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MIAOME: Human microbiome affect the host epigenome

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ABSTRACT

Besides the genetic factors having tremendous influences on the regulations of the epigenome, the microenvironmental factors have recently gained extensive attention for their roles in affecting the host epigenome. There are three major types of microenvironmental factors: microbiota-derived metabolites (MDM), microbiota-derived components (MDC) and microbiota-secreted proteins (MSP). These factors can regulate host physiology by modifying host gene expression through the three highly interconnected epigenetic mechanisms (*e.g.* histone modifications, DNA modifications, and non-coding RNAs). However, no database was available to provide the comprehensive factors of these types. Herein, a database entitled 'Human Microbiome Affect The Host Epigenome (MIAOME)' was constructed. Based on the types of epigenetic modifications confirmed in the literature review, the MIAOME database captures 1068 (63 genus, 281 species, 707 strains, *etc.*) human microbes, 91 unique microbiota-derived metabolites & components (16 fatty acids, 10 bile acids, 10 phenolic compounds, 10 vitamins, 9 tryptophan metabolites, *etc.*) derived from 967 microbes; 50 microbes that secreted 40 proteins; 98 microbes that directly influence the host epigenetic modification, and provides 3 classifications of the epigenome, including (1) 4 types of DNA modifications, (2) 20 histone modifications and (3) 490 ncRNAs regulations, involved in 160 human diseases. All in all, MIAOME has compiled the information on the microenvironmental factors influence host epigenome through the scientific literature and biochemical databases, and allows the collective considerations among the different types of factors. It can be freely assessed without login requirement by all users at: http://miaome.idrblab.net/ttd/

1. Introduction

Epigenome plays an essential role in regulating countless biological processes in kinds of developmental and environmental contexts [1,2]. The regulations of the epigenome are dynamic [3,4] and frequently influenced by multiple factors including genetic, physiological, and environmental factors (*e.g.* diet, lifestyle) [5–7], and these influences conduce to growth, development, and disease risk [8]. Besides the above factors having tremendous impacts on the epigenome, the microenvironmental factors have recently gained extensive attention for their roles in affecting the host epigenome [9–11]. Particularly, the human microbiome, which provides microenvironmental factors, can trigger host epigenetic modification [12]. Increasing evidence shows that the microbes, which as one type of environment hint, can regulate host physiology by modifying host gene expression through three highly interconnected epigenetic mechanisms (*e.g.* histone modification, DNA modification, and non-coding RNAs) [13–15].

There are three major types of microenvironmental factors that are continually considered in current epigenome studies [16–20]: (i) *microbiota-derived metabolites* (MDM, including fatty acids, bile acids, phenolic compounds, vitamins, tryptophan metabolites,

Abbreviations: MDM, microbiota-derived metabolites; MDC, microbiota-derived components; MSP, microbiota-secreted proteins; ncRNAs, non-coding RNAs; LPS, lipopolysaccharide; HDACs, histone deacetylases; miRNA, microRNA; EM, Epigenetic molecule.

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amino acids, choline metabolites, polyamines, phenolic compounds, *etc.*) are crucial in mediating host epigenetic reprogramming [21], affecting epigenetic mechanisms that contribute to human diseases [22], and revealing specific biomarkers and potential therapeutic targets [23]; (ii) *microbiota-secreted proteins* (MSP, including Listeriolysin O, HP0175, NuE, RomA, *etc.*) are tools used by pathogenic bacteria to induce epigenetic changes in the host to favor infection [24], they can alter the epigenetic type and gene expression pattern in the host cells [25], and facilitate human disease initiation and progression [26–28]; (iii) *microbiota-derived components* (MDC, including lipopolysaccharide, flagellum, β-glucan, *etc.*), for example, lipopolysaccharide (LPS) from *Fusobacterium nucleatum* induced transient acetylation of histone H3 lysine 9 in oral epithelial cells through the pattern recognition receptor pathway [29]. Besides, there are indications that the altered microbiome composition or decreased/increased abundances of microbes also have impacts on the host epigenetic modifications [30–32]. Since these microbe-induced epigenetic modifications are necessary for proper homeostasis in the host [14], the accumulation of anthropogenic factors that define such modifications could provide important insights into the current understanding of the microbiome and the study of its interaction with host epigenetic mechanisms.

Up to now, a number of human epigenome-related databases have been constructed and are currently open, the most of which focus on providing epigenetic modifications data related to diseases (CFEA [33], dbEM [34], DAnCER [35], EWASdb [36], DNMIVD [37], EWAS Data Hub [38], MethCNA [39], MOBCdb [40], MethylomeDB [41], DiseaseMeth [42]), while some others are specialized in containing particular classes of DNA modifications (EWAS Atlas [43], REBASE [44], MethDB [45], DNAmod [46] and MethMotif [47]), or histone modifications (HHMD [48], dbHiMo [49]). However, there still has no database has been developed for providing the data on microenvironment factors that affect the host epigenetic modifications.

Here, a newly developed database, as illustrated in Fig. 1, the human microbiome affect the host epigenome (MIAOME) was therefore introduced. First, a comprehensive literature review on host epigenome was conducted. Different types of epigenetic modifications involved in 20 histone modifications, 4 types of DNA modifications, and 490 types of ncRNAs regulations, were included in MIAOME. Second, based on these various epigenetic modifications, three microenvironmental factors (MDM, MDC and MSP) modulating each host epigenome were collected via literature review. Third, the crosslinks of each epigenome/microbe to disease associations were systematically discovered. These crosslinks could facilitate understanding the pathogenesis of diseases by integrating microbiome and epigenome. In a word, the MIAOME comprehensively provided the MDM, MDC and MSP information that affects the host epigenome, which allows the collective considerations among the different types of factors (among MDM, MDC and MSP; between microbiota and host). As the epigenetic modifications are affected by the microenvironmental factors [9–11], the MIAOME is expected to have implications for the future practice of epigenome-related studies on human physiology and health [23,50].

2. Methods

2.1. Epigenetic modifications data collection.

Epigenetic modification refers to stable and heritable changes in gene expression and cell function without altering its DNA sequence, usually caused by genetic and environmental factors. In the host, the epigenetic mechanism can regulate gene expression through a range of reversible epigenetic modifications [51], such as histone acetylation, histone phosphorylation, histone ubiquitylation, DNA methylation, and non-coding RNAs. Because of the diverse types of epigenetic modifications, the data of specific types of epigenetic modifications were collected by literature reviews in PubMed [52] using the keyword combinations of: 'Epigenetic modification', 'Epigenetic mechanism', 'histone + modification', 'DNA modification', *etc*. All retrieved information on epigenetic modification is the basis of earlier published literature (until December 31, 2021). The reference literature was reviewed to ascertain the diverse types of epigenetic modification. Based on a particular type of modification, we systematically collected the influence of microenvironmental factors on the host epigenome in the subsequent procedure.

2.2. The epigenetic modifications-associated microenvironmental factors collection.

Based on a particular type of modification, we systematically collected the influence of microenvironmental factors including MDM, MDC and MSP on the host epigenome in this procedure. In particular, the human microbe is well-known to produce varieties of metabolites, such as short-chain fatty acids including acetic acid, butyric acid, and propionic acid that can regulate a range of host physiological functions [53,54]. These MDMs act as critical modulators of epigenetic enzymes, influencing the DNA methylation and histone modifications, and mediating changes in microRNA expression [55,56]. And, the components of microbe cells (*e.g.* lipopolysaccharide of the cell wall, peptidoglycan of the cell wall, flagellin of flagellum) have been shown to influence the epigenetic modifications in host cells [57,58], and then induce changes in cellular expression profiles [17]. Besides, recent studies indicated that the microbiota-secreted proteins (such as Ankyrin A, Listeriolysin O, Rv2966c, *etc.*) were essential in reprogramming host epigenome [25], alternating the host cell epigenotype [59–61], and inducing the DNA methylation in host cells [50,62]. These factors are critical for further understanding the mechanisms of microbial infection [63] and discovering the epigenetic therapy potential targets [25].

PubMed [52] was systematically searched to find the impacts of host epigenome by MDM, MDC, and MSP. Particularly, keyword combinations such as 'human microbe + 'epigenetic modification'', 'human microbe metabolite + 'epigenetic modification'', 'human microbe metabolite + 'epigenetic mechanism'', 'human microbiota metabolite + 'DNA modification'', 'human microbiota metabolite + 'histone modification'', 'microbe protein + 'epigenetic modification'', 'human microbe protein + 'ncRNA'', and 'human microbe protein + 'histone modification'' were adopted for literature reviews. All retrieved information on microbial factors that influenced host epigenome is the basis of earlier published literature (until December 31, 2021). The reference literature was reviewed to ascertain the association of microenvironmental factors to each type of epigenetic modification. These MDM, MDC, and MSP, whose associations with host epigenome could not be confirmed based on the reference, were discarded. As a result, the collected information included the names of microbes, the specific types of MDM, MDC, and MSP, various types of epigenetic modifications (such as DNA methylation, histone acetylation, non-coding RNA regulation), and the effects of these microbial factors on the host epigenome (promotion/inhibition of host DNA methylation, up/down-regulation of host non-coding RNA, *etc.*).

Moreover, relevant information on the validated microbe/MDM/MDC/MSP, such as taxonomy ID, taxonomic lineage, oxygen dependency/tolerance, Gram-staining classification, diverse synonyms of each microbe, disease-related information, metabolite formula/synonyms/external links and so on was retrieved from

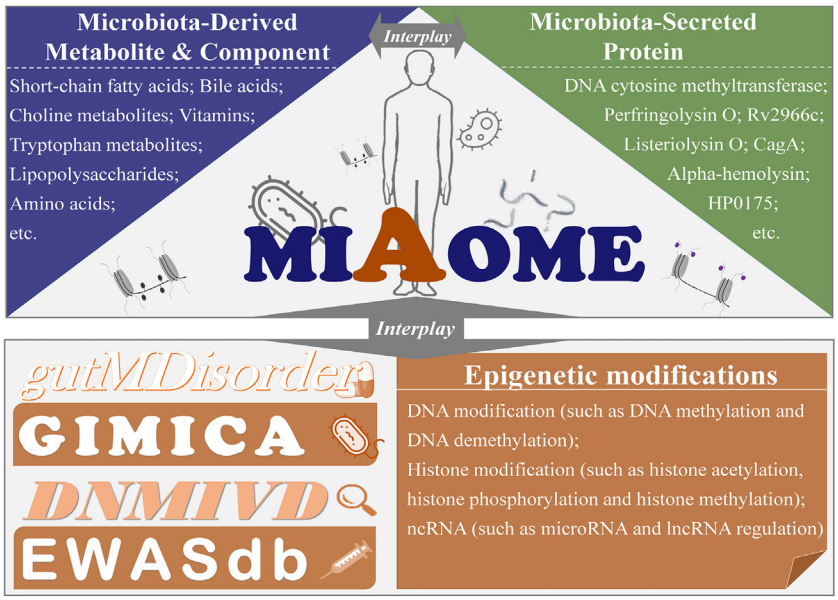

Fig. 1. MIAOME comprehensively described microenvironmental factors affecting human microbes, which allowed the collective consideration among different types of factors (between microbiota-derived metabolites & components, and microbiota-secreted proteins). By providing the crosslinks to available databases (EWASdb [35], DNMIVD [36], gutMDisorder [65] and GIMICA [66]) with host phenotypes information, MIAOME further enabled the collective consideration between the microenvironmental factors and host phenotypes.

online databases such as NCBI PubMed, NCBI Taxonomy [64], GIMICA [65], gutMDisorder [66], VMH [67] and UniProt [68].

2.3. Epigenome molecular collection.

The epigenome is a complete description of all chemical modifications of DNA and histones, which regulate the expression of genes in the genome. The epigenome defines the unique gene expression pattern and resulting cellular behavior in different cell types [69]. The epigenome is highly cell-type-specific [70,71]. Therefore, it's crucial to collect information on the influence of microenvironmental factors on the epigenome in a specific cell of the host. Moreover, identification of the genomic location of epigenetic modifications will assist in elucidating its functions [72]. The epigenetic modifications at different genomic locations (*e.g.* gene body, promoter, exon, and intron) may have different impacts on regulating the expression of genes [73] and even can lead to an opposite genetic outcome [74]. As a result, we collected the critical information on epigenetic modifications influenced by the above-mentioned three microbial factors, which include the cell types of host, biological conditions, and genomic locations of epigenome modifications. Besides, we have also provided the official full names, synonyms, UniProt entry, and Ensemble ID for these genes through searching Uniprot [68] and Ensembl [75]. In addition, according to the host gene data we have collected, the diverse types of diseases associated with these genes were also collected by further searching in the EWASdb [36] and DNMIVD [37] databases. All information can be retrieved using a variety of search strategies in both the homepage and subpages of the MIAOME.

2.4. Data standardization, access, and retrieval.

To facilitate access to MIAOME data convenient for all users, the collected information was carefully cleaned and systematically standardized. These standardizations included: (i) all microbes were standardized using NCBI Taxonomy [64], the extended data of each microbe could be accessed using crosslinks to NCBI Taxonomy [64], gutMDisorder [66], GIMICA [65], GOLD [76]; (ii) all MDM were standardized using VMH [67] and HMDB [77], the extended data of each metabolite could be accessed using crosslinks to KEGG [78] and METLIN [79]; (iii) all MSP were standardized using UniProt [68] database; (iv) all genes were standardized using Ensembl [75] database; (v) all diseases in MIAOME were standardized by the latest version of International Classification of Diseases (ICD-11, officially released by World Health Organization [80]) and the extended data of each gene could be accessed using crosslinks to UniProt [68], EWASdb [36] and DNMIVD [37].

3. Results and discussion

3.1. MIAOME database content.

The regulations of microbes on the host epigenome were frequently discovered to be caused by their derived metabolites, components, or secreted proteins [81,82]. For example, short-chain fatty acids produced by gut microbes promote the differentiation of naïve T cells into Treg by inhibiting histone deacetylases (HDACs), and this metabolite may cause abnormal immune response via epigenetic modifications, and lead to autoimmune diseases [23]. To gain a comprehensive understanding of the influence of microbes on the host epigenome, three microenvironmental factors were systematically reviewed and collected in MIAOME for each epigenetic modification. Consequently, the collected data included the names of microbes, MDM (16 fatty acids, 10 bile acids, 10 phenolic compounds, 11 vitamins, 9 tryptophan metabolites, 5 amino acids, 5 choline metabolites, *etc.*), MDC (lipopolysaccharide, flagellum, β-glucan, *etc.*), and MSP (HP0175, Listeriolysin O, NuE; RomA, Flagellin, Ankyrin A, InlB, *etc.*), various types of epigenetic modifications (DNA methylation, histone acetylation, histone phosphorylation, histone crotonylation, histone ubiquitination, histone methylation, miRNA regulations, *etc.*)

Furthermore, the genes modified by the above microenvironmental factors and the genome locations of modification were also collected, and provided 160 diseases related to them. Meanwhile, MIAOME provided the influences of each microbial factor on the host epigenome (promotion/inhibition of host DNA methylation,

up/down-regulation of host non-coding RNA, *etc.*). All epigenetic modification-related data caused by microbial factors can be retrieved using various search strategies on the homepage and subpages of the MIAOME database as shown in Fig. 2.

Besides the microbial factors above discussed, a variety of other factors (including ethnicity, age, lifestyle, and environment) have been reported to influence the host epigenome [83]. For instance, maternal diabetes/obesity during pregnancy could mediate the altered infant methylation patterns in the cord blood [84]. The perinatal nicotine exposure remodeled the DNA methylation in offspring spermatozoa [85]. Comprehensive considerations of microbial factors, host physiology, and environment could provide new insight into the host epigenome [86]. Current MIAOME focused on microbe influenced the host epigenome and lacked other critical environmental factors. The collective consideration of various factors types has great implications to serve comprehensive human health in the future.

3.2. MIAOME data and statistics.

All in all, the current version of MIAOME incorporates 1068 (63 genus, 281 species, 707 strains, *etc.*) human microbes, of which 967 produced 91 metabolites & components (valerate, lactate, folate, hydrogen sulfide, tryptophan, spermine, hexanoate, caproate, *etc.*), 50 secreted 40 proteins (Rv3763, Rv1988, LMP-1, Pneumolysin, TRP32, *etc.*); 98 microbes directly influence the host epigenetic modifications. These microbial factors modulate 514 types of epigenetic modifications, including (1) 4 types of DNA modifications (DNA methylation, DNA hypermethylation, DNA Hypomethylation, DNA demethylation); (2) 20 histone modifications (histone

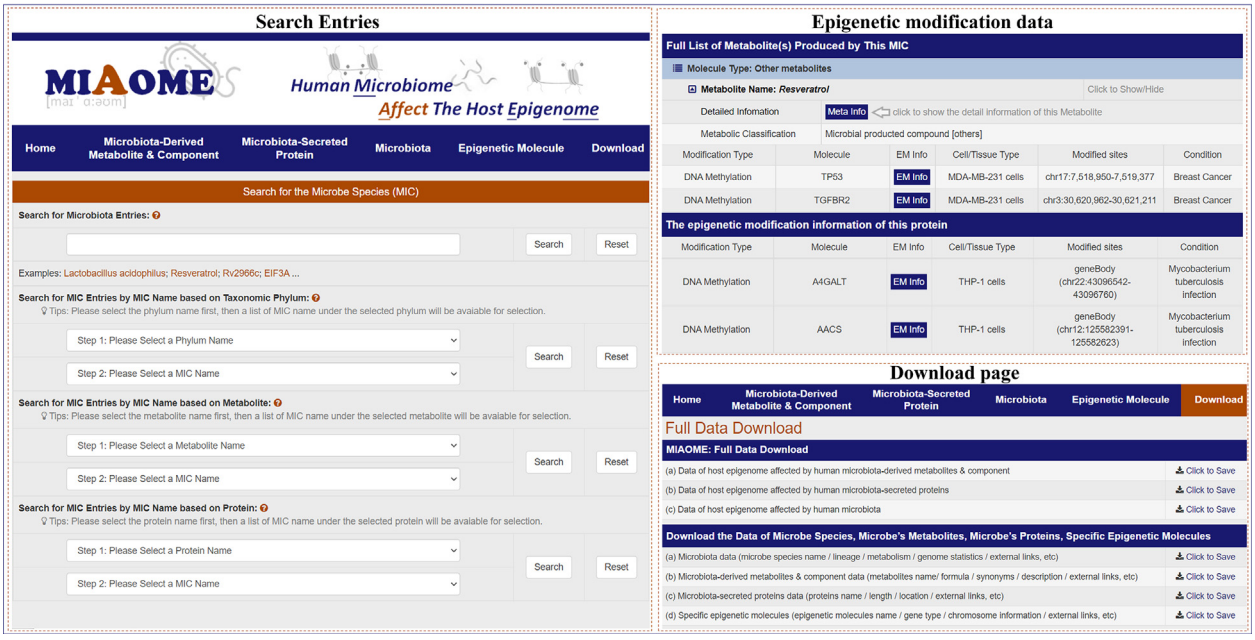

Fig. 2. Sample web interfaces. There are six major web pages in MIAOME: 'Home' page, 'Microbiota-Derived Metabolite & Component' page, 'Microbiota-Secreted Protein' page, 'Microbiota' page, 'Epigenetic Molecule' page, and 'Download' page.

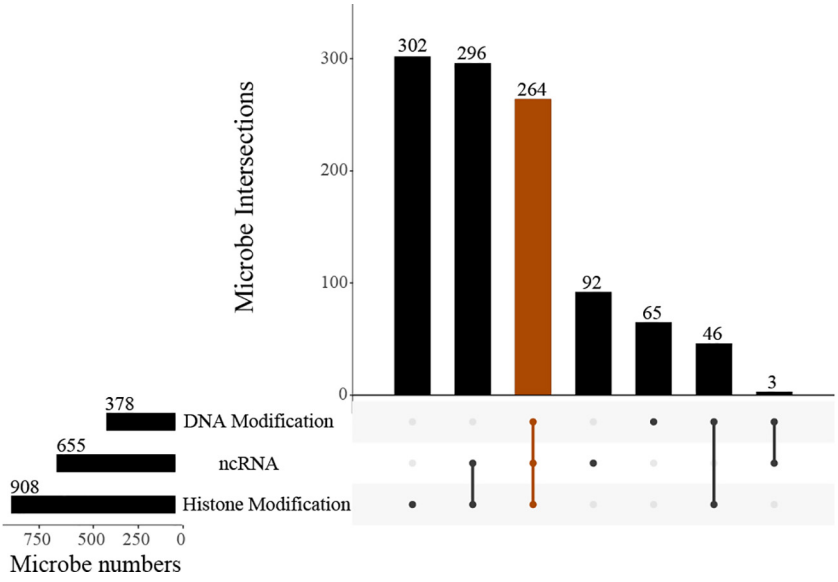

Fig. 3. An UpSetR plot shows the intersection of three types of microbe sets, which included microbe-affected host DNA modification, microbe-affected histone modification, and microbe-affected ncRNAs regulation. The brown line marks the microbes shared by three types of epigenetic modification.

acetylation, histone biotinylation, histone crotonylation, histone methylation, histone phosphorylation, histone ubiquitination, *etc.*) and (3) 490 ncRNAs regulations. Besides, we have also provided more than 12,000 host genes that are regulated by epigenetic modifications, 129 cell types, and 160 diseases related to these genes. With the data contained in MIAOME, we performed a statistical analysis on the distribution of epigenetic modification information caused by microbial factors. An UpSetR plot (Fig. 3) shows the intersections of microbes that influenced three types of epigenetic modifications. In general, histone modifications were influenced by most microbes, and 264 microbes can influence the host gene expression through the three epigenetic modifications.

Fig. 4. MIAOME offers different ways to search the entries, based on users' preferences. Users can find microbiota-inducted epigenetic modifications through several approaches, such as microbe names, MDM names, MDC names, MSP names, and Epigenetic molecule names in MIAOME.

3.3. MIAOME Search.

To construct a database with plentiful data, applying a good search algorithm with more convenient and efficient for users is very important. As illustrated in Fig. 4, MIAOME offers different ways to search the entries, based on users' preferences. Users can find microbiota-inducted epigenetic modifications by searching microbe names (*e.g.* '*Lactobacillus acidophilus*'), MDM names (*e.g.* 'equol'), MSP names (*e.g.* 'Rv2966c'), and their ID numbers (*e.g.* 'MC1011', 'MT104', 'PT007') among the entire textual component of MIAOME. The query can be submitted by entering keywords into the main searching frame. To facilitate a more customized input query, the wild characters of "*" and "?" are also supported in MIAOME. Moreover, users can click the corresponding '?' button to learn the detailed search steps. Fig. 5 demonstrates an example of searching by microbiota-derived metabolite name.

Searched results will be displayed on a separate web page. The page will display the basic information of searched queries (as shown in Fig. 5A). By clicking the "Meta Info" hyperlink button, the detailed information page of this metabolite will be displayed, this page is divided into three parts, "General Information of Metabolite", "The epigenetic modification information of this metabolite", "The microbes that produce this metabolite" (as shown in Fig. 5B). The general information of this metabolite includes its "Meta Name", "Unify name", "Synonym", "Formula", "Inchi Key" and "Description". If you want to know more about this metabolite, you can link to other related databases by clicking the hyperlinks in the "External Links" field. "The epigenetic modification information of this metabolite" includes the epigenetic modification information influenced by the searched metabolite, such as "Modification Type", "Molecule", "Cell/Tissue Type", and "Modified sites". Moreover, detailed information on each epigenetic molecule can be browsed on a new webpage by clicking on the specific "EM Info" (as shown in Fig. 5C). "The microbes that produce this metabolite" includes the microbe information that produced the searched metabolite, such as "Microbiota Name" and "Description". By clicking on the specific "MIC Info", the general information of this microbe will be displayed (as shown in Fig. 5D).

3.4. MIAOME download functionality.

MIAOME also provides functions for downloading all MIAOME data from various customized links. As Fig. 2 shows, MIAOME allows users to download the data of microbes, MDM, MDC, MSP, epigenetic molecules, and the epigenetic modifications induced by MDM, MDC, and MSP. All data can be readily downloaded by

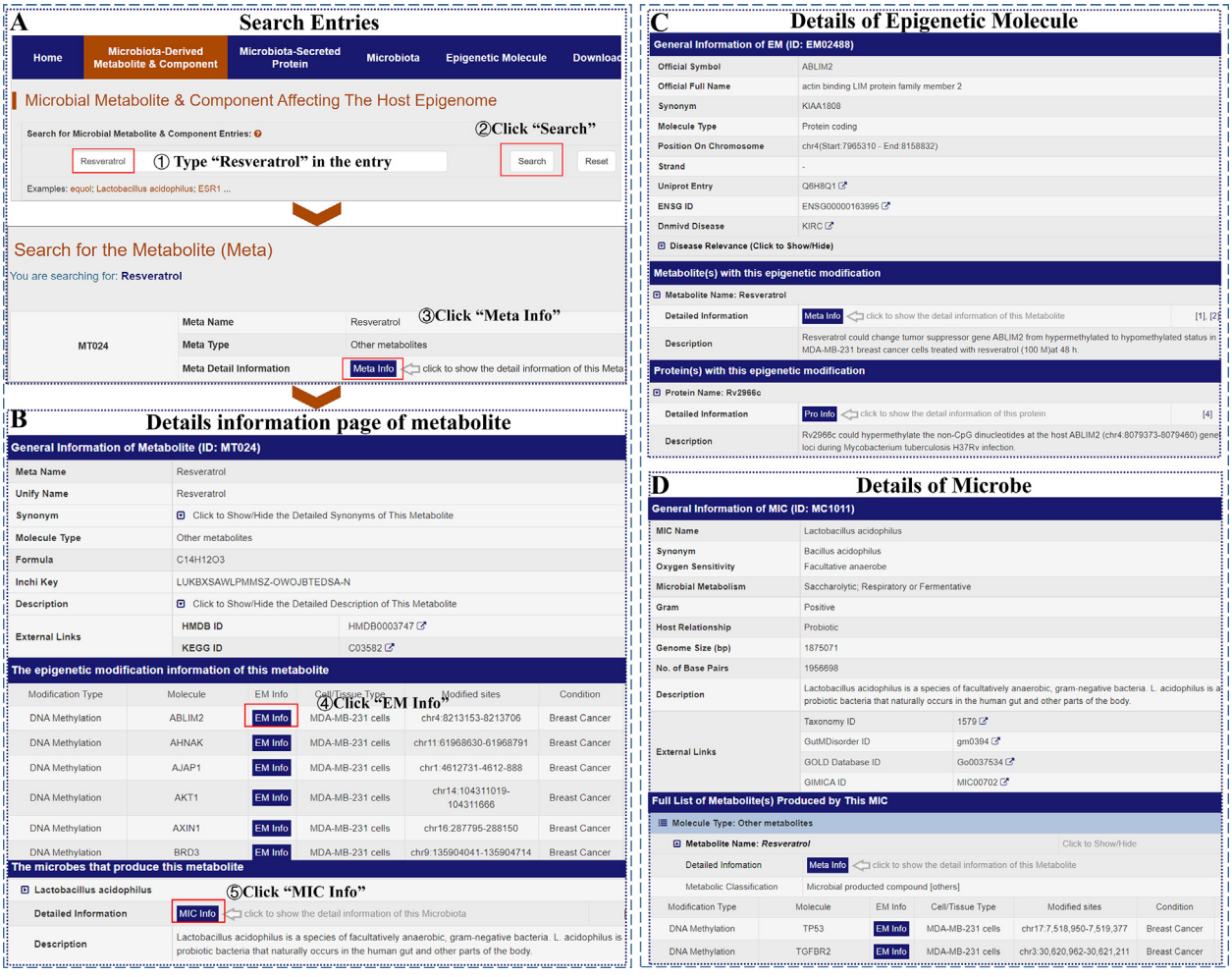

Fig. 5. An example for data accessing in MIAOME. Here, four different searches were supported, by MDM names, MDC names, the microbe names, and the epigenetic molecule names. (A) An example illustrates how to explore the epigenetic modifications through MDM names (Resveratrol is selected). (B) Typical search result webpage using the MDM name: Resveratrol as an example. The detailed information page of Resveratrol was displayed. Details of the metabolite are divided into three parts: General Information of Metabolite, Epigenetic modification information of this metabolite, and the microbes producing this metabolite. (C) The epigenetic molecule webpage consists of three major sections showing detailed information: General Information of EM, Metabolite/Component(s) and Protein(s) associated with this EM. (D) The microbe webpage consists of two major sections showing detailed information: General Information of MIC and Full List of Metabolite(s) Produced by This MIC.

simply clicking the corresponding "Click to Save" button. These files can beneficial to researchers that engaged in epigenome-related studies and provide basic data resources for discovering targets of epigenetic therapy.

4. Conclusions

MIAOME is a user-friendly and new freely available online resource that compiles information on the microenvironmental factors influence host epigenome through scientific literature and biochemical databases. These microenvironmental factors included the MDM, MDC, and MSP. Manually curated information on the type of epigenetic modification, the cell type/tissue, and the genomic location of modification along with supporting reference literature has been collated and included in MIAOME. Moreover, the links between the epigenome and host phenotypes are collectively provided in MIAOME. MIAOME is expected to significantly advance our understanding of the epigenetic regulation underlying human physiology and disease. MIAOME has been smoothly running for months and tested from various sites around the world and is freely assessable without login requirement by all users at: http://miaome.idrblab.net/ttd/.

Contributors

J.T. conceived the idea and supervised the work. L.W., W.Z. performed the research. F.Z., W.Z. constructed the database, developed the software and wrote the scripts. L.W., X.W., X.L., L.C., J.Z., Y.Y., Q. C., H.L., J.Z., and Y.D. prepared the data. J.T. and L.W. wrote manuscript. All authors reviewed and approved the final version of the manuscript.

CRediT authorship contribution statement

Lidan Wang: Data curation, Writing - Original Draft, Writing - Review & Editing. **Wei Zhang:** Data curation, Software. **Xianglu Wu:** Data curation, Investigation. **Xiao Liang:** Visualization, Software. **Lijie Cao:** Visualization, Data curation. **Jincheng Zhai:** Visualization, Data curation. **Yiyang Yang:** Visualization, Data curation. **Qiuxiao Chen:** Visualization, Data curation. **Hongqing Liu:** Visualization, Data curation. **Jun Zhang:** Visualization, Data curation. **Yubin Ding:** Supervision, Funding acquisition. **Feng Zhu:** Conceptualization, Project administration. **Jing Tang:** Conceptualization, Writing - Original Draft, Writing - Review & Editing, Supervision, Funding acquisition.

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.

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