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Host-microbe tryptophan partitioning in cardiovascular diseases

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ABSTRACT

The functional interdependencies between the molecular components of a biological process demand for a network medicine platform that integrates systems biology and network science, to explore the interactions among biological components in health and disease. Access to large-scale omics datasets (genomics, transcriptomics, proteomics, metabolomics, metagenomics, phenomics, etc.) has significantly advanced our opportunity along this direction. Studies utilizing these techniques have begun to provide us with a deeper understanding of how the interaction between the intestinal microbes and their host affects the cardiovascular system in health and disease. Within the framework of a multiomics network approach, we highlight here how tryptophan metabolism may orchestrate the host-microbes interaction in cardiovascular diseases and the implications for precision medicine and therapeutics, including nutritional interventions.

1. Introduction

Cardiovascular disease (CVD) is a leading cause of mortality and morbidity worldwide [1]. CVD encompasses a number of conditions involving the heart and the vasculature, including coronary and peripheral artery disease, cardiomyopathy, heart failure, hypertension, hyperlipidemia, atherosclerosis, arrhythmias and stroke. Major contributors to the burden of CVD include environmental and behavioral factors (e.g., smoking, high cholesterol diet, high-salt diet, and physical inactivity) combined with non-modifiable predispositions (e.g., age, race, ethnicity, sex, and genetics) [2]. Despite the heterogeneity in symptoms and outcomes among the different CVD conditions, shared pathologies, such as maladaptive inflammation – i.e., chronic and sustained, inflammation – also occur in the clinic [3,4], as uncovered by the CANTOS study (further discussed in Section 2). Of interest, inflammation pivotally contributes to myocardial repair after infarction, a multi-stage process that, despite significant advances, is still an unmet medical need [5,6]. Indeed, hallmarks of cardiac regeneration have been described [7], which include, among others, recovery of immune homeostasis. A balanced activation of the innate immune system is necessary to clear necrotic cells, initiate angiogenesis, and promote repair, whereas rapid resolution of inflammation is required to allow regeneration. Regardless of its etiology, the progress of the acute inflammation to subacute and chronic stages eventually leads to tissue remodeling, fibrosis, loss of myocardium architecture and contractile function, and dilated cardiomyopathy [8]. As a matter of fact, inflammatory and cardiac remodeling biomarkers are elevated in patients with heart failure [9], immune- and autoimmune-mediated myocarditis [10–12], such that benefits from immunosuppressive therapy have been observed in virus-negative inflammatory myocarditis [13–15] and in post-COVID-19 vaccination hypersensitivity myocarditis [16,17].

Considering that environmental components, such as diet, physical activity and smoking, might exert some of their pathogenic effect via modification of the intestinal microbiome [18], there is increased appreciation of the gut microbiome and metabolome features of the cardiometabolic disease spectrum [19–22], as well as of the altered intestinal function in CVD [23]. These studies have highlighted how gut dysbiosis impacts on oxidative stress, inflammation and dysregulated immunity, all conditions concurring to the pathogenesis of cardiovascular diseases.

It has been suggested that a holistic approach is needed for the prevention and treatment of CVD [24], including the bona fide reconstitution of the heart muscle [7]. This calls upon the recently developed high-throughput technologies for the generation of “omics data”, which have provided a deeper understanding of the processes and dynamic interactions involved in human diseases. The bottom-up molecular approaches (genes, mRNA, protein, metabolite, etc.) have laid the foundation of current biological knowledge, yet a single “omics” discipline

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may be insufficient to capture the biological complexity of the cellular regulatory networks driving biological [25,26]. The holistic study of an organism in health, perturbation, exposure to environment and disease, demands for a systems medicine approach that, while mimicking the systems biology approach, relies on the use of omics-based science, systems biology, bioinformatics and network theory to identify early transitions to cardiovascular diseases and to accelerate the translation into clinical practice. Cardiomics is the multiomics network medicine field that combines cardiovascular medicine with the multiomics approach (Box 1).

Based on a perspective of multiomics network medicine approaches, we highlight here the relevance of host and microbial tryptophan partitioning for precision medicine and therapeutics, including nutritional interventions, in cardiovascular diseases.

2. Gut microbes in cardiovascular diseases

The human gastrointestinal tract is home to somewhere between 300 and 1000 different species that belong to five main phyla: Firmicutes and Bacteroidetes, representing approximatively 85–90% of the total microbiota, Actinobacteria, Proteobacteria, and Verrucomicrobia [46]. Gut microbes perform several key roles by breaking down different food components and nutrients and by synthetizing a range of metabolites acting locally and at distal sites [47]. The importance of these gut microbiota-derived metabolites is reflected by the fact that they make up an estimated 10% of all molecules circulating in mammalian blood [48]. Notably, even though the gut microbiota composition of an individual is as unique as a fingerprint, the metabolic functions are remarkably conserved between individuals [49]. Systems biology approaches that combine genomic with proteomic/metabolomic with the aid of machine learning tools, have been instrumental in deciphering the interaction and the consequence of it between microbes and their host [50]. Changes in the composition of the human gut-associated microbiota (i.e., dysbiosis) and accompanying functional changes in metabolism have been implicated in the etiology of several CVD ranging from atherosclerosis, thrombosis, heart failure and hypertension to obesity and insulin resistance [51,52]. Bacterial DNA can indeed be detected in the blood of patients with CVD reflecting intestinal dysbiosis [53]. An increased abundance of the Enterobacteriaceae family (*Escherichia--Shigella* genus) and *Streptococcus* genus, a reduced abundance of *Lachnospiranaceae* (*Blautia* genus, *Bifidobacterium, Faecalibacterium, Bacteroides, Prevotella, Akkermansia* and *Roseburia*) associated with a dysregulated metabolism of short chain fatty acids (SCFAs) – the end products of dietary fiber fermentation and the primary energy source for colonocytes that preserve the gut mucosal barrier – are common in conditions promoting cardiometabolic adverse manifestations [54–56]. SCFAs-producing bacteria are also decreased in hypertension [57], consistent with the ability of SCFAs to regulate vasodilation [58]. As a matter of fact, low fiber intake is associated with gut microbiota alterations in chronic heart failure [59]. An increase in abundance of *Enterobacteriaceae* and *Streptococcus* spp. was described in atherosclerotic cardiovascular disease [22], which was association with copies of bacterial genes coding for the enzyme TMA lyase responsible for the generation of trimethylamine-N-oxide (TMAO), a gut microbiome-derived metabolite that plays a prominent role in atherosclerotic plaque enhancement [60], by exacerbating the vascular wall's inflammatory reactions, promoting reactive oxygen species production, and inhibiting cholesterol reverse transport [61,62]. A high abundance of bacterial species linked to TMAO production and TMAO levels was also linked to chronic heart failure [63]. More recently, a study found that about 75% of microbiome and metabolome features that distinguish individuals with ischemic heart disease from healthy individuals, after adjustment for effects of medication and lifestyle, are present in individuals exhibiting dysmetabolism, suggesting that major alterations of the gut microbiome and metabolome might begin long before clinical onset of the disease [64]. The authors further categorized microbiome

Box 1
The emerging field of cardiomics.

In common with most chronic non-communicable diseases the pathogenesis of cardiovascular disease involves a complex interplay among polygenic susceptibility, aging, sex and a multitude of environmental exposure. Several studies have successfully applied integrative omics approaches for advances in the pathophysiology of cardiovascular diseases [27–29], including the computation definition of different human cardiac niches [30] and cardiac regeneration [31]. At the same time, network medicine, by integrating these multiomics data systematically, has emerged as an interdisciplinary field that integrates systems biology and network science data for precision medicine and therapeutics [32]. By leveraging the large amount of biomedical data generated, network medicine artificial intelligence and machine learning [33] have ushered in a new era in biomedicine. Below are an update of the main findings in the following omics that will likely help to move forward the goal of precision medicine in CVD.

Genomics and epigenomics. Genomics continues to lead the way by bringing revolutionary technologies to researchers and providing an anchor upon which all other omics layers are built. Monogenetic causes of heart failure and of cardiomyopathies have been extensively studied [34]. By fully sequencing the cardiomyopathy-associated genes, the next-generation sequencing (NGS) testing has tremendously expanded the potential of genetic evaluation [35] and the use of the polygenic risk score, which calculate an individual's genetic risk for developing cardiovascular diseases based on multiple common genetic variants [36]. Capitalizing on genome-wide association studies (GWAS), pharmacogenomics has revealed genetic variations that influence an individual's response to certain cardiovascular medications [37]. Epigenomic tools have brought forth a more holistic view of the interplay between the genome and a very active epigenome in CVD [38,39].

Transcriptomics. RNA-sequencing (RNA-seq) is now ubiquitously deployed to identify differential gene expression, and the advent of single-cell RNA-sequencing (scRNA-seq) has opened new windows into the cell-to-cell heterogeneity of transcription programs in CVD [40]. In combination with genotyping, RNA-seq has been instrumental in determining functional variants (eQTL) associated with cardiometabolic risk among thousands of candidate GWAS variants [41]. In addition, RNA-sequencing has revealed the occurrence of aberrantly regulated non-coding (nc) RNAs, including short microRNAs, long ncRNAs and circular RNAs, across various heart diseases, indicating that ncRNAs are critical contributors to cardiovascular pathophysiology [42] and are of value as potential biomarker-guided therapies and patient stratification [43].

Proteomics. Plasma biomarkers that reflect molecular states of the cardiovascular system are key to clinical decision making. Through emerging technologies, including discovery and targeted mass spectrometry, DNA aptamer, and antibody-based approaches [44,45], the systematic profiling through the comprehensive plasma proteome has provided opportunities for unbiased discovery of novel disease pathways, and novel biomarkers for diagnosis/prognosis/responses to therapy.

and metabolome signatures related to prodromal dysmetabolism, specific to ischemic heart disease. Thus, discriminant analysis based on specific microbiome and metabolome features could better differentiate individuals with ischemic heart disease from healthy individuals or metabolically matched individuals as compared to the conventional risk markers, pointing to a pathophysiological relevance of these features. Not secondarily – and when contextualized to the complex environmental factors involved in the pathogenesis of cardiovascular diseases – the gut microbiome impacts on blood pressure, being hypertension negatively associated with the abundance of certain *Lactobacillus* species [65] as well as the development and progression of atherosclerosis [66,67]. As already mentioned, while phenotypically diverse, accumulating evidence suggests various CVD share inflammation as a common pathology, a finding that motivates a systems-based, holistic view of cardiovascular research, despite the heterogeneity within the same disease [68]. Considering the crucial role played by the gut microbiome in regulating the immune system [69], it follows that certain dysbiosis can lead to chronic low-grade inflammation, a known risk factor for increased morbidity and mortality in several diseases, such as cardiovascular disease, cancer, diabetes, autoimmune and neurodegenerative disorders [70].

In this regard, particular interest must be placed on the role played by the microbiota in modulating the activity of inflammasomes [71], potent drivers of cardiac inflammation, which eventually leads to pathologic cardiac remodeling, cell death, and dysfunction [72]. In a study of 316 patients with acutely decompensated hearth failure, the concentration of IL-1β, a cytokine of inflammasomes, was associated with increased disease severity and risk of death [73,74]. Increased inflammasome activation was also detected in cardiac biopsy samples from patients with heart failure [75], and over activation of the atrial NLRP3 inflammasome was associated with the occurrence of atrial fibrillation, overgrowth of harmful bacteria (such as *Streptococcus, Enterococcus* and *Escherichia coli*) and lower levels of SCFAs-producing commensals in patients at risk [76]. These results provide evidence for the involvement of the inflammasome in the development of cardiac pathology and indicate the inflammasome as a potential therapeutic target. Some studies have investigated the role of inflammasome inhibition in heart failure through targeting either the inflammasome per se or its downstream cytokines. Some inflammasome inhibitors are currently being investigated in clinical trials in patients with heart failure. Anakinra, the recombinant form of the naturally occurring IL-1 receptor antagonist IL-1Ra, suppressed the systemic inflammatory response in patients with acute decompensated heart failure [77] and reduced mortality and morbidity in patients presenting ST-segment elevation myocardial infarction [78]. While confirming that CANTOS study on the reduction of heart failure-related mortality in patients treated with the IL-1β inhibitor canakinumab [79], these results substantiate the promising therapeutic potential of inflammasome inhibitors as anti-inflammatory agents in cardiac pathology, as suggested elsewhere [80]. On a final note, the gut microbiome also helps maintain the integrity of the intestinal barrier, which prevents the entrance of harmful substances into the bloodstream. Disruption of the gut barrier has been linked to an increased risk of atherosclerosis as it allows the translocation of bacterial products or endotoxins into the circulation, triggering inflammation and contributing to plaque formation [81].

Modulating the gut microbiome through dietary interventions, drug therapy, probiotics, or other means may have potential therapeutic implications for preventing or managing the cardiovascular risk. Dietary patterns have been associated with cardiometabolic risk reduction [82]. A commonality between these dietary patterns is the emphasis on plant-based foods, such as diets high in dietary fiber and fermentable substrate (ie, nondigestible or undigested carbohydrates) leading, as said, to SCFAs production. The impact of the western diet and life style on the burden of non-infectious degenerative diseases, so called "civilization diseases", is also well known and involves gut dysbiosis causing significant distortions of the fine-tuned metabolism that has evolved over millions of years of human evolution [83]. Consistent with the amelioration of myocardial damage in mice by fecal microbiota transplantation from healthy stools [84], core probiotic genera such as *Lactobacillus, Bifidobacterium, Saccharomyces, Streptococcus* and *Enterococcus* have been found to improve several risk factors of cardiovascular diseases by improving endothelial function and reducing the vascular inflammatory response, reducing TMO levels and the relative abundance of TMAO-producing groups of bacteria (*Clostridia,* Clostridiales and *Lachnospiraceae*) [85] and decreasing cholesterol levels, particularly, *A. muciniphila* [86]. Of interest, medications used in the cardiovascular settings, not to cite antibiotics [87], also affect the microbiota composition, as observed with statins [88], metformin [89] and aspirin that promotes a beneficial microbiota composition by enriching protective species such as *Bacteroides, Prevotella, Ruminococcaceae* and *Barnesiella* [90]. Thus, the microbiome and metabolome are two interconnected areas of research activity that could lead to the identification of microbiota signatures in the different human cardiac niches with a similar utility for diagnosis and prognosis of cardiac pathology, regeneration and repair.

3. Host and microbial metabolomics in cardiovascular diseases

Different from proteomics, metabolomics involves the systematic measure and study of small-molecule metabolites across biological systems using different biosamples. Consistent with the disturbed cardiac metabolism observed in most CVD [91] – and as a consequence of systemic disturbances in metabolism that occur in a variety of diseases [92] – it is not surprising that metabolomics studies have contributed to a better understanding of the global metabolic changes that occur across a spectrum of cardiovascular disease states [93,94]. Studies of the metabolome have identified specific metabolites that are associated with cardiovascular diseases [95]. Despite the heterogeneity of the results, these metabolites may serve as biomarkers or indicators of disease risk, progression, or treatment response [96]. Because the metabolome more accurately represents a cell's actions at the functional level, it may be considered complementary to genomes, transcriptomics, and proteomics [97]. By integrating genomic, epigenetic, transcriptomic, and proteomic variation, in conjunction with being responsive to environmental factors such as dietary intake, gut microbiota variation, physical activity, and environmental exposures, targeted and nontargeted metabolomics and the use of different metabolomics platforms— mainly nuclear magnetic resonance and mass spectrometry—have captured the complexity of CVD while offering the potential to identify new cardiovascular disease biomarkers. Indeed, among the "omics" sciences, metabolomics has brought a paradigm shift to metabolic research as it allows the quantification of hundreds of circulating metabolites across multiple pathways in a single measurement thus capturing the complexity of metabolic networks. Single biomarkers are no longer sufficient to interpret or characterize complex biological phenomena, and new metabolomic approaches recognize the importance of characterizing the interrelation of metabolites—the metabolic "fingerprint" of disease and preclinical disease states. In this way, the metabolomic profiling may identify metabolic changes that precede irreversible organ damage and the appearance of disease and thereby may lead to the early identification of individuals at high cardiovascular risk. In addition, metabolomics findings may lead to a better understanding of the pathophysiology and biological mechanisms involved in the genesis of cardiovascular diseases, thus paving the way to new, evidence-based approaches in preventing and managing these diseases [98]. Targeted metabolomics methods have already identified molecular markers and metabolomic signatures of cardiovascular disease risk (including branched-chain amino acids (BCAA) linked to insulin resistance and type 2 diabetes mellitus [99], bile acids and selected lipid species linked to hypercholesterolemia, insulin resistance, atherosclerosis and heart failure [100,101] and TMAO linked to heart failure [102,103], thus in effect linking diverse exposures such as those from dietary intake and

the microbiota with cardiometabolic traits [95,98]. Metabolomics research has also focused on lifestyle behaviors that can alter the natural history of CVD, including exercise- and diet-based interventions, given their pleiotropic role in attenuating the effects of multiple traditional risk factors. For instance, an active exercise involved an increase in plasma markers of glycogenolysis, lipolysis, and adenine nucleotide catabolism, better lipoprotein cholesterol profiles and higher levels of polyunsaturated relative to saturated fatty acids and lower BCAA [98]. Moving forward, it will be essential to determine whether the prognosis-associated metabolites are causative or simply markers of disease, whether their dietary or pharmacological modulation (i.e., pharmacometabolomics) alters both metabolomic signatures and the associated natural history of CVD in humans, in that the majority of metabolomics biomarker studies to date have examined plasma obtained from fasting individuals and thus are agnostic to effects of metabolite variation in the fed or challenged state. Disentangling the relative contribution of various medical comorbidities and interventions to circulating metabolite levels will be also important in assessment of the potential value of select metabolites as markers of CVD risk. Similarly, changes in metabolite profiles over time, with aging, or after administration of a drug need to be assessed to define an individual's predisposition for disease and response to therapy. Ultimately, the ability to efficiently and effectively use metabolomics tools to conduct molecular phenotyping could serve to substantially advance the goals of precision medicine in CVD, a complex and multifactorial disease entity for which an integrated approach to understanding and targeting the links between genetic predisposition and external risk exposures is especially needed.

4. Tryptophan at the host-microbiota interface: an untapped source of biomarkers and drug discovery in cardiovascular diseases

Amino acid metabolism disorders have been linked with a number of pathological conditions, including metabolic, cardiovascular, immune diseases and cancer [104]. Notably, adequate protein nutrition is paramount to supply indispensable amino acids [105]. In immunity, amino acid metabolism regulates the function of effector T cells and regulatory T cells, thus affecting immune homeostasis and critically controlling inflammatory-related mechanisms [106]. Although the contributions of lipids and carbohydrates have been studied for years, there is increasing appreciation of the role amino acids play in CVD. As mentioned, BCAA, including leucine, isoleucine, and valine, and their metabolites are important metabolic signatures [107]. However, at variance with the cardioprotection exhibited by glycine and arginine, different and even opposite effects have been associated with the presence of glutamine and methionine [108]. A growing appreciation in cardiovascular biology and CVD is being attributing to L-Tryptophan (Trp), an essential amino acid obtained exclusively from dietary intake in humans [109, 110]. Trp metabolites have been shown to be closely related to inflammation and therefore to be involved in cardiovascular disease [111]. In addition, dysregulation of the Trp pathway is observed in several conditions – such as senescence, atherosclerosis, diabetes, chronic kidney disease, cirrhosis, and cancer – closely connected to

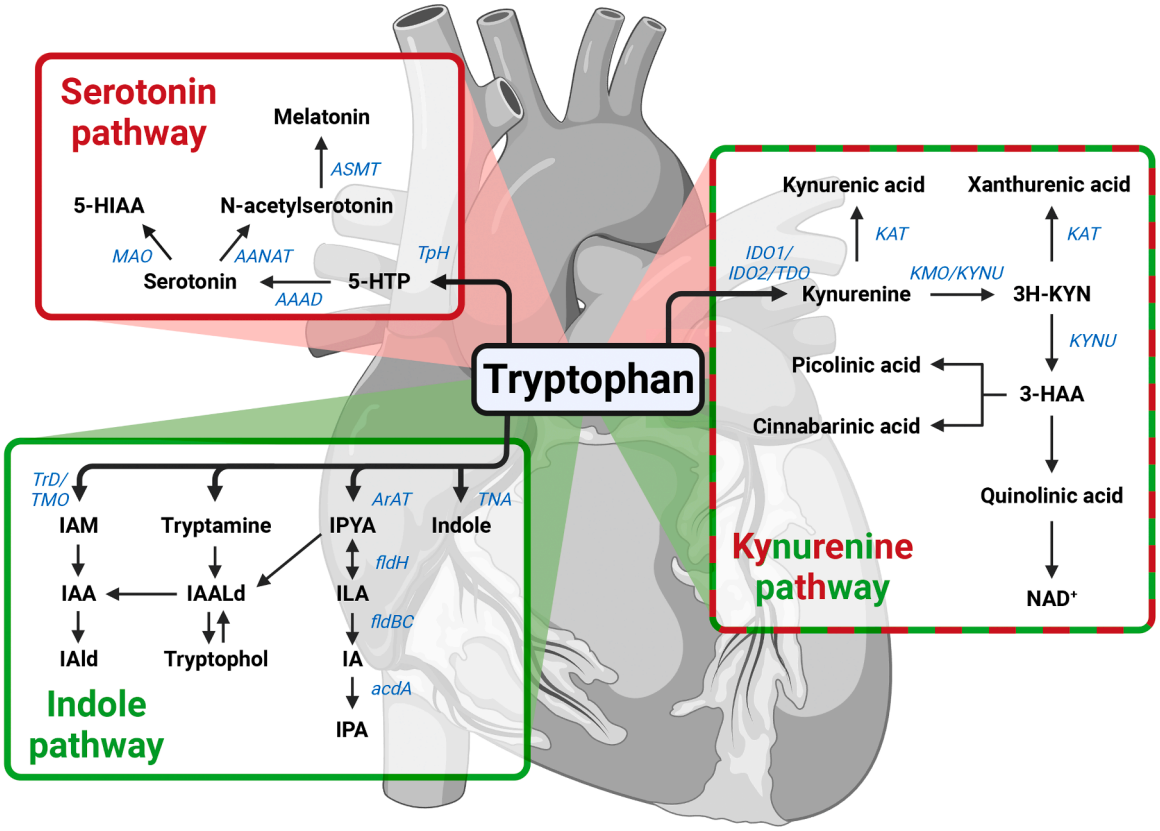

Fig. 1. The figure shows enzymes and metabolites of the different tryptophan metabolic pathways and the beneficial (green colored) or harmful (red colored) impact on cardiovascular diseases (see text for details). *ASMT*, Acetylserotonin O-Methyltransferase, *AANAT*, Aralkylamine N-Acetyltransferase, *AAAD*, Aromatic Aminoacid Decarboxylase, *MAO*, Monoamino Oxidase, *Tph*, Tryptophan Hydroxylase, 5-HTP, *5-Hydroxytryptophan*, 5-HIAA, 5-Hydroxyindoleacetic Acid; *TMO,* Tryptophan Monooxygenase, *TrD,* Tryptophan Decarboxylase, *ArAT,* Aromatic Amino Acid Aminotransferases, *TNA,* Tryptophanase, IPYA, Indole-3-pyruvate acid, *fldH*, Phenyllactate Dehydrogenase, *fldBC,* Phenyllactate Dehydratase, acdA, Acyl-CoA Dehydrogenase, ILA, Indole-3-lactic acid, IA, Indole acrylic acid, IPA, Indole-3-propionic acid, IAAld, Indole-3-acetaldehyde, IAM, Indole-3-acetamide, IAA, Indole acetic acid, IAld, Indole-3-aldehyde, *IDO1* and *2,* Indoleamine 2,3-Dioxygenase 1 and 2, *TDO,* Tryptophan 2,3-dioxygenase, 3-HAA, 3-Hydroxyanthranilic acid, 3 H-KYN, 3-Hydroxykynurenine, *KAT*, Kynurenine Aminotransferase, *KMO*, Kynurenine-3-Monooxygenase, *KYNU*, Kynureninase, NAD+, Nicotinamide Adenine Dinucleotide.

cardiovascular dysfunction. Trp is metabolized by the mammalian host into either the serotonin or kynurenine (kyn) pathway (Fig. 1). While the harmful vascular and cardiac effects of serotonin are well known [112], the kyn pathway – a major metabolic pathway of Trp degradation (>95%) in both bacteria and humans – has gained attention in CVD [113] and in the cardiovascular response to stress especially in ischemia [114]. Increased activity of the kyn pathway, that is, an elevated kyn/Trp ratio, has been observed in conditions such as atherosclerosis, myocardial infarction, vascular transplantation outcomes, heart failure and fatal cardiovascular events, conditions in which chronic inflammation plays a role (reviewed in [113]. However, the kyn pathway has been also associated with protection from incident CVD in chronic kidney disease [115] and atherosclerosis [116], a discrepancy to which the disparate effects of the different kyn metabolites on the cardiovascular system likely contribute. Indeed, kyn-derived metabolites induce oxidative stress, endothelial dysfunction, inhibit the activity of nitric oxide synthase and contribute to the progression of atherosclerosis. These metabolites are produced after the enzymatic conversion of Trp to N-formylkynurenine that is mediated by 3 enzymes, IDO1 (indoleamine-2,3-dioxygenase 1), IDO2, and TDO (tryptophan-2,3-dioxygenase). N-formylkynurenine is then converted to kyn and other bioactive metabolites such as anthranilic acid, kynurenic acid, 3-hydroxykynurenine, xanthurenic acid, 3-hydroxyanthranilic acid, and finally nicotinamide adenine dinucleotide (NAD+) (Fig. 1). Preclinical studies have shown that kyn and xanthurenic acid decrease blood pressure, but kyn also inhibit the production of nitric oxide; kyn and 3-hydroxyanthranilic acid prevent atherosclerosis; kynurenic acid supplementation and kynurenine 3-monooxygenase inhibition improve the outcome of stroke (reviewed in [113]). Of note, the IDO1/kyn pathway mediated the preservation of NAD+ during ischemic injury [117,118], a finding pointing to the beneficial effect of the kyn pathway in regeneration after cardiac ischemia. Considering that, with increasing age, the levels of NAD+ and of NAD-dependent histone deacetylases, Sirtuins, activity steadily decrease, this provides opportunities for Trp supplementation or diet-dependent modulation of NAD+ levels in heart failure-related cardiac remodeling and related pathology [119,120]. While these findings suggest a potential association between the kyn pathway and cardiovascular diseases, further research is needed for a clear understanding of the interdependency of the various arms of Trp metabolism, the exact downstream effects of Kyn metabolites and the establishment of causality.

That said, as the IDO1/kyn pathway has emerged as an important drug target with the development of several small molecules that are being tested in cancer and other diseases [110], the combination therapy with kyn pathway inhibitors and/or inducers could potentially be used to alleviate the therapy-induced cardiotoxicity. In this regard, it is worth mentioning that targeting specific components of the kyn pathway could potentially be exploited therapeutically in cardiovascular diseases in light of the knowledge that kyn and some metabolites are endogenous ligands of the Aryl hydrocarbon Receptor (AhR), a natural environment sensor endowed with potent immunomodulatory and antioxidant activities in different organs and at barrier sites [121]. Paralleling the link between environmental pollutants and cardiovascular diseases, the impact of AhR on the cardiovascular system is now well perceived and points to AhR as a key bridging molecule in the cardiovascular system, playing a role in both maintaining homeostasis and triggering pathogenesis [122], a finding consistent with its antagonistic pleiotropy function in regulating biological processes [123]. This may help to accommodate both the protective effect in atherosclerosis [124] and the deleterious effect in heart remodeling [125] of the IDO/kynurenine/AhR axis in cardiovascular diseases. Be defective or overactivated, dysfunctional AhR activity was found to be associated with abnormal cardiomyocyte differentiation and cardiac function, blood pressure, vascular dysfunction, and cardiovascular disease, such as myocarditis, hypertension, atherosclerosis, ischemic heart disease, and pulmonary arterial hypertension [122]. Cardiac hypertrophy and decreased cardiac output were observed in AhR knock-out mice [126] that were associated with overexpression of the hypoxia inducible factor-1alpha, a molecular marker of the myocardial response to ischemia [127]. Ultimately, the ability of AhR to multi-level tuning of the inflammatory and immune response [121], may predict a role in inflammatory cardiovascular diseases, including atherosclerosis.

In addition to kynurenines, endogenous AhR ligands include indigoids, heme metabolites, such as bilirubin, eicosanoids and dietary carotenoids, curcumin and indoles [128,129]. Nutritional studies have reported that diets rich in carotenoids [130] and indoles, derived from cruciferous vegetables [131], lead to healthier lives and reduced mortality from a number of chronic illnesses. Certain gut bacteria express enzymes responsible for Trp catabolism, more specifically decarboxylase and tryptophanase, thus producing indole metabolites, including indole pyruvic acid, indole propionic acid, indole acetic acid, indole-3-aldehyde, and indoxyl sulfate, known for their role in human health, from gut health to tissue repair and epithelial barrier strengthening [109,132,133] (Fig. 1). Beyond specific tissue types, indole derivatives may have broader implications in the cardiomics area. Research has indicated that indole derivatives possess cardiovascular protective properties, including antiplatelet and anticoagulant effects, which can be significant in preventing thrombotic events and promoting cardiac tissue repair [134]. Also, indole derivatives have shown anti-inflammatory and anti-oxidant properties, which can aid in tissue healing and regeneration [135]. Furthermore, the gut microbiome and its interaction with indole derivatives have gained attention in the context of tissue repair and regeneration. Ultimately, by affecting arterial blood pressure via peripheral and central serotonin signaling, indole and indoxyl sulfate have already been considered as being key mediators of the interaction between gut bacteria and the circulatory system [136]. Overall, despite the limitation of the context—and ligand—dependent AhR activity in the different organs [137,138]— the current major limitation of AhR-related therapies—indole derivatives offer a unique set of properties that make them promising candidates in cardiovascular diseases. As a matter of fact, in a recent metabolomic study, indole, indole-3-propionic acid and indole-3-aldehyde were significantly negatively associated with advanced atherosclerosis, while the kynurenine/Trp ratio was positively associated [139]. Of interest, building upon the concept of differential activation of AhR by host- derived vs. microbial derived ligands, a recent study has shown that the dynamic balance between host-derived and microbiota-derived ligands is required for the protective effect of AhR in ischemic stroke [140]. This suggests the potential role of these metabolites as new biomarkers for cardiovascular diseases and highlights the imperative need for the integration of the multi-dimensional omics data into a “cardiovascular systems biology” context.

5. Conclusion

Although the field of microbiome and metabolome research in the context of cardiometabolic diseases is still in its infancy, and more studies are needed to fully understand the intricate host/microbe interactions, this system approach could be likely exploited for omics-inspired biomarker discovery and targeted interventions in addition to hypothesis-driven interventions (Fig. 2). Strategies such as probiotics, prebiotics, and fecal microbiota transplantation have been explored for their effects on improving the gut microbiome composition and metabolic profiles in cardiovascular diseases. As to personalized medicine, the combination of microbiome and metabolome analysis also holds promise for personalized therapeutic and nutritional intervention approaches. Within the increasing global omics-based clinical trials market size (https://www.grandviewresearch.com/industry-analysis/omics-based-clinical-trials-market-report), this is a likely expectation.

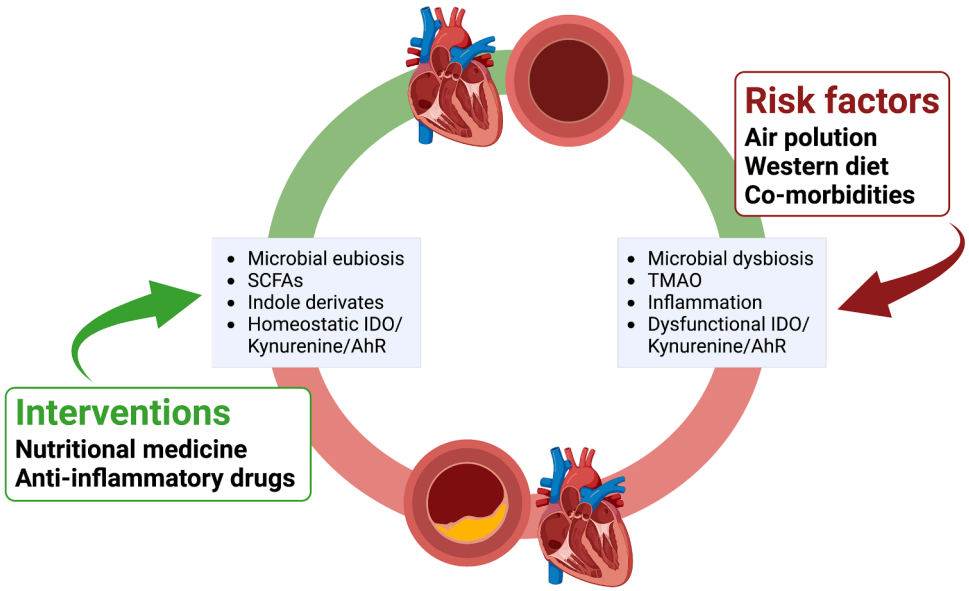

Fig. 2. The multiomics network medicine approach in cardiovascular diseases: relevance for patients' stratification and the implications for nutritional and pharmacological interventions.

CRediT authorship contribution statement

M.A.R., E.C., A.F. and M.F. conceptualized the article; C.C., E.N., V. O. P.P., and L.R. drafted the first and the revised version of the article, the graphical abstract and the figures. All authors read and agreed to the revised version of the manuscript.

Declaration of Competing Interest

None.

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