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Gut Microbiota Dysbiosis Drives Resistance Gene Transfer and Bacterial Adaptation

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Abstract. Antimicrobial resistance (AMR) has emerged as a global health crisis, threatening the efficacy of modern medicine. The gut microbiota, a densely populated microbial ecosystem, plays a critical role in modulating host immunity, metabolism, and resistance to pathogen colonization. Disruption of this microbial balance—gut dysbiosis—creates an environment conducive to the proliferation and horizontal transfer of antibiotic resistance genes (ARGs), contributing to the development of multidrug-resistant organisms (MDROs). This review explores the molecular and ecological mechanisms through which gut dysbiosis influences AMR and examines therapeutic approaches aimed at restoring microbial homeostasis to combat this pressing challenge. Antimicrobial resistance (AMR) is a pressing global health concern, and recent studies have revealed the human gut microbiota as a significant reservoir of resistance genes. Dysbiosis—an imbalance in the composition and function of gut microbiota—can enhance the persistence and transfer of antibiotic resistance genes (ARGs) among microbial populations. This review explores the mechanisms linking gut dysbiosis to AMR, highlights recent findings on microbial-host interactions, and discusses emerging therapeutic strategies such as probiotics, fecal microbiota transplantation (FMT), and microbiota-modulating diets to combat resistance development. Understanding these dynamics is critical for advancing personalized medicine and curbing the spread of drug-resistant infections.

Highlights:

1. Dysbiosis Promotes AMR – Gut imbalance helps antibiotic resistance genes spread.
2. Gut as ARG Reservoir – The gut hosts many resistance genes that can transfer between microbes.
3. Therapies Target Microbiota – Probiotics, FMT, and diets may restore balance and fight AMR.

Keywords: Gut Microbiota, Antimicrobial Resistance, Dysbiosis, Probiotics, Therapeutic Strategies

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Introduction

AMR genes could potentially be stored in any niche that supports a diverse array of bacterial flora. The host-associated environment, which is analogous to the natural world and includes the human intestine, is one example of such a niche. [1] The gut microbiota, AMR profile, and factors affecting movement, diversity, and the effects of AMR gene expression must all be investigated. Many healthy adults' gut "core microbiota" is mainly composed of bacteria from the genera Firmicutes and Bacteroidetes, with Actinobacteria, Cyanobacteria, Fusobacteria, Proteobacteria, and Verrucomicrobia following closely after. [2]. Smaller amounts of enteropathogenesis from the Enterobacteriaceae and Enterococcaceae make up the dynamic and diverse endogenous gut microbiota. This is interesting because these bacteria, which are now a major cause of nosocomial infections, can live in our stomachs. [3].

Antimicrobial resistance accounts for an estimated 1.27 million deaths annually, and projections suggest that by 2050, AMR may result in more deaths than cancer. While overuse of antibiotics in clinical and agricultural settings remains a key driver, recent studies underscore the importance of the gut microbiota as both a reservoir and conduit for resistance genes[4].

The human gut harbours over 10^{14} microorganisms, including bacteria, archaea, viruses, fungi, and protozoa. The integrity of this microbiota is essential for immune homeostasis, pathogen defence, and metabolic health. However, antibiotic exposure, poor diet, infections, and other environmental stressors can disrupt this balance, leading to gut dysbiosis [5]. This condition fosters the persistence and transmission of ARGs, making the gut a central battleground in the fight against AMR.

Results and Discussion

A. The Healthy Gut Microbiota: Composition and Function

The human gut microbiota comprises a complex and dynamic community of microorganisms that reside primarily in the colon, reaching densities of up to 10^{12} microbial cells per gram of intestinal content [6].This ecosystem plays a fundamental role in maintaining host physiology, influencing digestion, metabolism, immunity, and

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protection against pathogens[7].A stable and diverse microbiota is considered a hallmark of health, while deviations from this balanced state—termed dysbiosis—are associated with various diseases, including metabolic disorders, inflammatory conditions, and antimicrobial resistance [8].

1. Composition of a Healthy Gut Microbiota

a. Taxonomic Diversity

The majority of gut microbiota in healthy adults belong to five bacterial phyla:

1) Firmicutes (60–80%): This phylum includes numerous gram-positive, spore-forming anaerobes. Key genera include:
   - Clostridium (especially Clostridium clusters IV and XIVa, now reclassified to Ruminococcaceae and Lachnospiraceae)
   - Faecalibacterium (notably F. prausnitzii, a major butyrate producer with anti-inflammatory properties)
   - Lactobacillus (important in mucosal immunity and fermentation of carbohydrates). Bacteroidetes (15–25%) A dominant phylum consisting of gram-negative anaerobes. Notable genera:
   - Bacteroides (involved in polysaccharide digestion and bile acid metabolism)
   - Prevotella (associated with plant-rich diets)
2) Actinobacteria (<10%): Mainly composed of Bifidobacterium species, which are important in early life and for promoting immune maturation.
3) Proteobacteria (<5%): Includes facultative anaerobes like Escherichia, Klebsiella, and Enterobacter. While present in low abundance, their overgrowth is often associated with dysbiosis.
4) Verrucomicrobia: Especially Akkermansia muciniphila, a mucin-degrading bacterium linked to metabolic health and mucosal integrity.
5) Other phyla such as Fusobacteria, Cyanobacteria, and Spirochaetes are present in smaller proportions, and their roles are less well-defined in health.[9,10]

b. Microbial Richness and Evenness

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1) In Richness: Refers to the number of different species. High richness is associated with resilience against perturbations.
2) Evenness: Describes the relative abundance of different species. A balanced distribution supports functional redundancy and ecosystem stability.[11]
3) Interindividual variation in microbial composition is influenced by age, diet, genetics, geography, medication use (especially antibiotics), and early life exposures (e.g., mode of birth and breastfeeding).[12]

2. The Functions of a Healthy Gut Microbiota

The healthy gut microbiota plays an integral role in host well-being by regulating metabolism, modulating the immune system, preventing pathogen overgrowth, and preserving gut barrier function. [13] These functions form a tightly interconnected network that, when disturbed, can precipitate pathological states including enhanced antimicrobial resistance. A thorough understanding of these microbiota-driven functions provides insight into how gut dysbiosis contributes to the emergence and persistence of resistant microbial strains and offers a foundation for microbiota-targeted therapies.[14]

a. Metabolic Functions

1) Fermentation of Dietary Substrates

Short-Chain Fatty Acid (SCFA) Production: Gut microbes ferment indigestible dietary fibers and resistant starches to produce SCFAs such as butyrate, acetate, and propionate. [15] These SCFAs play critical roles in Providing energy to colonocytes (butyrate) , Modulating lipid and glucose metabolism (acetate and propionate) , Regulating immune responses and inflammation . Faecalibacterium prausnitzii and Roseburia spp. are prominent butyrate-producing species in healthy individuals [16]

2) Vitamin Biosynthesis

Commensal bacteria synthesize essential vitamins, including: Vitamin K2 (menaquinone), Vitamin B-complex: B1 (thiamine), B2 (riboflavin), B6 (pyridoxine), B9 (folate), and B12 (cobalamin) .These

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vitamins are essential cofactors in host metabolic pathways and contribute to hematologic and neurologic health.[17]

3) Bile Acid Transformation

Microbiota convert primary bile acids into secondary bile acids (e.g., deoxycholic acid) via deconjugation and dihydroxylation. These compounds aid in fat digestion and act as signaling molecules that regulate host metabolism and inflammation [18]

4) Xenobiotic and Drug Metabolism

Gut microbes enzymatically modify drugs and dietary compounds, influencing their absorption, efficacy, and toxicity. For example, microbial β-glucuronidases can reactivate drug metabolites, impacting chemotherapy and antibiotic clearance.[19]

b. Immunological Functions

The gut microbiota is essential in educating and modulating the immune system:

1) Immune System Maturation : Microbial antigens stimulate the development of gut-associated lymphoid tissue (GALT) and promote the differentiation of immune cells such as regulatory T cells (Tregs) and Th17 cells.
2) Anti-inflammatory Effects :Certain commensals, such as Bacteroides fragilis (via polysaccharide A), induce IL-10 production, reducing inflammation. SCFAs like butyrate promote Treg cell differentiation and downregulate NF-κB-mediated inflammatory responses.
3) Immune Tolerance : Healthy microbiota helps maintain a balanced immune response by promoting tolerance to food antigens and self-antigens, thereby preventing autoimmunity and allergies.[20]

c. Protection Against Pathogens (Colonization Resistance)

1) healthy microbiota prevents colonization by pathogenic organisms through several mechanisms:
   - Competitive Exclusion :Commensals compete for nutrients and attachment sites, limiting the ecological niches available for pathogens

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like Salmonella, Clostridioides difficile, and multidrug-resistant Enterobacteriaceae.

- Production of Antimicrobial Compounds: Microbes produce bacteriocins, SCFAs, and hydrogen peroxide, which inhibit or kill invading pathogens.
- Modulation of Host Defense : Commensals enhance mucosal immunity by inducing the expression of defensins, mucins, and IgA, reinforcing the gut's physical and immune barriers.[21]

d. Maintenance of Intestinal Barrier Integrity

The gut epithelium, composed of tightly connected epithelial cells, acts as a physical barrier against microbial translocation. Commensal microbes:

1) Stimulate mucin production by goblet cells
2) Reinforce tight junction proteins (e.g., occludin, claudins, and zonulin)
3) Reduce epithelial apoptosis and promote repair mechanisms
4) Disruption of this barrier—via dysbiosis or inflammation—can result in increased intestinal permeability ("leaky gut"), allowing microbial products like lipopolysaccharides (LPS) to enter systemic circulation and promote inflammation.[20,21]

3. Microflora and Pathogen Adaptation

The phrase "human gut microbiota" describes microorganisms such as viruses, bacteria, fungus, and protozoa. They reside inside the gut and carry out a number of beneficial functions for their hosts, including food fermentation, vitamin and amino acid production, immune system maturation and regulation, GI tract hormone release control, brain behavior control, and preventing the colonization of enteropathogenic bacteria. [22]. The typical human gut microbiota is composed of two major phyla, Firmicutes and Bacteroidetes, and two minor phyla, Actinobacteria and Proteobacteria. Although this broad profile remains constant, the gut microbiota exhibits both temporal and geographic shifts in distribution based on pH and aerobic conditions at the genus level and beyond. Moving from the distal oesophagus to the rectum will result in a discernible change in the type and amount of bacteria present; in the former, there are 101 bacteria per gram of

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contents, but in the latter, the colon and distal intestine have 1012 bacteria per gram of contents. [23].

4. Role of Microflora in Pathogen Evolution and Adaptation To AMR

The three most significant processes that can lead to antibiotic resistance include blocking the antibiotic's ability to bind to its target, breaking it down, and stopping it from getting into the target. [24] Through mutations, bacteria can become resistant, which can subsequently vertically propagate to daughter cells during cell division. As an alternative, bacteria can use horizontal gene transfer (HGT) to get mobile genetic elements (MGEs) that carry genes resistant to antibiotics. The mechanisms behind HGT include transformation, transduction, conjugation, and membrane-vesicle-mediated DNA transfer.[25]

Together, these HGT mechanisms facilitate the global dissemination of genes that give microorganisms resistance to antibiotics. Antibiotic-resistant genes are expected to proliferate particularly strongly in settings with high microbial diversity and abundance, like the bacterial communities seen in the human gut [13,14]. According to research, third-generation cephalosporin-resistant (3GC-R) Enterobacteriaceae were found in a sizable percentage of Taiwanese individuals. It has been demonstrated that the gut microbiota of carriers carrying 3GC-R Enterobacteriaceae is more varied than that of non-carriers. [15].

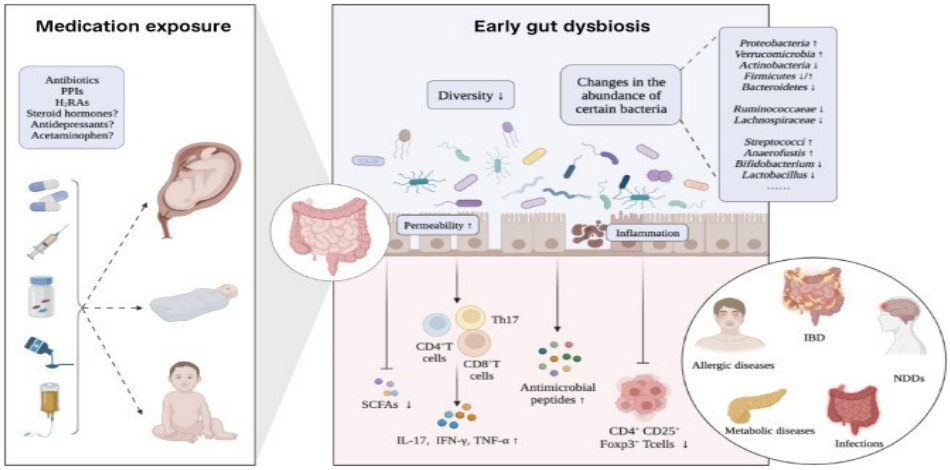

Figure 1. The Development of Human Gut Microbiota During Early Life is Influenced by Age, Birth Modes, and Feeding Patterns. Birth Modes and Feeding Patterns Affect Intestinal Microbial Colonization, With Vaginal and Breastfed Children Developing a

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5. Gut Microbiota and The Resistome

To say that antimicrobial resistance (AMR) is a problem would be an understatement. Antibiotic consumption is rising overall, according to Dr. Ramanan Laxminarayan, head of the Center for Disease Dynamics, Economics & Policy, who spoke during a panel on addressing the AMR epidemic at ASM's 2022 Microbe conference. Antibiotic use actually increased by 65% globally between 2000 and 2015, and if nothing is done, it might triple by 2030.[27]

Some of the factors contributing to the rise in antibiotic use include overuse (e.g., to treat viral diseases like COVID-19 or influenza), increasing antibiotic accessibility and cost, particularly in low- and middle-income areas, and agricultural applications. The world today confronts a bleak future where conventional treatments for microbial infections may not be adequate due to the emergence and spread of AMR. One part of stopping the development of AMR is identifying pools of resistant microbes. The human gut contains many microorganisms that are resistant to a broad range of medications. [28] This includes harmful organisms that are identified in the CDC's Antibiotic Resistance Threats Report, such as carbapenem-resistant Enterobacteriaceae and vancomycin-resistant Enterococci. Humans can acquire and spread antibiotic-resistance genes (ARGs) and AMR organisms from other reservoirs, such as animals. Thus, a key element of the AMR puzzle is the gut Resistome, a collection of ARGs that the microbiota contains.[29]

B. Antibiotic Resistance and the Gut Microbiota

Some bacteria that live in the gut are resistant to antibiotics by nature, while others pick up resistance from other bacteria. [5] Similar to ARGs, bacteria exchange genetic material through a variety of horizontal gene transfer (HGT) mechanisms, such as conjugation, which involves the transfer of DNA between cells, frequently through mobile genetic elements like plasmids and transposons; transduction, which involves the transfer of genes between bacterial hosts via bacteriophages; and

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transformation, which involves the absorption of environmental DNA and its incorporation into the bacterial genome.[30] When a large number of microorganisms are huddled together, HGT and the subsequent exchange of ARGs happen easily. The gut creates the perfect environment for bacterial interaction because there are so many of them around. The baseline level of HGT in the gut is actually thought to be 25 times higher than in soil, another habitat that is rich in microbes. The transfer of ARGs is only aided by the selection pressure that these microorganisms may experience from preventative or therapeutic antibiotics.[31]

A significant portion of the gut bacteria that harbor ARGs are anaerobic commensal species, and many of them do not represent a health risk. The issue arises when potentially harmful microorganisms gain ARGs. For example, a lesser number of facultative anaerobes, such as Enterobacteriaceae and Enterococcaceae spp., are nested among the robust populations of anaerobic gut bacteria. Multi-drug resistant strains of E. coli, Klebsiella pneumonia, and Enterococcus faecalis are among the bacteria that belong to these categories and are frequently responsible for AMR infections. [32]

ARGs can be acquired by these microorganisms from other gut microbiota members. For instance, gut anaerobes frequently carry a transposon containing the vanB gene, which provides resistance against vancomycin. The vanB gene can be passed from these bacteria to Enterococcus species. The CDC considers vancomycin-resistant Enterococci to be a "serious threat," therefore this is very alarming.[33]

1. Mechanisms of Microflora-Mediated AMR

Microflora-mediated antimicrobial resistance (AMR) occurs through several mechanisms, including horizontal gene transfer, biofilm formation, quorum sensing, metabolic interactions, and the role of microflora in host-pathogen interactions. These mechanisms allow bacteria to acquire resistance genes, protect themselves from antimicrobials, and facilitate the spread of resistance within and between bacterial populations. [34]

Horizontal Gene Transfer (HGT): HGT, the transfer of genetic material between cells that are not direct descendants, is a key mechanism for the spread of AMR genes. Bacteria can acquire resistance genes from other bacteria, even

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those of different species, through processes like conjugation, transduction, and transformation. [35]

Biofilm Formation: Biofilms are complex communities of bacteria encased in a self-produced matrix, which can protect bacteria from antimicrobials. The biofilm matrix can hinder the penetration of antibiotics, and the slow-growing cells within the biofilm are less susceptible to antibiotics that target actively dividing cells. [36]

Quorum Sensing (QS): QS is a communication system that allows bacteria to coordinate their gene expression in response to cell density. In the context of AMR, QS can influence biofilm formation, antimicrobial tolerance, and the expression of resistance genes.

Metabolic Interactions: The gut microbiota can influence AMR by directly interfering with the activity of antimicrobials, or by creating an environment that favors the growth of resistant bacteria. For example, some gut bacteria can metabolize antibiotics, reducing their effectiveness. [37]

Host-Pathogen Interactions: Microflora can act as a barrier against the colonization of pathogens, including antibiotic-resistant strains. Additionally, the gut microbiota can influence the host's immune response, which can affect the outcome of infections. [38]

In summary, microflora-mediated AMR involves a complex interplay of genetic, environmental, and community-level factors that enable bacteria to develop and spread resistance to antimicrobials.

2. Impact of Antibiotics on the Intestinal Microbiota

Antibiotics are required for bacterial infections, but they can also significantly alter the gut microbiota, a fragile ecology that is necessary for immunological development, metabolism, and general health (Figure 2). By reducing the number of beneficial genera (Bifidobacterium, Faecalibacterium) and changing important phyla (Firmicutes, Bacteroidetes, Actinobacteria, Proteobacteria), broad-spectrum drugs frequently cause dysbiosis, which leads to a loss of diversity and a distortion of community composition [39]. Reduced resistance to colonization creates an opening for opportunistic infections, such as Salmonella typhimurium and C. difficile.

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Gut homeostasis is further compromised by decreased SCFA synthesis. Through horizontal gene transfer, antibiotics can also hasten the development of antibiotic resistance [40]. It may take months or even years to recover from these disruptions, depending on the antibiotic's spectrum, dosage, and duration [41]. Disruptions in early life may have long-term effects on the immune system, metabolism, and cognition. Selective antibiotic regimens and probiotic or synbiotic supplements can lessen these negative effects, underscoring the importance of antibiotic stewardship [42]. An overview of treatment techniques based on the microbiota can be seen in Table 2.

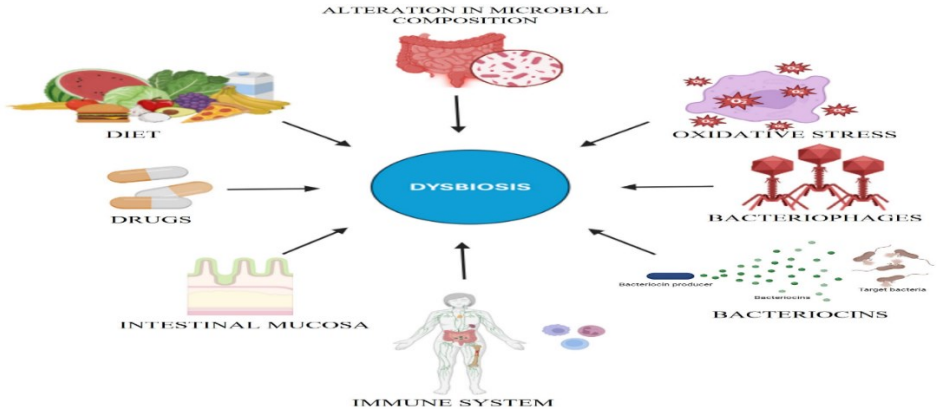

Figure 2. This Diagram Depicts the Multifactorial Contributors to Dysbiosis, a Disruption of Microbial Homeostasis. Key Factors Include Diet, Drugs, the Intestinal Mucosa, and the Immune System, Which Regulate Microbial Stability. Oxidative Stress, Bacteriophages, and Bacteriocins Further Modulate Microbial Composition, While Microbial Alterations Can Sustain Dysbiosis, Compromising Gut and Systemic Homeostasis.[43]

C. Strategies to Counteract Gut Microbiota-Driven AMR

1. Diet and Dietary Supplements

The genetic diversity and composition of the gut microbiota are influenced by dietary content. More research is being done on the effect of certain dietary factors, primarily the kind and ratio of fat, carbohydrate, and protein intake, in variations in gut microbiota [44]. Comparing the feces of vegetarians and lactovegetarians, it was found that omnivores had more species of the Clostridial clusters IV and XIVa, which are bacteria that may convert fiber to short chain fatty acids (SCFAs).

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[48,49]. In vitro, SCFAs can control the expression of Salmonella spp. or E. coli virulence genes [50]. Furthermore, mice fed a "Western" high-fat/simple carbohydrate or low-fat/complex plant polysaccharide diet in a research showed a higher proportion of Firmicutes, a lower proportion of Bacteroidetes, and less bacterial diversity than the mice fed a low-fat diet. [45].

We are aware that a microbiota with low bacterial variety is deemed "unhealthy" and that this is a risk factor for a reduction in colonization resistance.[46], Elderly persons who remained in long-term facilities and had little variation in their food, also had less gut bacterial diversity, compared to their counterparts that resided in the community; this was connected with worse health status [47]. Avoiding a high-protein diet may help maintain colonization resistance since in another experimental setting, a high-protein diet upset the gut microbiota. [48]. However, compared to a high-protein diet, a diet rich in fiber was linked to a faster recovery of the gut microbiota following antibiotic exposure [49]. Additionally, there have been reports of Chinese dietary treatments that have a positive impact on gut healing and of some compounds, such as konjac glucomannan (glucomannan produced from Amorphophallus konjac, a plant with edible tubers), having protective effects on the gut microbiota [50].

[57,58]. Conversely, a diet rich in fiber was linked to a faster recovery of the gut microbiota following antibiotic exposure than a diet rich in protein [51]. Additionally, certain compounds have been reported to have protective benefits on the gut microbiota, such as konjac glucomannan (glucomannan produced from the plant Amorphophallus konjac, which produces edible tubers) [52], as well as Chinese dietary cures that have positive effects on gut repair.

We will learn useful information on the relationship between food, gut microbiota, and MDROs from an ongoing cross-sectional study called the Wisconsin Microbiota Study [53]. Dietary modification to enhance bacterial variety may be an adjuvant technique to reduce antibiotic resistance, notwithstanding the paucity of pertinent human trials.

2. Targeted Probiotic and Prebiotic Therapy

"Selectively fermented ingredients that allow specific changes, both in the composition and/or activity in the GI microbiota that confer benefits upon host

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well-being and health" [64] is the definition of prebiotics. By altering the gut microbiota, prebiotics have been linked to positive impacts on human metabolism and are thought to promote the growth of lactobacilli or bifidobacteria [54,55]. In a study on mice, adding SCFAs or fructooligosaccharides to the diet changed the makeup of the microbiota.

The gut microbiota was also found to be restored by fructooligosaccharides , whilst other probiotics of the inulin type were found to prevent the disturbance of the gut microbiota by maintaining the commensal bacteria [56].

According to the World Health Organization, probiotics are "live microorganisms which when administered in adequate amounts confer a health benefit on the host." Bifidobacterium and Lactobacillus strains are the most often utilized probiotics. Rijkers et al. claim that probiotics have three beneficial effects: they affect the systemic immune system and other organs, they enhance the function of the mucosal barrier or mucosal immune system, and they hinder the growth or survival of pathogenic microorganisms in the gut lumen.[57]

In an experimental mouse investigation, it was demonstrated that Lactobacillus plantarum and Lactobacillus acidophilus decreased intestinal counts of multidrug resistant enteroaggregative E. coli .More research is necessary to identify the best probiotic for each dysbiosis-related disorder, though, due to the wide interindividual variability in gut microbiota and the various ways that dysbiosis contributes to disease.[58].

More recently, two investigations have used modified probiotics to specifically eradicate P. aeruginosa. In order to eliminate their target, these probiotics are designed to recognize quorum sensing molecules and, when they identify the pathogen, either express antimicrobial chemicals or activate other previously developed mechanisms [59]. In addition to probiotics, genetic engineering has focused on phages to allow for the targeted destruction of bacteria with AR or certain virulence features. [60] There are no extensive studies looking at how probiotics affect colonization resistance, despite the fact that there are numerous systematic reviews, including a recent umbrella review, that concentrate on the impact of probiotics in lowering infections in critically sick

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patients [61]. Numerous studies demonstrate their efficacy against gram-positive bacteria as MRSA or VRE , however the results for gram-negative pathogens are unsatisfactory

Future probiotic development now requires identifying the bacteria that may improve colonization resistance and creating a more individualized probiotic delivery system . Lastly, it is advised to take probiotic supplements cautiously in this population and always in the context of a clinical trial because there have been reports of clinically severe bacteremias with bacterial strains found in these supplements in intensive care unit patients.[62].

D. Fecal Microbiota Transplantation (FMT)

For more than 1,700 years, calecal microbiota transplantation (FMT), which involves transferring stool from a healthy donor into a patient's digestive tract, has been used to treat severe, chronic diarrhea and food poisoning. It has demonstrated notable therapeutic efficacy in getting rid of C. difficile, reducing relapses, and curing related symptoms. In order to replace harmful bacteria that invade the gut, FMT aims to replenish the colon with a balanced and healthy microbiota. By altering the luminal microenvironment and opposing nutrients and binding sites, the transplanted microbiota may prevent the colonization of harmful bacteria. [63]. By detecting signals from the microbiota or host-derived signals that have been altered by the microbiota, pathogenic bacteria can change their capacity for colonization or pathogenicity. Alterations in gut microbial metabolites may improve host responses, including T cell populations, IgA-mediated interaction restoration, and enrichment in secondary bile acids following FMT. FMT may be linked to a positive immunological response in murine models.[64]

Since the gut is the primary reservoir for gram-negative bacteria, FMT has also been investigated for gut decontamination from resistant infections. Only one RCT specifically targeting MDRO decontamination found a slight, non-significant decrease in ESBL and CRE colonization following the combination of antibiotics and FMT, indicating that RCTs have not demonstrated the positive effect of FMT. [65]. In order to eradicate Carbapenem-resistant Enterobacteriaceae (CRE) colonization, FMT seems to be a safe and maybe successful intervention.

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FMT seems to have a small number of self-limiting, frequently mild to moderate adverse effects, such as fever, cramps, diarrhea, constipation, nausea, and distension of the abdomen. On the other hand, severe adverse events have been documented, including aspiration pneumonia, bacterial and viral infections, temporary relapse of IBD, and procedure-related side effects. It has also been reported that the Van B resistance gene may be transmitted following FMT.[66]

Since multiple trials shown a decrease in the incidence of clinical infection following FMT in MDRO-colonized individuals, FMT may offer protection against intestinal translocation of MDROs, preventing bloodstream infections irrespective of gut decontamination. A number of studies are currently being conducted to assess the contribution of FMT to MDRO decolonization.[67]

E. Bacteriophage Therapy

Viruses known as bacteriophages (phages) specifically target and eliminate bacteria. They are the most prevalent naturally occurring organisms and are essential in controlling bacterial populations and affecting microbial environments. Phages are helpful because they can eliminate bacteria that are resistant to medications like antibiotics. Phages have a high degree of specificity in infecting their bacterial hosts. Human cells are not infected by them.

Our ability to treat bacterial infections is seriously threatened by antimicrobial resistance (AMR) on a worldwide scale. The development of new antibiotics has frequently proven to be costly and challenging. [68]

This has raised interest in employing phages, an earlier method of treating microbial illnesses. One promising strategy for managing AMR, one of the biggest risks to global public health and development, is phage therapy. The One Health approach, which takes into account the interdependence of environmental, animal, and human health, is a complex strategy that is necessary to address AMR. Phages offer physiologically novel solutions to the problem of AMR in a variety of fields, from potential replacement of antibiotics in agriculture to therapeutic usage in humans and animals.[69]

Nowadays, when all other options have been explored, phages are mostly employed for compassionate reasons in life-threatening circumstances.

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It will take more clinical research proof before phages are generally accessible for human use. For phage application and therapy to be effective, safe, and feasible across all One Health sectors, strong proof is needed.[70]

F. Microbiome-Sparing Antibiotics

When used to treat an infection, antibiotics affect not just the target pathogen but also the susceptible part of the microbiome, making the host susceptible to colonization and potential infection by multidrug-resistant bacteria like C. difficile. Generally speaking, these side effects are more noticeable with broad-spectrum antibiotics than with narrow-spectrum ones. In the past, experts have advocated for novel methods of developing antibiotics that reduce this collateral harm to the microbiome. [71]

"Microbiome-sparing" antibiotics are those that, in theory, have no effect on the microbiome and are extremely specific and targeted to pathogenic organisms. Drug development candidates should no longer be determined just by killing activity; rather, a balance between killing activity and microbiome-sparing effects should be used. [72] Microbiome-sparing antibiotics could greatly lessen the negative effects of microbiome disruption when used to treat infections where the causative pathogen is known, even though broad-spectrum antibiotics would still be essential for the empirical treatment of some presentations [73] (such as sepsis). (Fig. 3).

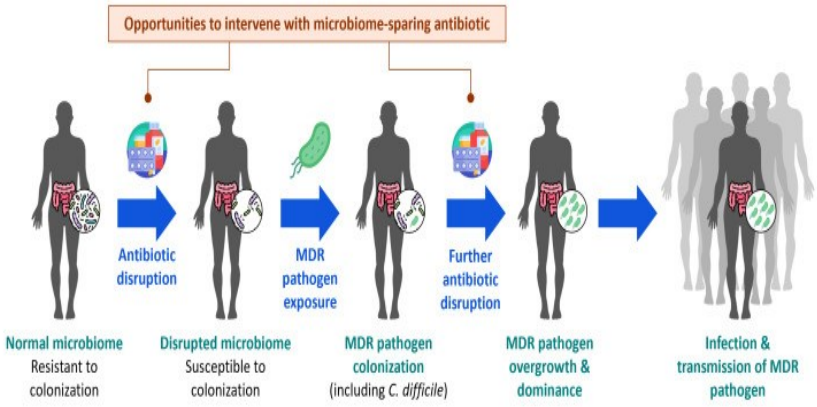

Figure 3. The Microbiome Health-effects Cascade: From Antibiotic-mediated Microbiome Disruption to Infection and Transmission. Mdr, Multidrug Resistant. (43)

G. CRISPR-Cas Systems

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Bacteria and archaea have an adaptive immune system called CRISPR-Cas that guards against infection by viruses, phages, and other foreign genetic material. It includes a set of CRISPR-associated (cas) genes that encode Cas proteins with endonuclease activity, as well as CRISPR repeat-spacer arrays that can be translated into CRISPR RNA (crRNA) and trans-activating CRISPR RNA (tracrRNA). [74] Cas proteins cut foreign DNA into small pieces when it invades, and these pieces are then incorporated as new spacers into the CRISPR array. The host is protected when the invader re-invades because crRNA identifies and bonds with the foreign DNA, directing the Cas protein to break target regions. There are two classes, six kinds, and numerous subtypes of CRISPR-Cas systems.[75]

The Streptococcus pyogenes-derived Type II CRISPR-Cas9 system is a popular and well-studied technology. It is made up of a single-guide RNA (sgRNA) that cleaves one strand of the target double-stranded DNA and RNA-guided Cas9 endonuclease. [76] One strand of the target double-stranded DNA is cleaved by the Cas9 protein, which possesses two nuclease domains, HNH and RuvC. A Cas9 ribonucleoprotein (RNP) that can bind and cleave the particular DNA target is formed by the sgRNA, a simplified form of crRNA and tracrRNA. For the Cas9 protein to bind to the target DNA, a protospacer adjacent motif (PAM) sequence is necessary. [77]

A double-strand break (DSB) is created during genome editing when sgRNA attracts Cas9 endonuclease to a particular location in the genome. This DSB can be fixed by the homology-directed repair (HDR) pathway or the error-prone non-homologous end joining (NHEJ) mechanism. Random insertions or deletions brought about by NHEJ may result in premature stop codons or frameshift mutations inside the open reading frame of the target gene.[78] HDR can use a homologous DNA repair template to precisely alter the genome at the target location. Figure (4):

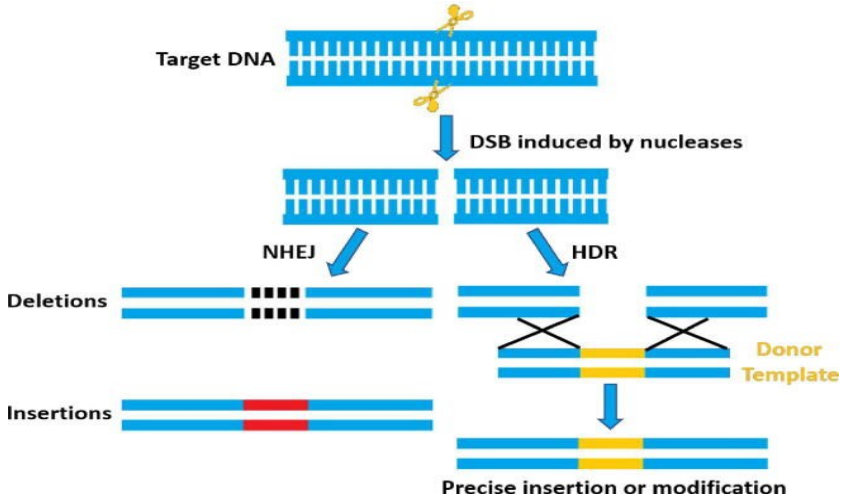

Figure 4. Genome Editing Mechanism. Both Homology-directed Repair (Hdr) and Non-homologous End Joining (Nhej) Pathways Can Be Used to Repair Double-strand Breaks (Dsb) Caused by Nucleases. At the Location of the Dsb, Nhej May Cause Random

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Insertions or Deletions (Indels) of Different Lengths. As an Alternative, Hdr Can Use a Homologous Dna Donor Template to Precisely Alter the Genome at the Target Location.

H. Future Perspectives

The interplay between gut microbiota and antimicrobial resistance is complex and multifactorial. Integrated "One Health" approaches that link human, animal, and environmental health are necessary to address AMR at its ecological roots. Advances in metagenomics, resistome analysis, and artificial intelligence will allow for better prediction, monitoring, and manipulation of gut microbial ecosystems to minimize resistance emergence.

Conclusions

Gut microbiota dysbiosis significantly contributes to the rise and persistence of antimicrobial resistance through ecological and molecular mechanisms. Understanding the gut as a dynamic reservoir of resistance offers novel opportunities for therapeutic intervention. Restoring microbial balance using microbiota-based therapies, phage applications, and microbiome-conscious antimicrobial stewardship represents a promising frontier in global efforts to curb AMR.

References

[1] Pamer, E. G., "Resurrecting the Intestinal Microbiota to Combat Antibiotic-Resistant Pathogens," Science, vol. 352, no. 6285, pp. 535–538, 2016.

[2] Van Schaik, W., "The Human Gut Resistome," Philosophical Transactions of the Royal Society B, vol. 370, no. 1670, 20140087, 2015.

[3] Becattini, S., Taur, Y., and Pamer, E. G., "Antibiotic-Induced Changes in the Intestinal Microbiota and Disease," Trends in Molecular Medicine, vol. 22, no. 6, pp. 458–478, 2016.

[4] Huang, H., Jiang, J., Wang, X., Jiang, K., and Cao, H., "Exposure to Prescribed Medication in Early Life and Impacts on Gut Microbiota and Disease Development," eClinicalMedicine, vol. 68, 102428, 2024.

[5] Forslund, K., et al., "Resistome Expansion in Disease-Associated Human Gut Microbiomes," Microbiome, vol. 11, p. 166, 2023.

ISSN 3063-8186. Published by Universitas Muhammadiyah Sidoarjo

https://doi.org/10.21070/ijhsm.v2i1.163

[6] The American Society for Microbiology, "The Gut Resistome and the Spread of Antimicrobial Resistance," 2022. [Online]. Available: https://asm.org/articles/2022/june/the-gut-resistome-and-the-spread-of-antimicrobial

[7] Health.com, "Steps You Can Take for Improved Gut Health," 2023. [Online]. Available: https://www.health.com/how-to-improve-gut-health-7507574

[8] PubMed, "The Impact of Antibiotic Therapy on Intestinal Microbiota: Dysbiosis, Antibiotic Resistance, and Restoration Strategies," 2023. [Online]. Available: https://pubmed.ncbi.nlm.nih.gov/40298495/

[9] Frontiers in Immunology, "Harnessing the Human Gut Microbiota: An Emerging Frontier in Combatting Multidrug-Resistant Bacteria," 2025. [Online]. Available: https://www.frontiersin.org/articles/10.3389/fimmu.2025.1563450/full

[10] Sekirov, I., Russell, S. L., Antunes, L. C., and Finlay, B. B., "Gut Microbiota in Health and Disease," Physiol Rev., vol. 90, no. 3, pp. 859–904, 2010.

[11] Koh, A., et al., "From Dietary Fiber to Host Physiology: Short-Chain Fatty Acids as Key Bacterial Metabolites," Cell, vol. 165, no. 6, pp. 1332–1345, 2016.

[12] Wilson, I. D. and Nicholson, J. K., "Gut Microbiome Interactions with Drug Metabolism, Efficacy, and Toxicity," Transl Res., vol. 179, pp. 204–222, 2017.

[13] Gopalakrishna, K. P., et al., "Maternal IgA Protects Against the Development of Necrotizing Enterocolitis in Preterm Infants," Nat Med., vol. 25, pp. 1110–1115, 2019.

[14] Selma-Royo, M., et al., "Perinatal Environment Shapes Microbiota Colonization and Infant Growth: Impact on Host Response and Intestinal Function," Microbiome, vol. 8, p. 167, 2020.

[15] Dawson-Hahn, E. E. and Rhee, K. E., "The Association Between Antibiotics in the First Year of Life and Child Growth Trajectory," BMC Pediatr., vol. 19, p. 23, 2019.

[16] Persaud, R. R., et al., "Perinatal Antibiotic Exposure of Neonates in Canada and Associated Risk Factors: A Population-Based Study," J Matern Fetal Neonatal Med., vol. 28, pp. 1190–1195, 2015.

[17] Leong, K. S. W., et al., "Associations of Prenatal and Childhood Antibiotic Exposure With Obesity at Age 4 Years," JAMA Netw Open, vol. 3, e1919681, 2020.

ISSN 3063-8186. Published by Universitas Muhammadiyah Sidoarjo

https://doi.org/10.21070/ijhsm.v2i1.163

[18] Slykerman, R. F., et al., "Antibiotics in the First Year of Life and Subsequent Neurocognitive Outcomes," Acta Paediatr., vol. 106, pp. 87–94, 2017.

[19] Y. Noh, E.-S. Kwon, J. Choi, Y. S. Choe, M. Kim, and H.-J. Yang, "Prenatal and Infant Exposure to Acid-Suppressive Medications and Risk of Allergic Diseases in Children," JAMA Pediatr., vol. 177, no. 2, pp. 146–154, Feb. 2023, doi: 10.1001/jamapediatrics.2022.5193.

[20] T. W. Sadler, M. W. Gillman, M. M. Dotterer, M. L. Glymour, and N. E. Adler, "Air Pollution and Neurodevelopmental Outcomes: A Review of the Current Literature and Public Health Implications," JAMA Pediatrics, vol. 177, no. 3, pp. 267–277, Mar. 2023, doi: 10.1001/jamapediatrics.2022.5946.

[21] Neuman, H., et al., "Antibiotics in Early Life: Dysbiosis and the Damage Done," FEMS Microbiol Rev., vol. 42, pp. 489–499, 2018.

[22] Y. Zhou, C. Qiu, Y. Jin, Z. Yang, and Y. Luo, "Intrauterine Antibiotic Exposure Affected Neonatal Gut Bacteria and Infant Growth Speed," Environmental Pollution, vol. 289, p. 117901, Nov. 2021, doi: 10.1016/j.envpol.2021.117901.

[23] L. Chen, Y. Yang, X. Jiang, Y. Xing, and Y. Chen, "Association Between Particulate Air Pollution and Risk of Depression in China: A Population-Based Study," Environmental Pollution, vol. 289, p. 117901, Jan. 2021, doi: 10.1016/j.envpol.2021.117901.

[24] Hutchings, M. I., Truman, A. W., and Wilkinson, B., "Antibiotics: Past, Present and Future," Curr Opin Microbiol, vol. 51, pp. 72–80, 2019.

[25] Antimicrobial Resistance Collaborators, "Global Burden of Bacterial Antimicrobial Resistance in 2019: A Systematic Analysis," Lancet, vol. 399, pp. 629–655, 2022.

[26] Young, V. B., "The Role of the Microbiome in Human Health and Disease: An Introduction for Clinicians," BMJ, vol. 356, j831, 2017.

[27] Li, J., et al., "Interplay Between Diet and Gut Microbiome, and Circulating Concentrations of Trimethylamine N-Oxide," Gut, vol. 71, pp. 724–733, 2022.

[28] Stiemsma, L. T. and Michels, K. B., "The Role of the Microbiome in the Developmental Origins of Health and Disease," Pediatrics, vol. 141, e20172437, 2018.

ISSN 3063-8186. Published by Universitas Muhammadiyah Sidoarjo

https://doi.org/10.21070/ijhsm.v2i1.163

[29] Guo, J., et al., "Gut Dysbiosis During Early Life: Causes, Health Outcomes, and Amelioration via Dietary Intervention," Crit Rev Food Sci Nutr., vol. 62, pp. 7199–7221, 2022.

[30] Schnizlein, M. K. and Young, V. B., "Capturing the Environment of the Clostridioides difficile Infection Cycle," Nat Rev Gastroenterol Hepatol, vol. 19, pp. 508–520, 2022.

[31] Willems, R. P. J., et al., "Incidence of Infection With Multidrug-Resistant Gram-Negative Bacteria and Vancomycin-Resistant Enterococci in Carriers," Lancet Infect Dis., vol. 23, pp. 719–731, 2023.

[32] Dubinsky-Pertzov, B., et al., "Carriage of Extended-Spectrum Beta-Lactamase-Producing Enterobacteriaceae and the Risk of Surgical Site Infection," Clin Infect Dis., vol. 68, pp. 1699–1704, 2019.

[33] Ianiro, G., et al., "Incidence of Bloodstream Infections and Survival in Patients With Recurrent Clostridioides difficile Treated With FMT or Antibiotics," Ann Intern Med., vol. 171, pp. 695–702, 2019.

[34] Pérez-Nadales, E., et al., "Prognostic Significance of KPC-Producing Klebsiella pneumoniae in Intestinal Microbiota," Microbiol Spectr., vol. 10, e0272821, 2022.

[35] Rao, K., et al., "Enterobacterales Infection After Intestinal Dominance in Hospitalized Patients," mSphere, vol. 5, e00450-20, 2020.

[36] Lee, N. C., Larionov, V., and Kouprina, N., "Highly Efficient CRISPR/Cas9-Mediated TAR Cloning in Yeast," Nucl Acids Res., vol. 43, 2015.

[37] Feng, Z., et al., "Efficient Genome Editing in Plants Using a CRISPR/Cas System," Cell Res., vol. 23, pp. 1229–1232, 2013.

[38] Jiang, W., et al., "CRISPR/Cas9-Mediated Gene Modification in Plants," Nucl Acids Res., vol. 41, 2013.

[39] Kim, H., et al., "A Co-CRISPR Strategy for Efficient Genome Editing in Caenorhabditis Elegans," Genetics, vol. 197, pp. 1069–1080, 2014.

[40] Bassett, A. R., et al., "Targeted Mutagenesis of Drosophila With the CRISPR/Cas9 System," Cell Rep., vol. 4, pp. 220–228, 2013.

[41] Hwang, W. Y., et al., "Efficient Genome Editing in Zebrafish Using a CRISPR-Cas System," Nat Biotechnol., vol. 31, pp. 227–229, 2013.

[42] Guo, X., et al., "RNA/Cas9-Mediated Genome Editing in Xenopus tropicalis," Development, vol. 141, pp. 707–714, 2014.

ISSN 3063-8186. Published by Universitas Muhammadiyah Sidoarjo

https://doi.org/10.21070/ijhsm.v2i1.163

[43] Wu, Y., et al., "Correction of a Genetic Disease in Mouse Using CRISPR-Cas9," Cell Stem Cell, vol. 13, pp. 659–662, 2013.

[44] Ma, Y., et al., "Generating Rats With Conditional Alleles Using CRISPR/Cas9," Cell Res., vol. 24, pp. 122–125, 2014.

[45] Song, Y., et al., "CRISPR/Cas9 Deletion of Glucokinase in Rabbit Leads to Hyperglycemia," Cell Mol Life Sci., vol. 77, pp. 3265–3277, 2020.

[46] Zou, Q., et al., "Generation of Gene-Target Dogs Using CRISPR/Cas9," J Mol Cell Biol., vol. 7, pp. 580–583, 2015.

[47] Ma, T., et al., "Melatonin-Enriched Milk via CRISPR/Cas9-Engineered Sheep," J Pineal Res., vol. 63, 2017.

[48] Niu, D., et al., "Inactivation of Porcine Endogenous Retrovirus in Pigs Using CRISPR-Cas9," Science, vol. 357, pp. 1303–1307, 2017.

[49] Niu, Y. Y., et al., "Generation of Gene-Modified Cynomolgus Monkey via Cas9/RNA," Cell, vol. 156, pp. 836–843, 2014.

[50] Xiong, X., et al., "CRISPR/Cas9 for Human Genome Engineering and Disease Research," Annu Rev Genomics Hum Genet., vol. 17, pp. 131–154, 2016.

[51] Zarei, A., et al., "Creating Cell and Animal Models of Human Disease by Genome Editing Using CRISPR/Cas9," J Gene Med., vol. 21, 2019.

[52] Rodríguez-Rodríguez, D. R., et al., "Application of CRISPR/Cas9 to Study Human Diseases," Int J Mol Med., vol. 43, pp. 1559–1574, 2019.

[53] Rydell-Törmänen, K. and Johnson, J. R., "Applicability of Mouse Models to Study Human Disease," Methods Mol Biol., vol. 1940, pp. 3–22, 2019.

[54] Platt, R. J., et al., "CRISPR-Cas9 Knockin Mice for Genome Editing and Cancer Modeling," Cell, vol. 159, pp. 440–455, 2014.

[55] Yang, S., et al., "CRISPR/Cas9-Mediated Gene Editing Ameliorates Neurotoxicity in Huntington's Disease," J Clin Invest., vol. 127, pp. 2719–2724, 2017.

[56] Li, P., et al., "Myo3a Y137C Knock-In Mice Display Hearing Loss and Hair Cell Degeneration," Neural Plast., vol. 2018, p. 4372913, 2018.

[57] Wang, L., et al., "CRISPR/Cas9-Mediated Gene Targeting Corrects Hemostasis in Factor IX-Knockout Mice," Blood, vol. 133, pp. 2745–2752, 2019.

[58] Matharu, N., et al., "CRISPR Activation of Promoter/Enhancer Rescues Obesity From Haploinsufficiency," Science, vol. 363, 2019.

ISSN 3063-8186. Published by Universitas Muhammadiyah Sidoarjo

https://doi.org/10.21070/ijhsm.v2i1.163

[59] Yang, Y., et al., "Dual AAV Enables Cas9-Mediated Correction of Liver Disease in Newborn Mice," Nat Biotechnol., vol. 34, pp. 334–338, 2016.

[60] Li, X. J. and Li, W., "Genetically Modifying Larger Animals to Model Human Diseases," J Genet Genomics, vol. 39, pp. 237–238, 2012.

[61] Yuan, L., et al., "CRISPR/Cas9-Mediated GJA8 Knockout Causes Cataracts in Rabbits," Sci Rep., vol. 6, p. 22024, 2016.

[62] Yuan, L., et al., "Mutation of αA-Crystallin Gene Induces Cataracts in Rabbits," Invest Ophthalmol Vis Sci., vol. 58, pp. BIO34–BIO41, 2017.

[63] Lv, Q., et al., "D-Repeat in the XIST Gene is Required for X Chromosome Inactivation," RNA Biol., vol. 13, pp. 172–176, 2016.

[64] Song, Y., et al., "Mutation of Sp1 Binding Site in SRY Causes Sex Reversal in Rabbits," Oncotarget, vol. 8, pp. 38176–38183, 2017.

[65] Song, Y., et al., "CRISPR/Cas9 Mutation of Tyr 3' UTR Induces Graying in Rabbit," Sci Rep., vol. 7, p. 1569, 2017.

[66] Xu, Y., et al., "Phenotype Identification of PAX4 Knockout Rabbit by CRISPR/Cas9," G3 (Bethesda), vol. 8, pp. 2833–2840, 2018.

[67] Chen, M., et al., "Truncated Fibrillin-1 Induces Marfanoid-Progeroid-Lipodystrophy in Rabbit," Dis Model Mech., vol. 11, 2018.

[68] Deng, J., et al., "Hoxc13-Ablated Rabbits Show Balance Disruption in Hair Follicles," FASEB J., vol. 33, pp. 1226–1234, 2019.

[69] Sui, T., et al., "A Novel Rabbit Model of Duchenne Muscular Dystrophy via CRISPR/Cas9," Dis Model Mech., vol. 11, 2018.

[70] Sui, T., et al., "CRISPR Engineered ANO5 Mutation Leads to Muscular Dystrophy in Rabbit," Cell Death Dis., vol. 9, p. 609, 2018.

[71] Sui, T., et al., "LMNA-Mutated Rabbits as a Model of Premature Aging," Aging Dis., vol. 10, pp. 102–115, 2019.

[72] Liu, T., et al., "DMP1 Ablation in Rabbit Results in Bone Microarchitecture Defects," J Bone Miner Res., vol. 34, pp. 1115–1128, 2019.

[73] Lu, Y., et al., "GADD45G Mutation Causes Cleft Lip in Rabbits," Biochim Biophys Acta Mol Basis Dis., vol. 1865, pp. 2356–2367, 2019.

[74] Liu, Z., et al., "Highly Efficient RNA-Guided Base Editing in Rabbit," Nat Commun., vol. 9, p. 2717, 2018.

ISSN 3063-8186. Published by Universitas Muhammadiyah Sidoarjo

https://doi.org/10.21070/ijhsm.v2i1.163

[75] Liu, H., et al., "Multiple Gene Knockout in Rabbit Using CRISPR/Cas9," Gene, vol. 647, pp. 261–267, 2018.

[76] Yang, H. and Wu, Z., "Genome Editing of Pigs for Agriculture and Biomedicine," Front Genet., vol. 9, p. 360, 2018.

[77] Zhou, X., et al., "Generation of Gene-Targeted Pigs via CRISPR/Cas9 and SCNT," Cell Mol Life Sci., vol. 72, pp. 1175–1184, 2015.

[78] Yan, S., et al., "A Huntingtin Knockin Pig Model Recapitulates Huntington's Disease," Cell, vol. 173, pp. 989–1002, 2018.