardiovasc Med.* (2022) 9:900381. doi: 10.3389/fcvm.2022.900381
- Kirk D, Costeira R, Visconti A, Khan Mirzaei M, Deng L, Valdes AM, et al. Bacteriophages, gut bacteria, and microbial pathways interplay in cardiometabolic health. *Cell Rep.* (2024) 43:113728. doi: 10.1016/j.celrep.2024.113728
- Fragoulis GE, Soulaïdopoulos S, Sfakakis PP, Dimitroulas T, D Kitas G. Effect of biologics on cardiovascular inflammation: mechanistic insights and risk reduction. *J Inflamm Res.* (2021) 14:1915–31. doi: 10.2147/JIR.S282691
- Puccetti M, Pariano M, Stincardini C, Wojtylo P, Schouppen A, Nunzi E, et al. Pulmonary drug delivery technology enables anakinra repurposing in cystic fibrosis. *J Control Release.* (2023) 353:1023–36. doi: 10.1016/j.jconrel.2022.11.043
- Abbate A, Toldo S, Marchetti C, Kron J, Van Tassell BW, Dinarello CA. Interleukin-1 and the inflammasome as therapeutic targets in cardiovascular disease. *Circ Res.* (2020) 126:1260–80. doi: 10.1161/CIRCRESAHA.120.315937
- Ji J, Jin W, Liu SJ, Jiao Z, Li X. Probiotics, prebiotics, and postbiotics in health and disease. *MedComm.* (2023) 4:e420. doi: 10.1002/mco.2420
- Ciernikova S, Sevcikova A, Drgona L, Mego M. Modulating the gut microbiota by probiotics, prebiotics, postbiotics, and fecal microbiota transplantation: an emerging trend in cancer patient care. *Biochim Biophys Acta Rev Cancer.* (2023) 1878:188990. doi: 10.1016/j.bbcan.2023.188990

48. Wang W, Fan J, Zhang C, Huang Y, Chen Y, Fu S, et al. Targeted modulation of gut and intra-tumor microbiota to improve the quality of immune checkpoint inhibitor responses. *Microbiol Res.* (2024) 282:127668. doi: 10.1016/j.micres.2024.127668
49. Yedlapati SH, Mendu A, Tummala VR, Maganti SS, Nasir K, Khan SU. Vaccines and cardiovascular outcomes: lessons learned from influenza epidemics. *Eur Heart J Suppl.* (2023) 25:A17–24. doi: 10.1093/eurheartjsupp/suac110
50. Pepera G, Tribali MS, Batalik L, Petrov I, Papanthasiou J. Epidemiology, risk factors and prognosis of cardiovascular disease in the coronavirus disease 2019 (COVID-19) pandemic era: a systematic review. *Rev Cardiovasc Med.* (2022) 23:28. doi: 10.31083/j.rcm2301028
51. Centers for Disease, C. & Prevention. Myocarditis and Pericarditis After mRNA Covid-19 Vaccination. <https://www.cdc.gov/vaccines/covid-19/clinical-considerations/myocarditis.html> (accessed October 10, 2023).
52. Yonker LM, Swank Z, Bartsch YC, Burns MD, Kane A, Boribong BP, et al. Circulating spike protein detected in post-COVID-19 mRNA vaccine myocarditis. *Circulation.* (2023) 147:867–76. doi: 10.1161/CIRCULATIONAHA.122.061025
53. Stephenson E, Savvatis K, Mohiddin SA, Marelli-Berg FM. T-cell immunity in myocardial inflammation: pathogenic role and therapeutic manipulation. *Br J Pharmacol.* (2017) 174:3914–25. doi: 10.1111/bph.13613
54. Neu N, Rose NR, Beisel KW, Herskowitz A, Gurri-Glass G, Craig SW. Cardiac myosin induces myocarditis in genetically predisposed mice. *J Immunol.* (1987) 139:3630–6. doi: 10.4049/jimmunol.139.11.3630
55. Lazzarini PE, Capecchi PL, El-Sherif N, Laghi-Pasini F, Boutjdir M. Emerging arrhythmic risk of autoimmune and inflammatory cardiac channelopathies. *J Am Heart Assoc.* (2018) 7:e010595. doi: 10.1161/JAHA.118.010595
56. Axelrod ML, Meijers WC, Screever EM, Qin J, Carroll MG, Sun X, et al. T cells specific for α -myosin drive immunotherapy-related myocarditis. *Nature.* (2022) 611:818–26. doi: 10.1038/s41586-022-05432-3
57. Toita R, Kawano T, Murata M, Kang J-H. Bioinspired macrophage-targeted anti-inflammatory nanomedicine: a therapeutic option for the treatment of myocarditis. *Mater Sci Eng C.* (2021) 131:112492. doi: 10.1016/j.msec.2021.112492
58. Seong E, Lee JH, Lim S, Park EH, Kim E, Kim CW, et al. Activation of aryl hydrocarbon receptor by ite improves cardiac function in mice after myocardial infarction. *J Am Heart Assoc.* (2021) 10:e020502. doi: 10.1161/JAHA.120.020502
59. Grohmann U, Puccetti P. The coevolution of IDO1 and AhR in the emergence of regulatory T-cells in mammals. *Front Immunol.* (2015) 6:58. doi: 10.3389/fimmu.2015.00058
60. Grohmann U, Mondanelli G, Belladonna ML, Orabona C, Pallotta MT, Iacono A, et al. Amino-acid sensing and degrading pathways in immune regulation. *Cytokine Growth Fact Rev.* (2017) 35:37–45. doi: 10.1016/j.cytogfr.2017.05.004
61. Gargaro M, Scalisi G, Manni G, Briseño CG, Bagadia P, Durai V, et al. Indoleamine 2,3-dioxygenase 1 activation in mature cDC1 promotes tolerogenic education of inflammatory cDC2 via metabolic communication. *Immunity.* (2022) 55:1032–1050.e14. doi: 10.1016/j.immuni.2022.05.013
62. Iacono A, Pompa A, De Marchis F, Panfilì E, Greco FA, Coletti A, et al. Class IA PI3Ks regulate subcellular and functional dynamics of IDO1. *Embo Rep.* (2020) 21:e49756. doi: 10.15252/embr.201949756
63. Munn DH, Mellor AL. Indoleamine 2,3 dioxygenase and metabolic control of immune responses. *Trends Immunol.* (2013) 34:137–43. doi: 10.1016/j.it.2012.10.001
64. Castro-Portuguez R, Sutphin GL. Kynurenine pathway, NAD(+) synthesis, and mitochondrial function: targeting tryptophan metabolism to promote longevity and healthspan. *Exp Gerontol.* (2020) 132:110841. doi: 10.1016/j.exger.2020.110841
65. Mellor AL, Munn DH. Tryptophan catabolism prevents maternal T cells from activating lethal anti-fetal immune responses. *J Reprod Immunol.* (2001) 52:5–13. doi: 10.1016/S0165-0378(01)00118-8
66. Pallotta MT, Orabona C, Volpi C, Vacca C, Belladonna ML, Bianchi R, et al. Indoleamine 2,3-dioxygenase is a signaling protein in long-term tolerance by dendritic cells. *Nat Immunol.* (2011) 12:870–8. doi: 10.1038/ni.2077
67. Chen W. IdO: more than an enzyme. *Nat Immunol.* (2011) 12:809–11. doi: 10.1038/ni.2088
68. Bello C, Heinisch PP, Mihalj M, Carrel T, Luedi MM. Indoleamine-2,3-dioxygenase as a perioperative marker of the immune system. *Front Physiol.* (2021) 12:766511. doi: 10.3389/fphys.2021.766511
69. Klaessens S, Stroobant V, De Plaen E, Van Den Eynde BJ. Systemic tryptophan homeostasis. *Front Mol Biosci.* (2022) 9:897929. doi: 10.3389/fmolb.2022.897929
70. Mylenko M, Boland S, Penkov S, Sampaio JL, Lombardot B, Vorkel D, et al. NAD⁺ is a food component that promotes exit from dauer diapause in *Caenorhabditis elegans*. *PLoS One.* (2016) 11:e0167208. doi: 10.1371/journal.pone.0167208
71. Iwaniak P, Owe-Larsson M, Urbańska EM. Microbiota, tryptophan and aryl hydrocarbon receptors as the target triad in Parkinson's disease—a narrative review. *Int J Mol Sci.* (2024) 25:2915. doi: 10.3390/ijms25052915
72. Ye X, Li H, Anjum K, Zhong X, Miao S, Zheng G, et al. Dual role of indoles derived from intestinal microbiota on human health. *Front Immunol.* (2022) 13:903526. doi: 10.3389/fimmu.2022.903526
73. Sanchez-Gimenez R, Ahmed-Khodja W, Molina Y, Peiró OM, Bonet G, Carrasquer A, et al. Gut microbiota-derived metabolites and cardiovascular disease risk: a systematic review of prospective cohort studies. *Nutrients.* (2022) 14:2654. doi: 10.3390/nu14132654
74. Chen X, Zhang H, Ren S, Ding Y, Remex NS, Bhuiyan MS, et al. Gut microbiota and microbiota-derived metabolites in cardiovascular diseases. *Chin Med J (Engl).* (2023) 136:2269–84. doi: 10.1097/CM9.0000000000002206
75. Levy M, Blacher E, Elinav E. Microbiome, metabolites and host immunity. *Curr Opin Microbiol.* (2017) 35:8–15. doi: 10.1016/j.mib.2016.10.003
76. Teunis CJ, Stroes ESG, Boekholdt SM, Wareham NJ, Murphy AJ, Nieuwdorp M, et al. Tryptophan metabolites and incident cardiovascular disease: the Epic-Norfolk prospective population study. *Atherosclerosis.* (2023) 387:117344. doi: 10.1016/j.atherosclerosis.2023.117344
77. Grohmann U, Fallarino F, Puccetti P. Tolerance, DCs and tryptophan: much ado about IDO. *Trends Immunol.* (2003) 24:242–8. doi: 10.1016/S1471-4906(03)00072-3
78. Fallarino F, Grohmann U, You S, McGrath BC, Cavener DR, Vacca C, et al. The combined effects of tryptophan starvation and tryptophan catabolites down-regulate T cell receptor ζ -chain and induce a regulatory phenotype in naive T Cells. *J Immunol.* (2006) 176:6752–61. doi: 10.4049/jimmunol.176.11.6752
79. Zelante T, Fallarino F, Bistoni F, Puccetti P, Romani L. Indoleamine 2,3-dioxygenase in infection: the paradox of an evasive strategy that benefits the host. *Microbes Infect.* (2009) 11:133–41. doi: 10.1016/j.micinf.2008.10.007
80. Matteoli G, Mazzini E, Liev L, Mileti E, Fallarino F, Puccetti P, et al. Gut CD103⁺ dendritic cells express indoleamine 2,3-dioxygenase which influences T regulatory/T effector cell balance and oral tolerance induction. *Gut.* (2010) 59:595. doi: 10.1136/gut.2009.185108
81. Grohmann U, Orabona C, Fallarino F, Vacca C, Calcinaro F, Falorni A, et al. Ctl α 4-Ig regulates tryptophan catabolism *in vivo*. *Nat Immunol.* (2002) 3:1097–101. doi: 10.1038/ni846
82. Puccetti P, Grohmann U. IDO and regulatory T cells: a role for reverse signalling and non-canonical NF- κ B activation. *Nat Rev Immunol.* (2007) 7:817–23. doi: 10.1038/nri2163
83. Gaspar F, Halmi D, Demjan V, Berkecz R, Pipicz M, Csont T. Kynurenine pathway metabolites as potential clinical biomarkers in coronary artery disease. *Front Immunol.* (2021) 12:768560. doi: 10.3389/fimmu.2021.768560
84. Romani L, Fallarino F, De Luca A, Montagnoli C, D'angelo C, Zelante T, et al. Defective tryptophan catabolism underlies inflammation in mouse chronic granulomatous disease. *Nature.* (2008) 451:211–5. doi: 10.1038/nature06471
85. Ala M, Eftekhari SP. The footprint of kynurenine pathway in cardiovascular diseases. *Int J Tryptophan Res.* (2022) 15:11786469221096643. doi: 10.1177/11786469221096643
86. Sudar-Milovanovic E, Glivic Z, Obradovic M, Zanic B, Isenovic ER. Tryptophan metabolism in atherosclerosis and diabetes. *Curr Med Chem.* (2022) 29:99–113. doi: 10.2174/0929867328666210714153649
87. Ramprasath T, Han YM, Zhang D, Yu CJ, Zou MH. Tryptophan catabolism and inflammation: a novel therapeutic target for aortic diseases. *Front Immunol.* (2021) 12:731701. doi: 10.3389/fimmu.2021.731701
88. Song P, Ramprasath T, Wang H, Zou MH. Abnormal kynurenine pathway of tryptophan catabolism in cardiovascular diseases. *Cell Mol Life Sci.* (2017) 74:2899–916. doi: 10.1007/s00018-017-2504-2
89. Van Nueten JM, Janssens WJ, Vanhoutte PM. Serotonin and vascular reactivity. *Pharmacol Res Commun.* (1985) 17:585–608. doi: 10.1016/0031-6989(85)90067-0
90. Cerrito F, Lazzaro MP, Gaudio E, Arminio P, Aloisi G. 5HT₂-receptors And serotonin release: their role in human platelet aggregation. *Life Sci.* (1993) 53:209–15. doi: 10.1016/0024-3205(93)90671-0
91. Ma Y, Liang X, Li C, Li R, Tong X, Zhang R, et al. 5-HT_{2A} Receptor and 5-HT degradation play a crucial role in atherosclerosis by modulating macrophage foam cell formation, vascular endothelial cell inflammation, and hepatic steatosis. *J Atheroscler Thromb.* (2022) 29:322–36. doi: 10.5551/jat.58305
92. Zelante T, Puccetti M, Giovagnoli S, Romani L. Regulation of host physiology and immunity by microbial indole-3-aldehyde. *Curr Opin Immunol.* (2021) 70:27–32. doi: 10.1016/j.coi.2020.12.004
93. Puccetti M, Xiroudaki S, Ricci M, Giovagnoli S. Postbiotic-enabled targeting of the host-microbiota-pathogen interface: hints of antibiotic decline? *Pharmaceutics.* (2020) 12:624. doi: 10.3390/pharmaceutics12070624
94. Kumar A, Sperandio V. Indole signaling at the host-microbiota-pathogen interface. *mBio.* (2019) 10:e01031-19. doi: 10.1128/mBio.01031-19
95. Cason CA, Dolan KT, Sharma G, Tao M, Kulkarni R, Helenowski IB, et al. Plasma microbiome-modulated indole- and phenyl-derived metabolites associate with advanced atherosclerosis and postoperative outcomes. *J Vasc Surg.* (2018) 68:1552–62.e7. doi: 10.1016/j.jvs.2017.09.029

96. Lu Y, Chong J, Shen S, Chammas JB, Chalifour L, Xia J. Trpnet: understanding tryptophan metabolism across gut microbiome. *Metabolites*. (2021) 12:10. doi: 10.3390/metabo12010010
97. Pulakazhi Venu VK, Saifeddine M, Mihara K, Tsai YC, Nieves K, Alston L, et al. The pregnane X receptor and its microbiota-derived ligand indole 3-propionic acid regulate endothelium-dependent vasodilation. *Am J Physiol Endocrinol Metab*. (2019) 317:E350–61. doi: 10.1152/ajpendo.00572.2018
98. Siddique S, Ahmad KR, Nawaz SK, Ahmad SN, Ali R, Inayat I, et al. Evaluation of the anti-inflammatory, analgesic, anti-pyretic and anti-ulcerogenic potentials of synthetic indole derivatives. *Sci Rep*. (2023) 13:8639. doi: 10.1038/s41598-023-35640-4
99. Zhang SS, tan QW, Guan LP. Antioxidant, anti-inflammatory, antibacterial, and analgesic activities and mechanisms of quinolines, indoles and related derivatives. *Mini Rev Med Chem*. (2021) 21:2261–75. doi: 10.2174/138955752166621011145011
100. Lee J, Lee W, Kim MA, Hwang JS, Na M, Bae JS. Inhibition of platelet aggregation and thrombosis by indole alkaloids isolated from the edible insect *Protaetia brevitarsis seoulensis* (kolbe). *J Cell Mol Med*. (2017) 21:1217–27. doi: 10.1111/jcmm.13055
101. Hajra S, Patra AR, Basu A, Bhattacharya S. Prevention of doxorubicin (DOX)-induced genotoxicity and cardiotoxicity: effect of plant derived small molecule indole-3-carbinol (I3C) on oxidative stress and inflammation. *Biomed Pharmacother*. (2018) 101:228–43. doi: 10.1016/j.biopha.2018.02.088
102. Li Q, Xia B, Wu J, Yuan X, Lu X, Huang C, et al. Indole-3-carbinol (I3C) protects the heart from ischemia/reperfusion injury by inhibiting oxidative stress, inflammation, and cellular apoptosis in mice. *Front Pharmacol*. (2022) 13:924174. doi: 10.3389/fphar.2022.924174
103. Singh N, Aggarwal RC, Singh CP. Cardiovascular activity of indole derivatives by incorporating oxadiazole, azetidinone and thiazolidinone moieties: a review. *Int J Drug Dev Res*. (2014) 6:30–9.
104. Ramakrishna K, Krishnamurthy S. Indole-3-carbinol ameliorated the isoproterenol-induced myocardial infarction via multimodal mechanisms in wistar rats. *Nat Prod Res*. (2022) 36:6044–9. doi: 10.1080/14786419.2022.2041632
105. Gu P, Wu Y, Lu W. New perspectives on the role and therapeutic potential of melatonin in cardiovascular diseases. *Am J Cardiovasc Drugs*. (2024) 24(2):171–95. doi: 10.1007/s40256-024-00631-x
106. Quintana FJ, Basso AS, Iglesias AH, Korn T, Farez MF, Bettelli E, et al. Control of T_{reg} and T_H17 cell differentiation by the aryl hydrocarbon receptor. *Nature*. (2008) 453:65–71. doi: 10.1038/nature06880
107. Stockinger B, Di Meglio P, Gialitakis M, Duarte JH. The aryl hydrocarbon receptor: multitasking in the immune system. *Annu Rev Immunol*. (2014) 32:403–32. doi: 10.1146/annurev-immunol-032713-120245
108. Gutiérrez-Vázquez C, Quintana FJ. Regulation of the immune response by the aryl hydrocarbon receptor. *Immunity*. (2018) 48:19–33. doi: 10.1016/j.immuni.2017.12.012
109. Bessede A, Gargaro M, Pallotta MT, Matino D, Servillo G, Brunacci C, et al. Aryl hydrocarbon receptor control of a disease tolerance defence pathway. *Nature*. (2014) 511:184–90. doi: 10.1038/nature13323
110. Moura-Alves P, Faé K, Houthuys E, Dorhoi A, Kreuchwig A, Furkert J, et al. AhR sensing of bacterial pigments regulates antibacterial defence. *Nature*. (2014) 512:387–92. doi: 10.1038/nature13684
111. Zelante T, Iannitti RG, Cunha C, De Luca A, Giovannini G, Pieraccini G, et al. Tryptophan catabolites from microbiota engage aryl hydrocarbon receptor and balance mucosal reactivity via interleukin-22. *Immunity*. (2013) 39:372–85. doi: 10.1016/j.immuni.2013.08.003
112. Pernomian L, Duarte-Silva M, De Barros Cardoso CR. The aryl hydrocarbon receptor (AhR) as a potential target for the control of intestinal inflammation: insights from an immune and bacteria sensor receptor. *Clin Rev Allergy Immunol*. (2020) 59:382–90. doi: 10.1007/s12016-020-08789-3
113. Dong F, Perdew GH. The aryl hydrocarbon receptor as a mediator of host-microbiota interplay. *Gut Microbes*. (2020) 12:1859812. doi: 10.1080/19490976.2020.1859812
114. Han H, Safe S, Jayaraman A, Chapkin RS. Diet-host-microbiota interactions shape aryl hydrocarbon receptor ligand production to modulate intestinal homeostasis. *Annu Rev Nutr*. (2021) 41:455–78. doi: 10.1146/annurev-nutr-043020-090050
115. Hou Y, Li J, Ying S. Tryptophan metabolism and gut microbiota: a novel regulatory axis integrating the microbiome, immunity, and cancer. *Metabolites*. (2023) 13:1166. doi: 10.3390/metabo13111166
116. Puccetti M, Pariano M, Wojtylo P, Schoubben A, Giovagnoli S, Ricci M. Turning microbial AhR agonists into therapeutic agents via drug delivery systems. *Pharmaceutics*. (2023) 15:506. doi: 10.3390/pharmaceutics15020506
117. Paeslack N, Mimmler M, Becker S, Gao Z, Khuu MP, Mann A, et al. Microbiota-derived tryptophan metabolites in vascular inflammation and cardiovascular disease. *Amino Acids*. (2022) 54:1339–56. doi: 10.1007/s00726-022-03161-5
118. Puccetti M, Pariano M, Costantini C, Giovagnoli S, Ricci M. Pharmaceutically active microbial AhR agonists as innovative biodrugs in inflammation. *Pharmaceutics (Basel)*. (2022) 15:336. doi: 10.3390/ph15030336
119. Puccetti M, Giovagnoli S, Zelante T, Romani L, Ricci M. Development of novel indole-3-aldehyde-loaded gastro-resistant spray-dried microparticles for postbiotic small intestine local delivery. *J Pharm Sci*. (2018) 107:2341–53. doi: 10.1016/j.xphs.2018.04.023
120. Modoux M, Rolhion N, Mani S, Sokol H. Tryptophan metabolism as a pharmacological target. *Trends Pharmacol Sci*. (2021) 42:60–73. doi: 10.1016/j.tips.2020.11.006
121. Puccetti M, Gomes Dos Reis L, Pariano M, Costantini C, Renga G, Ricci M, et al. Development and *in vitro-in vivo* performances of an inhalable indole-3-carboxaldehyde dry powder to target pulmonary inflammation and infection. *Int J Pharm*. (2021) 607:121004. doi: 10.1016/j.ijpharm.2021.121004
122. Guerra-Ojeda S, Suarez A, Valls A, Verdú D, Pereda J, Ortiz-Zapater E, et al. The role of aryl hydrocarbon receptor in the endothelium: a systematic review. *Int J Mol Sci*. (2023) 24:13537. doi: 10.3390/ijms241713537
123. Mannarino MR, Bianconi V, Scalisi G, Franceschini L, Manni G, Cucci A, et al. A tryptophan metabolite prevents depletion of circulating endothelial progenitor cells in systemic low-grade inflammation. *Front Immunol*. (2023) 14:964660. doi: 10.3389/fimmu.2023.964660
124. Fernstrom JD. A perspective on the safety of supplemental tryptophan based on its metabolic fates. *J Nutr*. (2016) 146:2601S–8. doi: 10.3945/jn.115.228643
125. Pakmehr A, Mousavi SM, Ejtahed HS, Hoseini-Tavassol Z, Siadat SD, Hasani-Ranjbar S, et al. The effect of fecal microbiota transplantation on cardiometabolic risk factors: a systematic review and meta-analysis. *Clin Ther*. (2024) 46:e87–e100. doi: 10.1016/j.clinthera.2023.11.015
126. Kennedy PJ, Cryan JF, Dinan TG, Clarke G. Kynurenine pathway metabolism and the microbiota-gut-brain axis. *Neuropharmacology*. (2017) 112:399–412. doi: 10.1016/j.neuropharm.2016.07.002
127. Parolisi S, Montanari C, Borghi E, Cazzorla C, Zuvadelli J, Tosi M, et al. Possible role of tryptophan metabolism along the microbiota-gut-brain axis on cognitive & behavioral aspects in phenylketonuria. *Pharmacol Res*. (2023) 197:106952. doi: 10.1016/j.phrs.2023.106952
128. Lewis CV, Taylor WR. Intestinal barrier dysfunction as a therapeutic target for cardiovascular disease. *Am J Physiol Heart Circ Physiol*. (2020) 319:H1227–33. doi: 10.1152/ajpheart.00612.2020