Computational and Structural Biotechnology Journal 21 (2023) 5434–5445

Contents lists available at ScienceDirect

Computational and Structural Biotechnology Journal

journal homepage: www.elsevier.com/locate/csbj

Review article

Exercise and microbiome: From big data to therapy

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ARTICLE INFO

Keywords:
Physical exercise
Microbiome
Microbiomics
Therapy

ABSTRACT

Exercise is a vital component in maintaining optimal health and serves as a prospective therapeutic intervention for various diseases. The human microbiome, comprised of trillions of microorganisms, plays a crucial role in overall health. Given the advancements in microbiome research, substantial databases have been created to decipher the functionality and mechanisms of the microbiome in health and disease contexts. This review presents an initial overview of microbiomics development and related databases, followed by an in-depth description of the multi-omics technologies for microbiome. It subsequently synthesizes the research pertaining to exercise-induced modifications of the microbiome and diseases that impact the microbiome. Finally, it highlights the potential therapeutic implications of an exercise-modulated microbiome in intestinal disease, obesity and diabetes, cardiovascular disease, and immune/inflammation-related diseases.

1. Introduction

Physical exercise provides numerous benefits for human health, including controlling weight, reducing the risk of chronic illnesses, enhancing cognitive abilities and improving cardiovascular function [1]. Increasing evidence suggests that exercise can protect a variety of diseases, including obesity, diabetes, cardiovascular disease, brain diseases, and neoplastic conditions. Regular physical activity and exercise training can enhance body weight control and cardiorespiratory fitness [1], thereby mitigating the incidence of type 2 diabetes mellitus [2–4]. Combining weight loss with aerobic and resistance exercise significantly improves functional status in obese older adults [5]. Exercise is crucial for attenuating cardiovascular risk factors and events [6,7], and it sustains cardiovascular health by promoting cardiac physiological hypertrophy, and inducing beneficial cardiac metabolic adaptations, angiogenesis, lymphangiogenesis and systemic responses [8–10]. In addition, there has been extensive studies into the relationship between physical exercise and mental health, especially in terms of Parkinson's disease, Alzheimer's disease, and major depressive disorder [11,12]. It has been demonstrated that engaging in physical activity could reduce cancer risk and restrict tumor growth [13], thereby contributing to cancer prevention and treatment [14–17]. Exercise improves human health through a variety of processes, including protecting the integrity of barriers, promoting repair and regeneration, maintaining local homeostasis and benefiting recycling and turnover [18]. Specifically, exercise inhibits excessive cytochrome C release from mitochondria to protect mitochondrial integrity, repairs DNA strand breaks and lesions by upregulating BDNF, activates angiogenesis production and $CD4^{+}$T cell proliferation to promote wound healing, and induces autophagy through AMPK-ULK1, FoxO, PGC1α signaling pathways to maintain cellular homeostasis [19–22]. As a consequence, improvements are observed in muscle function, cardiorespiratory fitness, gut microbiome diversity, metabolism, immunosurveillance and mental health [18].

The term 'microbiome' encompasses the genomes of both the microbiota and host, as well as the environmental conditions. These conditions include the products of the microbiota and the surrounding

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https://doi.org/10.1016/j.csbj.2023.10.034
Received 13 June 2023; Received in revised form 16 October 2023; Accepted 17 October 2023
Available online 19 October 2023

environment [23]. The microbiome, consisting of trillions of microorganisms, plays an important role in maintaining human health, including maintaining and strengthening the gut barrier, supporting the digestive system, promoting metabolism, maintaining immune function, and regulating neurocognition [24,25]. The multiple metabolites produced by the gut microbiota have been extensively investigated as mechanisms that influence diseases. Notably, lipopolysaccharide (LPS) , peptidoglycan, choline, secondary bile acids and short chain fatty acids (SCFAs) are mainly involved in regulating gluconeogenesis, insulin resistance, inflammatory cytokine release, cholesterol absorption, macrophage phenotype reprogramming and blood pressure [26–31]. Dysfunctions within the microbiome correlate with many diseases ranging from gastrointestinal disorders [32,33], metabolic issues [34–37], cardiovascular conditions [38–40], to inflammation-associated diseases [41–43]. Thus, the gut microbiome has a significant influence on human health.

The relationship between the gut microbiome and exercise has been elucidated in recent studies [44,45]. The composition of gut microbiome differs between those who engage in exercise and those not. Gut microbiome in elite athletes or people with moderate exercise tends to be more health-oriented and exhibits greater species diversity [45]. In those who exercise, there's a higher prevalence of gut microbes that produce beneficial metabolites like SCFAs and secondary bile acids. These microbes play a role in resisting chronic inflammation and bolstering immunity [44]. The association between gut microbiome and exercise is bidirectional. A healthier gut microbiome can enhance exercise capacity by regulating energy production, skeletal muscle maintenance, metabolism, and nutrient sensing pathways such as the mTOR and AMPK pathways [46]. Therefore, maintaining a healthy microbiome and engaging in regular exercise are pivotal for maintaining optimal human health [47,48].

In this review, we initially provide an overview of the evolution of microbiomics and associated databases, followed by a comprehensive description of the multi-omics technologies for microbiome. We then summarize the research on exercise-induced modifications of the microbiome as well as diseases influencing the microbiome. Finally, we discuss the potential therapeutic roles of exercise-induced microbiome in intestinal diseases, obesity and diabetes, cardiovascular disease, and immune/inflammation-associated diseases.

2. The evolution of microbiomics and databases

The study of microbiomics can be traced back to the upsurge of interest in biological systematics in the 1960 s. In 1977, Sanger first described the dideoxy chain-termination method for DNA sequencing. This method provided a new way to deduce the phylogenetic relationships of organisms. Based on nucleic acid sequences, it allowed for a more accurate determination [49]. Building upon this notion, the cellular world could be classified into eukaryotes, prokaryotes, and archaea based on organisms' rRNA [50]. The evolutionary relationships among different organisms were established in a reliable and quantitative manner based on phylogenetic characteristics. This significantly impacted traditional microbial classification rules that were predicated on nutritional and morphological characteristics. Therefore, this reliable and quantitative understanding of biological evolution should supplant traditional vague and ambiguous microbial classification criteria [51]. The broad utilization of 16 S and 18 S rRNA as molecular markers for prokaryotes and eukaryotes, respectively, markedly propelled the field of microbiology. Traditional microbiological research was based on pure culture techniques, but a considerable portion of microorganisms in nature pose difficulties in culture within laboratory settings [52]. The variable regions of 16 S rRNA was targeted as amplicons to systematically study bacteria, marking a shift in microbiology from culture-based methods to culture-independent molecular biology approaches. The total DNA in a specific environment could be approached as a collective entity and assessed microbial genomics diversity by estimating the richness of microbial species based on total DNA. The concept of 'soil metagenome' was raised subsequently which enabled more comprehensive study of microbial diversity from different perspectives [53]. Concurrently, in a collaborative project, seven European labs proposed a method to isolate, amplify, and sequence 16 S rRNA from fecal samples in order to monitor the dynamic changes in gut microbiota in response to diet. This technique has had considerable success in subsequent studies, demonstrating that the variety of microbiota increases with age [54].

The development of microbial genomics-based classification criteria and dynamic monitoring techniques has provided a foundation for understanding microbial diversity. A significant number of oligonucleotide probes have also laid groundwork for microbial identification. However, to enhance detection resolution, the development of more microbial databases and standard genomic libraries is urgently required. Before the Human Microbiome Project, there were early attempts to establish microbial databases, such as the human oral microbiota database [55]. Following the completion of the Human Genome Project, the Earth Microbiome Project and the Human Microbiome Project were launched successively. The interaction between humans and microbes forms a 'superorganism' that has extensive interactions. To gain a deeper understanding of human health needs, identify microbial health markers, and provide rational dietary recommendations, the Human Microbiome Project sequenced microbial populations in five major habitats: the oral cavity, nasal cavity, skin, urogenital tract, and gastrointestinal tract [56]. The subsequent Integrated Human Microbiome Project viewed as the second phase of the Human Microbiome Project, focuses on research areas such as pregnancy and preterm birth, inflammatory bowel disease, and diabetes with different predisposing factors. It aims to elucidate the relationship between microbiota and the host, while providing a research framework for microbiome studies [21]. In 2017, the Global Microbiome Project was launched with the objective of establishing a standardized microbiome database worldwide. One hundred microbiologists from around the world are working to collect and analyze microbiome genomic information from various countries and regions [57]. To investigate the role and function of the microbiome, the Unified Human Gastrointestinal Protein (UHGP) and the Unified Human Gastrointestinal Genome (UHGG) microbiome data assemblage and reference genome databases were established [58].

The development of microbial databases can be seen as a microcosm of the broader progression in microbial technology. In a way, it mirrors the research necessities in the field of microbiology. Generating microbiome data involves several key steps. Researchers first collect microorganisms from the environment, animals, or plants. Subsequently, they extract DNA, RNA, proteins, or metabolites from these collected microorganisms. The final stage involves both quantitative and qualitative analyses of these extracts [59].

Researchers obtain raw data for metagenomics and metatranscriptomics by sequencing either genomic DNA or reverse transcribed cDNA. This is followed by assembly, mapping, and annotation of the captured data [60]. Technologies such as mass spectrometry are utilized to identify and analyze proteins or metabolites of microbiota. This aids in obtaining data on microbial proteins and metabolomics. By collecting and organizing various sets of data, the database has greatly promoted the development of multi-omics within the microbiome field.

Microbiome databases can be categorized into three types based on their functionalities. The first kind facilitates the storage, querying, and downloading of raw data. Here, researchers curate standardized datasets from public repositories or various projects and establish pathways for data uploads to support microbiome research. The second database type centers around assembly, annotation, and classification, providing structured information and reference genomes for microbiome researchers. The third variant directly processes and summarizes microbial data allowing researchers to discern changes in microbial abundance across different environments. Collectively, these databases all contribute to the advancement of microbiome research. In this review, we have summarized microbiome-related databases or online

tools in the table (Table 1).

3. Multi-omics for microbiome

Multi-omics for microbiome has emerged as a powerful tool for high-throughput analysis of intricate microbial communities. This includes metagenomics, metatranscriptomics, metaproteomics, metabolomics and scRNA-seq for microbiome, providing comprehensive and unprecedented insights into the study of microbiome (Fig. 1).

3.1. Metagenomics

Metagenomics investigates the genomes of microbiota directly extracted from environments. It not only focuses on the genome of individual microorganisms but also emphasizes the genetic information of the entire microbiota. Metagenomics is a powerful method for studying the classification and function of the microbiome.

Broadly speaking, metagenomics includes two main approaches: marker-based sequencing and whole-genome sequencing. Marker-based sequencing involves the use of markers like 16 S rRNA/rDNA for bacteria and archaea, 18 S rRNA/rDNA for eukaryotes, and ITS sequencing for fungi. This marker-based sequencing method is also known as amplicon sequencing. Amplicon sequencing plays a crucial role in studying phylogeny, microbial classification, and changes in compositional abundance. It allows for the rapid analysis of small biomass samples, even without concerns about contamination from host DNA [61].

While amplicon sequencing offers the advantage of quickly assessing microbial community structure, it also comes with certain limitations. Amplicon sequencing focuses solely on specific gene regions, which poses several drawbacks. Due to the omission of a large portion of the genetic information, microbial classification may be inaccurate, particularly in cases involving highly similar sequences within the target gene regions. Furthermore, the classification resolution of amplicon sequencing is typically restricted to the genus level and is heavily influenced by PCR bias [59]. Furthermore, amplicon sequencing has significant limitations in the study of microbial functions. It does not provide information about the metabolism and functions of microorganisms. Since amplicon sequencing relies on PCR amplification, it may result in the loss of some low-abundance microbial sequences.

Compared to the genus-level resolution of amplicon sequencing technology, metagenomic sequencing can also facilitate functional analysis of the microbiome. Additionally, metagenomic sequencing technology can enhance species resolution to the level of individual species or even strains [61]. The diversity of human intestinal archaeal viruses was revealed through a comparative analysis of metagenomic sequencing and existing archaeal virus sequences [62]. In addition, metagenomic sequencing enables the functional annotation of microorganisms within various habitats by analyzing functional gene clusters. For instance, metagenomics can identify the taxonomy of microbiome, and detect antimicrobial resistance and bacteriophages. Thereby, metagenomics can enhance our understanding of microbiota [63].

However, while metagenomic sequencing offers insights into the functions of microorganisms, deducing their functional and metabolic potential can be challenging. This sequencing process requires the assembly of short reads, and due to the vast diversity and complexity of microorganisms, many of these reads lack a reference genome. Therefore, the assembly of microorganisms, especially from highly complex samples, becomes particularly challenging [59]. Furthermore, given the high sensitivity of metagenomic sequencing, sample contamination and degradation can profoundly impact the results [61]. Both DNA degradation and contamination can compromise the quality of metagenomic data.

Table 1
Multi-omics for Microbiome Related Databases or Online Tools.

Name	Website	Description
CRAMdb [145]	http://www.ehbio.com/CRAMdb	CRAMdb collects 516 animals from 475 projects. It concentrates on noted metagenomics from different kinds of animals (exclude human). It allows users analysis the composition and associations of microbiome.
MGnify [146]	https://www.ebi.ac.uk/metagenomics	MGnify provides an automate process to manage microbiome data. It allows users to assemble, infer and analysis microbiome data. Users can upload their own data for the repository purpose or request datasets in European Nucleotide Archive (ENA) for study purpose.
IMG/M [147,148]	https://img.jgi.doe.gov/m/	IMG/M database offers data uploading, annotation and analysis service. Now, it contains more than 200,000 datasets, 27 T basepairs and 77B genes of genomes and microbiomes information.
Greengenes2 [149] Greengenes [150]	http://ftp.microbio.me/greengenes_release/	Greengene is a 16 S rRNA and metagenomics database and can be used for taxonomic annotation. Recently, a new version Greengene2 has been released.
Animalmetagenome DB [151]	https://doi.org/10.6084/m9.fgshare.19728619	Animalmetagenome DB collected 82,097 metagenomes from 4 kinds of livestock and 540 wildlife. The sequencing raw data can be downloaded in fgshare.
MarinemetagenomeDB [152]	https://webapp.ufz.de/marmdb/	MarinemetagenomeDB allow users quickly download marine metadata which are stored in public database STA and MG-RAST.
ADDAGMA [153]	http://addagma.omicsbio.info/	ADDAGMA collects the different kind of livestock's gut metagenomics in other public databases. It allows users search and download microbe-phenotype related data.
HumGut [154]	http://arken.nmbu.no/~larssn/humgut/	HumGut includes the microbiome data of healthy human guts.
GMrepo [155,156]	https://gmrepo.humangut.info	GMrepo is a manual screening humankind databases, including 71,642 samples from 353 studies with 132 humankind characters.
gutMEGA [157]	http://gutmega.omicsbio.info/	gutMEGA collects 59,132 metagenomics cases including 776 conditions. Users can use advanced search function in the database to find their interesting data.
TerrestrialmetagenomeDB [158]	https://webapp.ufz.de/tmdb/	TerrestrialmetagenomeDB aims to help researchers to search interest land metagenomics data easier, containing about 15,022 terrestrial metagenomic data

(continued on next page)

Table 1 (*continued*)

Name	Website	Description
		from SRA and MG-RAST databases.
HumanmetagenomeDB [159]	https://webapp.ufz.de/hmgdb/	HumanmetagenomeDB aims to help researchers to search interest mankind metagenomics data easier, containing about 69,822 human metagenomic data from SRA and MG-RAST databases.
UNITE [160]	https://unite.ut.ee/	UNITE is an online sequence databases for fungi, including approximatedly 1,000,000 fungal ITS sequences. It regularly updates its data by exchanging information from other databases
PLSDB [161]	https://ccb-microbe.cs.uni-saarland.de/plsdb	PLSDB collect 13,789 plasmid terms from NCBI nucleotide databases. The web server can help user's blast and analysis additional meta data and plasmids information in an interactive way.
FUNGuild [162]	http://www.funguild.org/	FUNGuild is a python-based annotation tool for fungal community classification. It depends on ecological guide rather than sequencing platform. It contains over 13,000 fungal taxa in the dependent databases.
PATRIC [163]	https://ngdc.cncb.ac.cn/databasecommons/database/id/230	PATRIC is a comprehensive database that aims to combine bioinformatics and analysis methods. It focuses on research about important pathogens.
SILVA [164]	https://www.arb-silva.de/	SILVA offers extensive, quality-assured, and frequently refreshed ribosomal RNA (rRNA) sequences, including small subunit (16 S/18 S, SSU) and large subunit (23 S/28 S, LSU), for all three domains of life (Bacteria, Archaea, and Eukarya).
MG-RAST [165]	https://www.mg-rast.org/	MG-RAST is a database focusing on metagenomics. It allows users upload or download metagenome data. Users can also use the open source code to classification, functional classification and comparison.

3.2. Metatranscriptomics

Metatranscriptomics is used to study the RNA sequences of specific microbiota , revealing the functions of microbial communities by examining the entire microbial transcriptome in a given environment [64]. Metatranscriptomics focuses on how external factors affect gene expression in microbial communities. For example, in a study where eight soil metatranscriptomic samples were taken from areas with stable natural temperature gradients, researchers were able to determine if and how microbes adjusted their cellular activity and function in response to climate changes [65]. Another study demonstrated differences in gut microbiota during acute inflammatory responses by measuring the metatranscriptome, suggesting that specific microbiota can exist in many functional states depending on the immune status of the host [66]. Compared to metagenomics, metatranscriptomics provides more detailed and dynamic information. For example, it can reveal the microbial response to environmental shifts (e.g., host immune status), and offer insights into the activities and characteristics of non-coding RNAs [67]. Metatranscriptomics is an important tool for studying gene expression in microbiota, reflecting, to a degree, the functional and metabolic potential of microorganisms. However, metatranscriptomics captures transient snapshots in dynamic ecosystems and may not fully reflect the dynamics of ecosystems. Since low-abundance species tend to produce limited mRNA, metatranscriptomics might struggle to detect low-abundance mRNA and may display a bias toward microorganisms with high transcription rates [59]. Furthermore, microorganisms often undergo numerous post-transcriptional and post-translational modifications when encountering different environmental stresses. Therefore, metatranscriptomics may require combined analysis with microbial metabolome methods when inferring specific metabolic activities.

3.3. Metaproteomics

The concept of 'metaproteomics' was first introduced around 2004 when protein components were extracted from a laboratory-scale activated sludge system [68]. The metaproteome comprises the entirety of proteins expressed by environmental microorganisms at a given moment [68]. Metaproteomics enriches data derived from metagenomics and metatranscriptomics, offering a more comprehensive insight into the biological signatures of microbes. In metaproteomics, researchers do not need to account for the influence of dead microorganisms and can directly detect functional changes in living microbes. However, due to the complexity of metaproteomics, and despite decades of development, the field is still in its infancy. Moreover, the results of metaproteome analysis can be influenced by the databases used for identification, quantification, and functional annotation [69]. Compared to the metagenome, metaproteome database resources are relatively limited, not encompassing the protein information of all microbial species. Thus, database selection presents a big challenge [70]. For secretory proteins, sampling can be problematic in metaproteomics, especially when reference databases are lacking. It can be tough to distinguish proteins from food debris in fecal matter. In addition, identifying distinct proteins is challenging due to the high presence of structural proteins in microbial communities. Unlike transcriptomes, which can instantaneously reflect microbial states in response to environmental changes, the metaproteome can only indicate shifts in microbial community functions to a certain degree due to protein modifications and the absence of protein subcellular localization data.

3.4. Metabolomics for microbiome

The microbial metabolome encompasses all metabolites derived from the microbial community, including small molecule compounds like glucose, fatty acids, amino acids, and nucleotides. The metabolome provides a comprehensive description of an organisms' metabolic profile in *vivo*, offering insights into the metabolic characteristics and alterations of the organism under various physiological, biochemical, and pathological states. It is universally acknowledged that microorganisms and hosts exist in a symbiotic state. This symbiosis largely depends on the diverse ecological niches within metabolism, wherein microorganisms rely on small molecules supplied by the host for metabolism, with their metabolites subsequently reverting back to the host organism [71]. However, identifying microbiome-host interactions based on metabolites presents many challenges. Metabolites secreted by microorganisms often resemble or are identical to those found within the host. Moreover, functional metabolites often need to be secreted outside the microbial community to exert biological functions. Therefore, drawing direct conclusions from the metabolome about the relationship between microorganisms and other organisms can be elusive. To address this, researchers frequently employ joint-analysis of host metabolomes (e.g.,

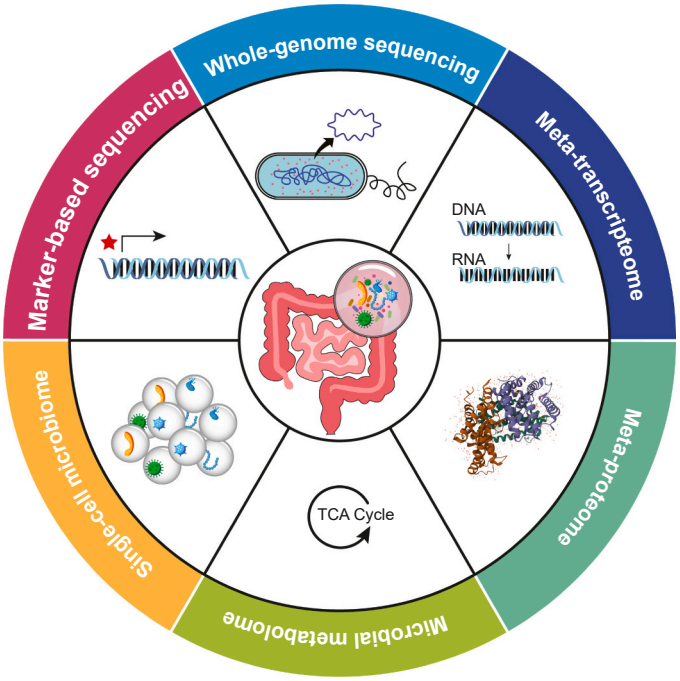

Fig. 1. Multi-omics Techniques for Microbiome and Their Characteristics. Multi-omics techniques for microbiome, including metagenomics (marker-based sequencing and whole-genome sequencing), metatranscriptomics, metaproteomics and microbial metabolomics, offer a broad perspective on microbial abundance changes, gene expression and metabolic features. In addition, single-cell RNA-seq technique for microbiome provides an in-depth, high-resolution insight into microbial behavior at the cellular level.

human fecal or plasma metabolome) and metagenomes to study microbial and host metabolic relationships. Alternatively, they might use isotope labeling to confirm a direct metabolic connection between the host and microorganism.

3.5. High-throughput single-cell technology for microbiology

Although current multi-omics methods for microbiome adequately perform species identification and functional analysis of biological communities, they often fail in detecting the genetic potential and functional diversity of microorganisms at the cellular level. Notably, detecting low-abundance microorganisms is especially challenging. Single-cell microbial sequencing emerges as a viable solution to these challenges [72]. The novel microbial single-cell RNA-seq technology, combining microbial analysis with single-cell RNA-seq technology, does not treat the microbial community as a homogeneous population. Instead, it categorizes microorganisms into functional subgroups based on their genetic profiles. The recent evolution of single-cell RNA-seq technology has paved the way for its application in microbial populations. Technological advancements such as microfluidic droplet-based [73] techniques and split-pool barcoding technologies [74] have lent critical support to single-cell microbial sequencing. This technique has been utilized for higher-resolution biological phenomena, including the study of mobile genes between microbes and hosts [75], viruses and microorganisms [76], and various cell types [77]. Although microbial single-cell RNA-seq has been successfully applied to both the environmental and human-related microbiome, several challenges exist. For example, the diversity of cell wall structures in complex communities combined with the instability of low-abundance mRNA pose great challenges to the microbial single-cell RNA-seq technology [72].

3.6. The computation challenges of multi-omics for microbiome

The metagenomic analysis framework was established over a decade ago, and has been continually refined since then [78–81]. However, in recent years, the exponential growth of microbiome data has introduced significant computational challenges to microbial multi-omics analysis. One primary challenge is the classification and identification of microorganisms. Although several methods currently exist for the classification of microbial multi-omics—such as marker-based algorithms like MetaPhlAn2 [82] and mOTUs2 [83], DNA-based algorithms like metaOthello [84] and taxMaps [85], and protein-based algorithms like DIAMOND [86], Kaiju [87] and MMseqs2 [88]–their efficacy varies across different evaluation metrics [89].

4. The impact of big data on exercise-induced microbiome

Exercise, a vital aspect of lifestyle, renders positive effects on human health. Regular and moderate exercise offers benefits for both physical and mental health. Large-scale clinical studies indicate that physical exercise can decrease the risk of chronic diseases and improve various disease outcomes [62,90–94]. Exercise can decrease all-cause mortality from cardiovascular disease and cancer [95]. Compared to participants who do not engage in vigorous physical activity, those whose vigorous physical activity accounts for 50%– 70% of their overall activity observed a 17% decrease in all-cause mortality from cardiovascular disease and cancer [96]. Moreover, participants who maintain regular exercise tend to have a better prognosis [97].

The mechanisms underlying the beneficial effects of exercise are diverse and complex. For instance, exercise can prompt muscles to release factors that promote liver autophagy, offering metabolic advantages that protect liver function [98]. A surge in exercise-related anti-inflammatory factors can be detected in plasma post-exercise. These factors were shown to exert a positive effect on learning and memory [99]. Additionally, there is evidence indicating that exercise can also confer its benefits by regulating the gut microbiome [46,100,101]. The composition of the gut microbiome is largely influenced by external stresses, such as types of exercise and emotional stress, as well

as dietary habits [63,102–104].

Exercise-induced changes in the microbiome can enhance an individual's exercise capacity through metabolic pathways. For instance, post-exercise fecal samples from marathon runners, revealed an increase in *Veillonella atypica*. Inoculating mice with this genus significantly enhanced their exercise capacity. Isotope tracing determined that this increase in exercise capacity resulted from the bacterium's unique ability to metabolize lactate into propionate [95]. Furthermore, exercise can induce adaptive changes in gut microbiota with these changes potentially augmenting exercise capability. Notably, professional cyclists displayed variations in the abundance of *Methanobrevibacter smithii*, which is linked to methane, energy, and carbohydrate metabolism, compared to amateur cyclists [105]. Moreover, voluntarily exercising rats showed alterations in the levels of short-chain fatty acids, n-butyrate, and associated microbes compared to sedentary counterparts [94].

Exercise-induced variations in the microbiota can benefit individuals by metabolizing molecules that are advantageous to health. Analysis of public databases on the composition of the gut microbiome in athletes revealed a marked increase in the metabolism of short-chain fatty acids. Some microbial communities in athletes were capable of metabolizing and producing beneficial molecules like vitamin B12, substantiating the symbiotic relationship between the host and its gut microbiome [106]. Similarly, metagenomic and metabolomic studies found that the athlete group had significant enrichment in amino acids, antibiotic biosynthesis, and carbon metabolism pathways, in conjunction with high relative content of short-chain fatty acids (SCFAs) such as propionate, acetate, and butyrate [107].

Although other research reached similar conclusions, it asserted that the frequent combination of extreme diets with an athletic lifestyle makes it challenging to determine whether the changes in specific microbiota are purely exercise-induced or the result of an interplay between exercise and extreme diet [108].

Exercise-induced changes in microbiota can affect the motivation to exercise through the gut-brain axis. Recent discoveries highlight a gut-brain metabolic axis pathway, where gut microbes prompt the brain to produce more dopamine, thereby enhancing exercise motivation [109]. This provides fresh insights and concepts regarding the symbiotic relationship between gut microbes and the host.

Clearly, exercise-induced changes in microbiota play a crucial role in the benefits of exercise. A wealth of evidence demonstrates that exercise can protect individuals from diseases [1–9,11–16]. However, it remains to be determined whether the health advantages attributed to exercise can be linked directly to changes in the gut microbiota. Nevertheless, some current studies suggest a correlation between exercise-induced changes in microbiota and protective functions.

5. The role of big data in disease-related microbiome

Under normal circumstances, the human gut microbiome maintains a relatively balanced state, with a low abundance of components that produce harmful metabolites. Diverse factors, including poor diet and chronic infections, can lead to imbalances in the gut microbiome [110]. Numerous studies, based on big data analysis of human disease samples, have shown that disorders in the gut microbiome are associated with the onset and progression of several diseases, including neurological disorders, mental illnesses, cardiovascular diseases, gastrointestinal issues, autoimmune diseases, metabolism-related conditions, and tumors [32].

5.1. Obesity and diabetes

The worldwide prevalence of obesity and related health complications is escalating, with overeating identified as a major contributing factor. A correlation between food addiction in obese women and gut microbiome dysbiosis has been identified [111]. To investigate the gut microbiome characteristics of obese women more comprehensively, obese patients (OB) and normal weight (NW) women were enrolled. Analysis was conducted using various methods including 16 S rRNA sequencing, metagenomics sequencing, metatranscriptome sequencing, and targeted lipidomics. A highly diverse gut microbiome was revealed in NW women, exhibiting a high transcriptional activity. Fecal samples from NW women were enriched in secondary bile acids and GABA, both of which are critical to gut-brain communication in healthy individuals. Conversely, the gut microbiome of OB women was less diverse. There was a decreased abundance of the *Lachnospiraceae* and *Ruminococcaceae* families, known for producing SCFAs and contributing to health maintenance. Moreover, there was an increased abundance of the Ruminococcus genus, particularly species such as *Ruminococcus* torques, *Ruminococcus* obeum, and *Ruminococcus bromii*, all of which are associated with disease. These findings suggest a detrimental impact on gut-brain communication in obese women [112].

Growing evidence suggests that gut microbiome significantly impacts the progression of type 2 diabetes. Three microbiome genera, *Ruminococcus*, *Fusobacterium*, and *Blautia*, have been identified as having a positive correlation with type 2 diabetes. In contrast, five microbiome genera, *Akkermansia*, *Bifidobacterium*, *Faecalibacterium*, *Bacteroides*, and *Roseburia*, show a negative correlation [113]. Specific gut microbiome genera influence the digestion and absorption of glucose as well as the production of digestive hormones, consequently affecting glucose metabolism [114]. Additionally, some gut microbiome species can impact the intestinal barrier function, potentially affecting the onset of type 2 diabetes [115]. For instance, *Bifidobacterium lactis* enhances glycogen synthesis and glucose absorption, ultimately reducing blood glucose levels [116]. Additionally, two bacteria types, *Bacteroides vulgatus* and *Bacteroides dorei*, have been found to increase the expression of genes that preserve intestinal barrier function. This reduces intestinal permeability, preventing harmful metabolic products from gut bacteria from entering the bloodstream. Furthermore, lipopolysaccharides, once they cross the intestinal barrier and enter the bloodstream, can lead to chronic inflammation in the body [117].

5.2. Cardiovascular diseases

Cardiovascular disease (CVD) represents a significant threat to human health, accounting for approximately 17 million deaths globally each year [118]. In the last decade, several clinical studies have revealed the profound role of the 'gut-heart axis' in various CVDs, signifying the association between cardiovascular health and gut microbiota as a critical research area. Atherosclerosis (AS), the pathological foundation of CVD, lacks effective targeted therapeutic interventions. A significant negative correlation between the abundance of *Parabacteroides merdae* and CVD has been found. Transplanting ApoE$^{-/-}$ atherosclerosis mice with a human-origin strain of *Parabacteroides merdae* significantly alleviated atherosclerosis symptoms. Subsequent targeted metabolomic analysis revealed an increased concentration of branched SCFAs in mouse feces and a decrease in fecal and blood branched-chain amino acids post-transplantation [119]. In addition, 16 S rRNA sequencing was used to analyze the gut microbiome of patients with myocardial infarction, unstable angina and stable coronary artery disease. After that, specific gut microbiome enrichment and metabolites changes were identified and analyzed for their associations with different phenotypes and subgroups of coronary artery disease. Changes in the abundance of certain gut microbiota, such as *Roseburia*, *Clostridium IV*, *Klebsiella*, and *Ruminococcaceae*, has been identified to affect the development of atherosclerosis by regulating the metabolic activity of bile acids and aromatic compounds [120].

A potential correlation between inflammation levels, metabolic disorders and heart failure (HF) has been suggested [121]. 16 S rRNA sequencing was used to determine the gut microbiome of chronic HF patients and a significant reduction in microbiome abundance was found. In specific, they found a decrease in the abundance of some species belongs to the *Lachnospiraceae* family, which produces butyrate. Butyrate has been found to increase the production of regulatory T cells,

which plays an anti-inflammatory role in the intestinal mucosa [122, 123]. The ratio of *Firmicutes* to *Bacteroidetes*, a dysbiosis marker of gut microbiota, was lower in HF patients with preserved ejection fraction (HFpEF) compared to the healthy subjects, although statistical significance was not reached using multiple hypothesis testing [124].

5.3. Brain diseases

Numerous studies have demonstrated an association between dysregulation in the gut microbiome ecosystem and central nervous system disorders, known as the brain-gut-axis. Gut microbiome dysregulation in Alzheimer's disease (AD) patients were investigated through bacterial 16rRNA sequencing. A reduced abundance of *Firmicutes* and *Actinobacteria* and an increased abundance of *Bacteroidetes* at the phylum level were observed. Moreover, a decrease in the abundance of specific families belonging to *Firmicutes*, such as *Turicibacteraceae*, *Ruminococcaceae*, *Clostridiaceae*, *Peptostreptococcaceae*, and *Mogibacteriaceae* was revealed. The abundance of *Bifidobacteriaceae* belonging to *Actinobacteria* decreased, while the abundance of *Rikenellaceae* and *Bacteroidaceae* belonging to *Bacteroidetes* increased. In addition, the bacterial taxa in the AD patient's gut were associated with cerebrospinal fluid biomarkers related to AD pathology [125].

There is growing evidence suggesting a connection between gut microbiome and Parkinson's disease. Fecal DNA from Parkinson's disease (PD) patients and control subjects were analyzed using deep shotgun sequencing. Their large-scale metagenome-wide association studies, revealed a wide range of gut microbiome dysfunctions in PD patients. PD patients exhibited increased levels of *Actinomyces oris*, *Bifidobacterium dentium*, *Lactobacillus fermentum* and *Streptococcus mutants*. Genera associated with SCFAs production, such as *Eubacterium*, *Roseburia*, *Ruminococcus*, and *Faecalibacterium prausnitzii*, were depleted [126].

5.4. Cancers

A correlation between the gut microbiome and cancer, as well as the modulation of anti-cancer drug efficacy has been indicated. The gut microbiome composition of colorectal cancer/normal tissues using whole-genome sequencing, PCR reactions, and 16 S rDNA sequence analysis was examined. Their findings revealed alterations in the gut microbiome of colorectal cancer patients. *Fusobacterium* was found to be enriched in colorectal cancer tissues, while *Bacteroidetes* and *Firmicutes* were depleted. However, the exact role of *Fusobacterium* in the pathogenesis of colorectal cancer is unclear [127]. Chronic inflammation and cancer development has been linked to the gut microbiome. Moreover, chemotherapy failure is a major reason for colorectal cancer recurrence and poor prognosis. The role of the gut microbiome in chemotherapy resistance among colorectal cancer patients has been investigated. A high abundance of *Fusobacterium nucleatum* in recurrent colorectal cancer tissues after chemotherapy has been observed, suggesting that *Fusobacterium nucleatum* may promote chemoresistance in colorectal cancer [128].

Overall, the abundance of gut microbiome is balanced in healthy individuals. Diseases are contributed to by an imbalance of gut microbiome. For a better understanding of beneficial or harmful microbiome, we summarized disease-related gut microbiome changes in Table 2.

Table 2
Observed Variations in Gut Microbiota Abundance in Different Diseases are Observed.

DISEASE	Bacteria	Abundance Changes	Reference
Parkinson's disease	*Actinomyces oris*	up	[126]
	Bifidobacterium dentarius	up	
	Lactobacillus fermentum	up	
	Streptococcus mutants	up	
Type 2 diabetes	*Ruminococcus*	up	[113]
	Fusobacterium	up	
	Blautia	up	
	Akkermansia	down	
	Bifidobacterium	down	
	Faecalibacterium	down	
	Bacteroides	down	
	Roseburia	down	
Coronary heart disease	*Roseburia*	down	[120]
	Klebsiella	down	
	Ruminococcaceae family	down	
Obesity	*Ospiraceae family*	down	[112]
	Ruminococcaceae family	down	
	Ruminococcus torques	up	
	Ruminococcus obeum	up	
	Ruminococcus bromii	up	
Heart failure	*Lachnospiraceae family*	down	[122]
	Firmicutes	down	[124]
	Bacteroidetes	down	
Atherosclerosis	*Parabacteroides merdae*	down	[119]
Alzheimer's disease	*Bacteroidetes*	up	[125]
	Firmicutes	down	
	Actinobacteria	down	
	Bifidobacterium	down	
Colorectal cancer	*Fusobacterium*	up	[127]
	Bacteroidetes	down	
	Firmicutes	down	

6. Therapeutic implications of exercise-induced microbiome alterations

Exercise induces changes in the gut microbiome, thereby regulating metabolism and reducing symptoms associated with various diseases. Both basic and clinical studies have utilized exercise interventions to treat patients or animals with diseases and have investigated the mechanisms through various gut microbiome analyses. In addition, fecal microbiota transplantation (FMT) involves the transfer of fecal material from a healthy donor to an individual's gastrointestinal tract to directly affect and normalize the gut microbiota composition. Previous studies and clinical trials have demonstrated the therapeutic effects of FMT in various diseases.

6.1. Intestinal diseases

A 12-week free running wheel exercise intervention has been conducted in obese mice on a high-fat diet to examine changes in intestinal inflammation and components of anti-obesity microbes influenced by exercise. Specific enrichments of three components that belong to the *Clostridiales* family, namely, *Faecalibacterium prausnitzi*, *Clostridium spp.*, and *Allobaculum spp.*, has been revealed in the feces of the exercise group [129]. In obese mice the duodenum/ileum barrier function was impaired, resulting in increased inflammatory cells, inflammatory infiltration in the intestinal villi, and elevated expression of pro-inflammatory factors such as COX-2. However, exercised mice exhibited normal intestinal morphology and significantly reduced inflammatory response. Another study also conducted a 12-week free running wheel exercise intervention in high-fat diet-induced obese mice. Compared to Campbell's study, they observed that exercise significantly improved the changes in gut microbiome composition caused by the high-fat diet. Specifically, exercised mice showed increased abundance of *Bacteroidetes* in the intestines, while *Firmicutes* exhibited a decreasing trend [130].

6.2. Obesity and diabetes

In order to determine the beneficial effect of exercise-conditioned

FMT on obesity disease, mice were subjected to a high-fat diet, treadmill running training, and FMT treatment. It was found that the relative abundance of *Turicibacter*, *Sutterella* and *Prevotella* was the highest in the fecal bacteria of healthy diet mice. The relative abundance of *Odoribacter*, *AF12*, and *Helicobacter* was the greatest in mice after exercise. Transplantation of normal mouse fecal microbiota to obese mice effectively reduced the weight and fat content. Similarly, transplanting fecal microbiota from exercised mice to obese mice alleviated gut microbiome disorders in obese mice. *Odoribacter*, *Helicobacter* and *AF12* were the top three abundant gut microbiome after receiving FMT from exercised mice. Furthermore, FMT from exercised mice to obese mice mitigated obesity symptoms, leading to reduced body weight, decreased fat deposition in the liver, significantly reduced blood parameters (fasting blood glucose, IPGTT, ALT, and LDL), and decreased expression of inflammation-related factor Il1a. These findings indicate that the beneficial effects of exercise can be transmitted through FMT, providing therapeutic benefits for diseases [131].

In another study, low-intensity treadmill exercise was performed on mice with diabetes and it was found that exercise had a strong effect on the microbiota in the cecum of diabetic mice. The abundance of select *Firmicutes* species in caecum increased significantly while *Bacteroides/Prevotella spp.* decreased [132]. Exercise has been demonstrated as an effective intervention for the prevention and treatment of diabetes, while the metabolic levels of some patients do not respond to exercise intervention. In addition, exercise interventions were performed in patients with prediabetes and it was found that gut microbiome and its metabolites were important factors in determining the improvement of glucose homeostasis and insulin sensitivity through exercise. Responders had an increase in *Lanchospiraceae bacterium* that produces butyrate, an increase in the replication rate of some species belonging to *Bacteroides* genus that produce propionate, a decrease in *Alistipes shahii*, which related to inflammation, and a decreased growth rate of *Prevotella copri* that associated with Branched-Chain Amino Acid (BCAAs) production and insulin resistance. In contrast, non-responders had a decrease in the *Ruminococcus gnavus* and an increase in the bacterium *Alistipes shahii*. Finally, it was found that obese mice receiving FMT from responders had ameliorated insulin resistance and glucose intolerance. Thus, gut microbiome and its metabolites are expected to be biomarkers for predicting and assessing the effect of exercise intervention for diabetes [133].

6.3. Cardiovascular diseases

Our group found that exercise training provided cardiac protection from myocardial infarction (MI) and enhanced the gut microbial richness in mice post-MI [134]. Exercise-induced improvements in cardiac function were associated with a higher abundance of *Bacteroidetes* and a lower abundance of *Firmicutes* in exercised versus sedentary mice. Mice receiving FMT from the exercised group exhibited significantly improved heart function compared to those receiving FMT from the sedentary group. Additionally, exercise-induced metabolites 3-hydroxyphenylacetic acid (3-HPA) and 4-hydroxybenzoic acid (4-HBA) were found to be cardioprotective. Our study demonstrates that the beneficial effects of exercise training on MI can be transmitted through FMT [134].

Regular exercise also helps alleviate hypertension via gut microbiome modulation. Various exercise interventions such as endurance training, ambulatory resistance training, isometric strength training effectively reduced systolic blood pressure [135]. Exercise training was performed on spontaneously hypertensive rats (SHR) and associated changes in the fecal microbiota and related physiological parameters including intestinal inflammation, permeability and pathology, number of activated brain microglia and neuroinflammation were analyzed. It was found that exercise training contributed to a persistent decrease in systolic blood pressure in SHR, linked to increased microbial diversity and the enrichment of beneficial bacterial genera, indicating that the antihypertensive effects of exercise involve a remodeling of the gut microbiota [136].

6.4. Immune/inflammation-related diseases

Strength exercise significantly increased the gut microbial diversity and changed the composition of gut microbiome of autoimmune encephalomyelitis (EAE) mice, which was characterized by the decrease of *Firmicutes/Bacteroidetes* ratio. FMT experiments showed that strength exercise reduced the permeability of intestinal mucosa, alleviated the immune response of central nervous system of EAE, and mitigated the disease severity and neuropathology of EAE by changing the composition of gut microbiome [137].

Exercise could also reduce joint pain, decrease inflammatory marker levels, and lead to higher gut microbiome abundance and increased levels of SCFAs and endocannabinoids. Approximately one third of the anti-inflammatory effects of SCFAs produced by the gut microbiome are attributed to an increase in endocannabinoids while the remainder is tied to alternative pathways that regulate the immune system [138].

Metabolites produced by beneficial gut microbiomes, which offer protective effects against various diseases, greatly broaden the repertoire of therapeutic approaches. Previous studies have demonstrated the efficacy of the FMT method, presenting a new horizon for the treatment of complex diseases. The aforementioned potential therapies are summarized in Fig. 2.

Exercise has been shown to alleviate disease symptoms and improve quality of life and mortality outcomes for patients with various diseases. In addition, transplantation of healthy gut microbiome is a viable clinical intervention. The clinical indication of FMT technology is the treatment of recurrent diarrhea caused by antibiotic-resistant *Clostridium difficile* infection [139]. However, transplantation carries a risk of transmitting infections to the recipient. Furthermore, the specific mechanism by which exercise improves gut microbiome imbalances remains unclear. Therefore, the therapeutic potential of athletes' fecal microbiome or post-exercise fecal samples from animals remains a subject of ongoing research, primarily in laboratory animal models, and has yet to find application in treating human diseases.

7. Future outlook

Modifying the community composition of gut microbiota, among other human microbial habitats, is perceived as a potential avenue for therapeutic interventions aimed at treating diseases related to ecological imbalances [48]. However, a fundamental obstacle to clinical transformation lies in the intricate and elusive mechanism of interaction between the host and the microorganisms [140]. Thus, the development of innovative methods for pure culture and the continual advancement of various omics technologies are vital for unraveling the mechanisms of host-microbiota interaction [141].

In addition, with the ongoing refinement of high-throughput sequencing technology will inevitably lead to a decrease in sequencing costs. Consequently, microbiome deep sequencing will be available for an increased number of microbial samples. This will further provide an unprecedented wealth of data for microbiology research. Even though a comprehensive high-throughput omics computational framework [142], has been established, and new exemplary deep learning algorithms have emerged [143,144], there remains a need for further exceptional algorithms tailored to the various requirements of microbiome multi-omics integration, microbial-host interactions, microbial community functional phylogeny, and microbe-environment interactions.

Current studies suggest that various factors such as diet, exercise, medication, and external stress contribute to alterations in the gut microbiota. Notably, changes induced by healthy diet and exercise promote modifications in intestinal metabolites and provide nutrients to beneficial microbiome. Investigating the relationships between exercise-related microbiome and hosts relationships will provide new insights for

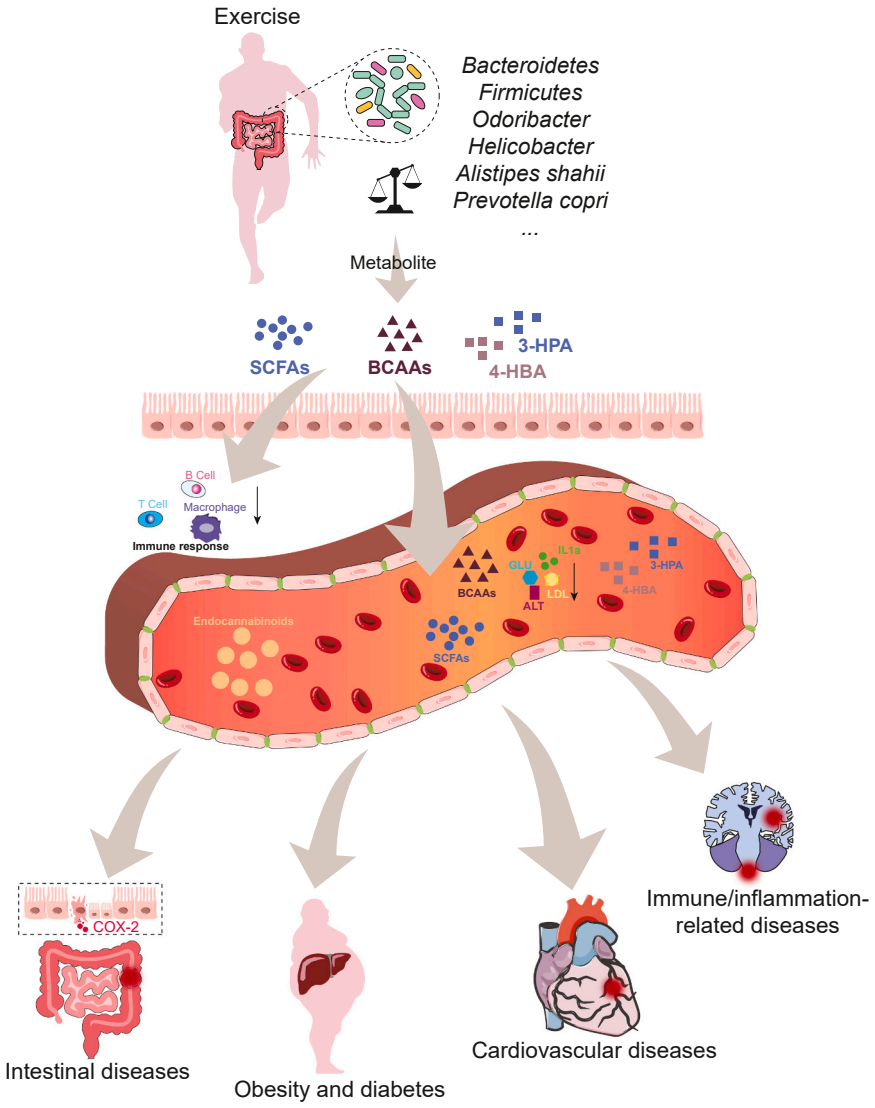

Fig. 2. An Overview of Exercise-related Microbiota Enrichment and Functions in Disease Treatment. The gut microbiota, induced by physical exercise, produce metabolite to affect the processes of diseases such as intestinal disease, obesity and diabetes, cardiovascular disease and immune/inflammation-related disease. The metabolites, such as SCFAs, BCAAs and 3-HPA or 4-HBA, have beneficial effects on the aforementioned diseases and function as ligands or signals, protecting individuals from hazard of disease. On the one hand, the altered microbiome reduces inflammation level through COX-2 or IL1A etc. On the other hand, they can balance the metabolite in blood vessels, and reduce some risk indicators like glucose, ALT and LDL.

treating gut microbiome-related diseases.

CRediT authorship contribution statement

Junjie Xiao: Conceptualization, Funding acquisition. **Qiulian Zhou**: Conceptualization, Writing – original draft, Funding acquisition, Writing – review & editing. **Danni Meng:** Writing – original draft. **Songwei Ai:** Writing – original draft. **Michail Spanos:** Writing – original draft. **Xiaohui Shi:** Writing – original draft. **Guoping Li:** Writing – review & editing. **Dragos Cretoiu:** Writing – review & editing. **Junjie Xiao:** Writing – review & editing. All authors have read and approved the final manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

This work was supported by the grants from National Natural Science Foundation of China (82020108002 and 82225005 to J Xiao, 82200321 to QL Zhou), the grant from Science and Technology Commission of Shanghai Municipality (23410750100, 20DZ2255400 and 21XD1421300 to J Xiao), Shanghai Sailing Program (21YF1413200 to QL Zhou), the 'Dawn' Program of Shanghai Education Commission (19SG34 to J Xiao).

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