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Gut Microbiology in the Age of CRISPR, AI, and Omics: A Review

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Gut Microbiology in the Age of CRISPR, AI, and Omics: A Review

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Abstract

The human gut microbiome, composed of trillions of microorganisms including bacteria, viruses, fungi, and archaea, plays a critical role in health, metabolism, immunity, and disease susceptibility. Over the last decade, the complexity and dynamism of the gut microbiota have been increasingly appreciated, revealing intricate interactions with host physiology that influence conditions ranging from obesity, diabetes, and cardiovascular disease to neurodegenerative disorders and cancer. Understanding and manipulating this microbial ecosystem requires integrative approaches that combine advanced molecular techniques, computational analytics, and precise genetic interventions. Recent advances in CRISPR genome editing, high-throughput omics technologies, and artificial intelligence (AI) have collectively transformed gut microbiology research, opening new avenues for predictive modeling, therapeutic interventions, and personalized medicine. This review gathers recent researches in CRISPR, AI and omics in the field of gut microbiology and further discussed future outlooks and perspectives.

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Introduction

The human gut microbiome plays a pivotal role in health, metabolism, immunity, and disease susceptibility. Advances in high-throughput omics technologies, including metagenomics, metatranscriptomics, metaproteomics, and metabolomics, have enabled comprehensive profiling of microbial composition and function, uncovering intricate host–microbe interactions. However, the complexity and scale of multi-omic datasets present analytical challenges that require sophisticated computational approaches. Artificial intelligence (AI), encompassing machine learning and deep learning, offers powerful tools to integrate multi-omic data, identify disease-associated microbial signatures, predict microbial metabolic outputs, and model host–microbe interactions [1]. Complementing these computational insights, CRISPR-Cas genome editing provides a precise means to manipulate microbial genes, validate predicted functions, and engineer microbial communities for therapeutic or biotechnological applications. The combination of AI, CRISPR, and omics technologies enables iterative cycles of prediction, experimental validation, and functional characterization, advancing mechanistic understanding of the gut ecosystem [2,3]. This integrative approach not only illuminates fundamental microbial ecology and evolution but also holds promise for developing microbiome-informed diagnostics, personalized interventions, and novel therapeutics. Collectively, the convergence of gut microbiology with CRISPR, AI, and omics represents a transformative paradigm for precision medicine and functional microbiome research. This review gathers recent researches in CRISPR, AI and omics in the field of gut microbiology and further discussed future outlooks and perspectives.

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Multi-Omics in Gut Microbiology and Recent Researches

High-throughput omics technologies, including metagenomics, metatranscriptomics, metaproteomics, and metabolomics, provide a comprehensive molecular snapshot of the gut ecosystem [4]. Metagenomic sequencing enables the identification of microbial species and their genetic potential, revealing the composition and diversity of the microbiota. Metatranscriptomics captures gene expression profiles, highlighting functional activity under different conditions, while metaproteomics and metabolomics illuminate the functional output of microbial communities, including the production of metabolites that impact host physiology [1]. These multi-omic datasets allow researchers to link microbial composition to functional pathways and health outcomes. However, the high dimensionality, sparsity, and interdependence of omics data pose significant analytical challenges, necessitating advanced computational tools.

Shi et al. Utilized multi-omics integration to unearth the functional signatures of gut microbiome in atherosclerosis [5]. They have identified five tripartite associations linking microbes, metabolites, and host genes in ankylosing spondylitis (AS), involving five microbial genera (*Gemella, Actinomyces*, *Veillonella, Bacteroides*, and *Eisenbergiella*), two metabolites (ethanol and H_2O_2), and two host genes (FANCD2 and GPX2), and confirmed the reliability of these interactions [5]. These five microbial genera showed strong potential as noninvasive diagnostic biomarkers, with their performance validated through 5-fold cross-validation, study-to-study transfer validation, and leave-one-study-out (LOSO) validation [5]. The specificity of the biomarkers was further confirmed in cohorts with hypertension, inflammatory bowel disease (IBD), diabetes, and obesity. Their study revealed functional insights into gut microbiota interactions with atherosclerosis host genes and emphasized the promise of gut microbes as both diagnostic markers and therapeutic targets for atherosclerosis [5]. Nevertheless, the results should be interpreted cautiously, considering the heterogeneity of the integrated datasets and the preliminary nature of the biomarker validation [5]. Hernández-Cacho et al. performed another multi-omic study to reveal gut microbiome signatures associated with depression [6]. Individuals with depression showed notable alterations in gut microbial composition and metabolic profiles [6]. Key differentially abundant taxa included *Acidaminococcus*, *Megasphaera* and *Christensenellaceae* R-7 group, among others [6]. Metabolomic analysis identified 15 significantly changed metabolites, mainly lipids, organic acids, and benzenoids, some of which were associated with specific microbial features [6]. These findings underscore the relationship between gut microbiota and depression, providing a foundation for future studies to explore whether gut microbes contribute to depression pathophysiology or simply reflect changes linked to the condition [6]. Several reviews were also in agreement that multi-omics orchestrate indispensable roles in diagnosis and personalized therapies against various chronic diseases [7–9].

CRISPR-Cas in Gut Microbiology and Recent Researches

CRISPR-Cas technologies provide a complementary approach, allowing targeted manipulation of microbial genomes within complex communities. CRISPR can be employed to knock out, modify, or regulate genes in gut bacteria, facilitating functional studies to determine the causal roles of specific microbes or microbial genes in health and disease [10]. For example, CRISPR interference (CRISPRi) can repress gene expression in gut bacteria to investigate their metabolic contributions, while CRISPR activation (CRISPRa) can enhance the expression of beneficial pathways [11]. In addition, CRISPR-based antimicrobials can selectively deplete pathogenic strains without disturbing the overall microbiota, offering a precision tool for modulating gut ecosystems [12]. Coupling CRISPR with high-throughput omics allows researchers to measure the systemic effects of targeted genetic perturbations, providing a deeper understanding of microbiome-host interactions [12].

Zheng et al. have successfully utilized the CRISPR/fnCas12a genome editing system to modify the human gut commensal *Bacteroides* species, namely *Bacteroides ovatus*, *Bacteroides fragilis* and *Bacteroides uniformis* [13]. They anticipate that CRISPR/Cas genome editing technologies for *Bacteroides* will significantly advance mechanistic research on this gut commensal and support the

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creation of engineered live biotherapeutic interventions [13]. Brödel et al. attempted *in situ* targeted base editing of bacteria (*Escherichia coli* and *Klebsiella pneumoniae*) in the mouse gut [14]. As a result, their study demonstrated that bacteria can be directly modified within the gut, providing a novel approach to explore bacterial gene functions and paving the way for the development of microbiome-targeted therapies [14]. Just recently, Zhang et al. reported that CRISPR-Cas spacer acquisition occurs infrequently within the human gut microbiome [15]. Their results indicated that horizontal gene transfer (HGT) of a complete CRISPR-Cas system contributed three times as many spacers compared to local CRISPR-Cas acquisition in *Bifidobacterium longum* [15]. Overall, their study highlights important ecological and evolutionary determinants of prokaryotic adaptive immunity [15].

Artificial Intelligence in Gut Microbiology and Recent Researches

The integration of AI with CRISPR and multi-omics creates a powerful framework for predictive and personalized microbiome research. AI models trained on multi-omic datasets can identify potential microbial targets for intervention [16], while CRISPR enables experimental validation and manipulation of these targets. This iterative loop: AI-guided prediction, CRISPR-based manipulation, and omics-based monitoring allows researchers to systematically explore cause-and-effect relationships within the gut ecosystem. For instance, AI could predict which microbial genes influence the production of short-chain fatty acids, which are known to modulate inflammation and metabolic health [17]. CRISPR could then selectively edit those genes in model microbial communities, and metabolomic profiling could confirm the predicted changes, closing the feedback loop.

Jo et al. believes that AI accelerates the discovery and functional study of lactic acid bacteria, predicting SCFA and AMP production as well as host–microbe interactions using multi-omics data [18]. AI could also provide guidance in personalized probiotic design and optimizes industrial fermentation, formulation, and safety of LAB-based products [18]. Romano et al. employed machine learning-based meta-analysis to discover gut microbiome signatures associated with Parkinson's disease [19]. Interestingly, pathways in gut microbes involved in solvent and pesticide biotransformation are more abundant in Parkinson's disease [19]. These findings are consistent with epidemiological data linking exposure to these compounds with increased Parkinson's disease risk and suggest that the gut microbiota may influence their toxicity [19]. Catacutan et al. Used AI to elucidate mechanisms of narrow-spectrum antibiotic against Enterobacteriaceae bacteria species such as adherent-invasive *E. coli* [20]. Mechanism-of-action studies guided by molecular substructure analysis and deep learning showed that enterololin disrupts lipoprotein trafficking via the LolCDE complex [20]. Laboratory-evolved resistant mutants primarily carried mutations in lolC and lolE, with an *in vitro* resistance frequency of approximately 10^{-8} to 10^{-7} [20]. Their study demonstrates the effectiveness of deep learning in predicting molecular interactions and uncovers a promising antibacterial candidate targeting Enterobacteriaceae for further advancement [20].

Applications and Recent Researches on the Integration of AI with CRISPR and Multi-Omics

Applications of this integrative approach are vast. In therapeutic contexts, precision editing of the gut microbiome could enable novel strategies for treating metabolic disorders, inflammatory bowel disease, or neurodegenerative diseases via modulation of microbial metabolites [21]. Personalized nutrition could be guided by AI models that integrate a person's microbiome composition, host genomics, and dietary inputs to optimize gut health [22]. Furthermore, understanding microbial contributions to drug metabolism through omics and AI could enhance pharmacokinetics and reduce adverse effects, ushering in a new era of microbiome-informed precision medicine [23].

Bhat et al. deemed that the integration of AI with CRISPR-Cas genome editing technology enhances cancer therapeutics in their systematic review [24]. It has been vastly known that gut microbiome can greatly influenced both cancer progression and the gut-brain-axis disease development [25,26]. Bhat et al. emphasizes how artificial intelligence can improve the precision of CRISPR by optimizing on-target activity and minimizing off-target effects, which is essential for its wider use in cancer therapy [24]. Pan and Barrangou highlighted the combination CRISPR-based genome editing and omics technology to elucidate food microbes [27]. They examined how this integrated strategy facilitates the engineering of food microbes to create improved probiotic strains, develop innovative biotherapeutics, and modify microbial communities within food systems [27].

Challenges, Future Outlooks and Conclusion

Despite these advances, challenges remain. The gut microbiome is highly dynamic and context-dependent, making reproducibility and translation to clinical applications difficult. AI models require large, well-annotated datasets to achieve predictive accuracy, and biases in training data can limit generalizability [28]. CRISPR interventions in complex microbial communities face technical hurdles, including efficient delivery, off-target effects, and ecological consequences for the microbiome [29]. Multi-omics analyses are costly and computationally intensive, and integrating datasets from different platforms requires robust statistical frameworks. Ethical considerations also arise when manipulating human-associated microbiomes, particularly regarding long-term safety and ecological impacts.

The integration of CRISPR, AI, and multi-omics technologies positions gut microbiology at the forefront of precision medicine and functional microbiome research. In the future, AI-driven predictive models combined with high-resolution omics datasets are likely to enable personalized mapping of an individual's gut ecosystem, identifying key microbial signatures that influence health and disease. CRISPR-based genome editing will facilitate targeted manipulation of gut microbes, allowing validation of causal relationships and the design of engineered strains with therapeutic potential. This convergence may lead to the development of next-generation microbiome-based interventions, including precision probiotics, metabolite-modulating therapies, and microbiome-informed drug delivery systems. Furthermore, iterative AI-guided experimentation can accelerate discovery, optimize microbial consortia for functional outcomes, and anticipate off-target effects, enhancing both safety and efficacy. As computational power, data availability, and genome engineering techniques continue to advance, the gut microbiome is poised to become a highly tractable system for both mechanistic studies and translational applications, ultimately transforming disease prevention, diagnostics, and individualized treatment strategies.

In conclusion, the convergence of gut microbiology, CRISPR, AI, and multi-omics represents a transformative paradigm in biomedical research. Multi-omic technologies provide a high-resolution view of microbial communities and their functional outputs. AI enables the interpretation of complex datasets, pattern recognition, and predictive modeling. CRISPR allows precise functional perturbation and therapeutic targeting [30]. Together, these approaches offer unprecedented opportunities to understand, predict, and modulate gut microbial ecosystems for human health. The integration of these tools not only enhances our mechanistic understanding of host-microbe interactions [31,32] but also lays the foundation for next-generation interventions in personalized medicine, nutrition, and disease prevention. As computational models, genetic tools, and omics technologies continue to advance, the predictive and therapeutic potential of gut microbiome research will only expand, heralding a new era of precision gut health.

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