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An Inter Mammalian Microbiome-Immune-Axis MIA

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Author's contribution

The sole author designed, analyzed, interpreted and prepared the manuscript.

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Opinion Article

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ABSTRACT

There is a mutual bidirectional cross-talk between mammalian microbiomes MM and their respective immune systems during the host homeostatic and disease states, the microbiome-immune axis. The objective of the present opinion paper was to map the current status of the microbiome-immune axis updates. Human gut microbiome diversity decreases rapidly after autologous stem cell transfer. Myelopoiesis in human is regulated by signals from microbiome reaching the bone marrow. Some animal heat treated gut bacterial antigens induces proinflammatory cytokines in rabbits ileal and villus cultures while other animal heat treated gut bacterial antigens initiated anti-inflammatory cytokines using same test culture systems. Rabbits gut microbiome modulates brain development and function with coordinative helping role of the immune system. Rabbit models for rhino-sinusitis and cystic fibrosis were found associated with microbiome dysbioses in nose and gut microbiomes respectively and simulating that of man. When the development of mice microbiome became arrested the immune system undergoes stunting growth and development. Obese mice have shown dysbiotic microbiome. Thus, the paradigm of microbiome-immune axis MIA have shown that the potentials of the monkeys, rabbit and mice microbiomes can be translated to human welfare providing some limitations.

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1. INTRODUCTION

Axis in the functional sense means the presence of mutual bidirectional signaling between two rather different or inter-related biologic entities. As an example, the microbiome-immune axis and it is expressed as a crucial relationship between microbiome and the immune system. A diverse microbiome is essential for maintaining balanced and healthy immune systems (Shitara, 2023). Gut microbiome possess an intensive influences on gut associated lymphoid tissue GALT.GALT displayed an immune modulatory role on gut mucosal responses leading to maintain of tolerance to harmless bacteria and responding to pathogens. Early exposure to beneficial microbiome can enhance immune maturation and protect against allergic and autoimmune diseases in early life. In the past three decades, the change in the composition and function of microbiome have shown to be associated with obesity, inflammatory bowel disease, type II diabetes, liver cirrhosis, drug treatment responses (Zeevi et al., 2016). Microbiome cross-talk with T cells leading to cancer, allergic inflammations and autoimmune disease (Shim et al., 2023 Campbell et al., 2023). The objective of the present opinion paper was to map human and representative mammalian microbiome-immune axis.

2. AN OLD IS BEING REVISTED AND RE-CREATED

Pioneer generation microbiologists look to normal microbe living in or no human body as commensals and can prevents establishment of pathogens (Parente, 2019). In the sixteens notion of the 20th century microbiologist was the global realization of cultivable/non-cultivable normal human microflora. In 19th of the past century, molecular genomic studies had led to evolution of microbiome concept, Table 1. Commensal human mirco-flora have been revisited and recreated as microbiota/microbiome (Grice and Segre, 2011).

3. MICROBIOME VERSUS MICROBIOTA

Microbiota refers to the profile of the normal cultivable microflora. While, microbiome as a term means the profile of cultivable and genetically determined uncultivable normal microflora inhabiting both in and on various mammalian body sites. So microbiome equal to;

Microbiome= Cultivable + in-cultivable (normal commensal microflora)

Table 1. Microbiome timeline

Achievements	Reference/Date
1. Five different bacteria of human mouth	Leewenhook 1688
2. Flora and funa within living animals	Leidy 1853
3. Some of human associated micro-organisms prove to be pathogenic in same niche	Nissle 1917
4. Cultivation of anaerobic microbiota in the laboratory	1940-1950
5. Realization of the theme for cultivable/non-cultivable microbiota	1960s
6. The theme of commensal microflora in healthy body	Crucishank et al.1974
7. Genetic and molecular based studies on human normal microbiota	Woese, Pace, Fox and others 1996-2005
8. Popularization of microbiome/microbiota research theme	Gordon group 2006
9. Advisory Microbiome mapping guide	ASM 2015
10. Microbiome strategic plans	ASM 2016
11. National Microbiome data collaboration	ASM2019
12. Microbiome Research Congress	ASM 2021
13. Inclusion of the microbiome in the USA innovation act	ASM 2022

Table 2. Characteristics of human and mammalian microbiomes

Features	Human	Monkey	Rabbit	Mice
First genome	MHC	MnMHC	RMHC	MMHC
Second genome	Microbiome genes	Microbiome genes	Microbiome genes	Microbiome genes
Regulation of neonate and ageing immune system	Regulate	Regulate	Regulate	Regulate
Coevolution with immune system	Co-evolved	Co-evolved	Coevolved	Coevolved
Association with homeostasis	Associated	Associated	Associated	Associated
Dysbiosis	Immune mediated diseases			Immune mediated diseases
Translation	In applicable	Non-tempted till now	Tempted	Tempted

Human microbiome composed of trillion of microbial spectra like bacteria, viruses, fungi and archea inhabiting various body compartments such as; gut skin, genitourinary and respiratory tracts. Diverse microbiome is crucial for maintaining a balanced and healthy immune system. The composition and diversity of these microbial communities vary between individuals and affected by; diet, genetics and environmental factors (Crucishank et al., 1974, Parente, 2019, Grice and Segre, 2011, Whiteside et al., 2015, Levinson et al., 2018) Table 2.

4. MICROBIOME-IMMUNE AXIS

Axis in the functional sense refers to the presence of mutual bidirectional cross-talk between two different or inter-related biologic entities such as microbiome and that of the human cells of the immune system cells (Shitara, 2023, Zeevi et al., 2016, Shim et al., 2023, Campbell et al., 2023).

5. FIRST VERSUS SECOND GENOME

The first genome concerned with the host/immune system genetic system, while the second genome invented to designate the collective genomes of the members forming the microbiome. Microbiome signals talking to host. Host genome signals to cross-talk the components of the microbiome. This sort of signaling one -another usually followed by functional events within the microbiome-immune axis (Shitara, 2023, Zeevi et al., 2016, Shim et al., 2023, Campbell et al., 2023).

6. MICROBIOME

6.1 Human Microbiome

Human microbiota is defined as a set of microbes inhabiting and interacting with human body. These interactions took three main forms as commensalism, mutualism and parasitism (Grice and Segre, 2011). They form complex and solitary ecosystem that adapt to the environmental conditions of the host niche. The human microbiome is constantly evolving in response to the host factors. Human microbiome HM consists of an array of; bacteria, archea, viruses and eukaryotes.HM colonize various sites on or in of the body. Facultative anaerobe colonize gastro-intestinal tract while strict anaerobe colonize skin, oral cavity and respiratory tract.HM impacts human physiology and immunology both in health and disease (Crucishank et al., 1974, Parente, 2019, Grice and Segre, 2011, Whiteside et al., 2015, Levinson et al., 2018).

6.2 Mammalian Microbiome

Animals belongs to carnivores, omnivores and herbivores groups have shown variable compositions of microbiota and maintained complexicity and stability which explain the difficulty to induce long term change in their compositions. They are competing for the essential nutrients and they alter the conditions required for growth of bacteria through production of bacteriocins that kills the competitors and controls pathogens by

stimulating host immunity and mucosal barrier functions .They provide signals for optimize immune functions .Generally speaking ,mammalian microbiomes are somewhat similar one to another in nature for their members but they are different in proportion quantities, composition and diversity .In healthy animals, gram negative Protebacteria , bacteriodetes and gram positive firmicutes including Closteridiales and Lactobacillales are the major phyla inhabiting large and small intestines. All of these organisms are adapted to the intra-intestinal environment and generally formed stable and complex population (Tizard, 2023). Studies onto gut/ileal microbiomes of rabbit and pig have shown that dominant phyla of pig ileum were Firmicutes while the dominant phyla of rabbits ileal microbiome was Bacteriodatae (Cui and Xu, 2016).

6.3 Non-Human Primate Microbiome

Monkey gut microbiome offers an insight into primate nutrition, physiology and immune system function (Clayton et al., 2018). Geography, genetics, climate, vegetation and diet related to microbiome community structure. There was more high degree of regional specificity in the microbiome composition which was associated with; host genetics, available plant food which affect diet. Genetic differences, drove differences in gut microbiome community composition, while, vegetation as a diet drove regional gut mircobiome compositional differences (Mesquita et al., 2021). Monkey gut microbiome adopt characteristic enterotype which was compositionally analogous to that of human. Such gut microbiome enterotype have stable microbial signature over time (Campbell et al., 2020, Moeller et al., 2012).

6.4 Rabbits Microbiome

Rabbits are both monogastric and herbivore animal with special digestive and physiological properties. Their gut microbiome be stable and diverse by this it expresses significant resistant to intestinal disease (Chen et al., 2017). Different rabbit maternal strains showed different microbiome compositions (Biada et al., 2020). Rabbits may serve medical and nonmedical uses. The non-medical use include; Textile production, meat production. While medical uses includes; bioreactor to produce polyclonal antibodies and as a biomedical model for human disease. Whole rabbits body microbiome has shown Firmicutes 62.3 %, Proteobacteria 13.44 % and Bacteriodate 11.84% (Montoro-Dasi et al., 2022, Hu et al., 2021). Rabbits gut microbiome plays a key role in maintaining health and in regulation and development of the immune system (Kylie, 2016).

6.5 Mice Microbiome

Mice microbiome consists of a number of bacteria, viruses, fungi and eukaryotes. Members of mouse microbiome distributed to gut, skin, respiratory and genitourinary tract. Microbiome composition constitutes proportional amounts of Firmicuts and Bacteriodaiceae. Mouse microbiomes are useful tool impactful in gaining a better understanding of human microbiome. There are 80 genera of mice similar to that of man, these are constituting 15% overall similarity of mouse to human microbiome (Maue and Lundberg, 2017, Kennedy et al., 2018, Ansaldo et al., 2021).

7. MICROBIOME-IMMUNE AXIS

7.1 Human Microbiome-Immune Axis

Human immune system co-evolved with an extensive microbiome diversity on the mucosal barrier sites. It is evident and clear that microbial antigens belong to the microbiome members engage in constant dialogue with the immune system leading to microbiota specific immune responses that occur in the absence of inflammation. This constitute a form of immunity including B cell, innate like T cell and co-evolutional T cell helper and T reg cell responses. Microbiome induces innate like T cell and adaptive immune responses. These microbiomes - immune potentials indicate that microbiome involved with cross-talk with the immune cells during immune response development (Ansaldo et al., 2021). Vital period for mammals to be colonized with microbiome is in the early life. Such colonization is profoundly influence the intestinal immune functions. The intestinal immune system is critical for neonates in order to resist intestinal infections (Yang et al., 2022). The initial colonization of an infant gut by microbes plays a pivotal role in shaping the immune system. Early exposure to probiotics can enhances the immune system maturation and protects against allergic and autoimmune disease (Shitara, 2023). There are a specific microbial groups take part in the immune system development and have a role in the functional changes that occur to the immune cell population through ageing (Tibbs et al., 2019). Human

myelopoiesis in the bone marrow is regulated by environmental signals including that of microbiome. Microbiota derived signals can be sensed directly or indirectly by the hemopoietic stem cells and progenitor cells in bone marrow, thereby giving rise to myeloid cell lineages at steady state and during inflammation. These microbial signals affect the myelopoiesis during inflammation and infection (Kim and Kamada, 2023).

The human gut microbiome acts as a signaling hub that integrates exposome with genome and metabolic pathways Its impacts are wide across human body systems including the immune system (Institute of Functional Medicine, 2025). The gut and skin microbiome both act as a barrier between human body and environment through sharing similar structure and function and allowing for cross-talk between them. Such cross-talk is assisted by cytokines and microbial metabolites (Owlstone Medical, 2024). Gut microbiome diversity decreases rapidly after autologous stem cell transplantation. There are specific bacterial families and certain immune cell subsets in patients receiving autologous stem cell transplantation (Becker et al., 2024).

7.2 Mammalian-Immune Axis

Using rabbits ileum and villus culture to elucidate the inflammatory response induce by heat killed intestinal bacterial antigens of rabbit and pig.it has been found that rabbits intestinal bacterial antigen RIBA induced higher expression of TLR4,while that of pigs PIBA induced TLR2 and TLR3.PIBA and RIBA induced increased expression of INFalpha,IL6.PIBA stimulate INF beta and IL10.High appearance of gram negative in rabbit ileum do not lead to proinflammatory cytokine but high amounts of Lactobacilli in pigs ileum was more expressive to anti-inflammatory cytokines (Cui and Xu, 2016).

7.3 Monkey Microbiome-Immune Axis

Short term antibiotic treatment in rhesus monkeys induced gut microbiome dysbiosis. Such dysbiosis lead to increase in CD3+ T cells, CD4+ T cells, and CD16+ NK cells. But, decreased the number of T reg cells and CD20 B cells in peripheral blood cells (Li et al., 2020).

7.4 Rabbit Microbiome-Immune Axis

Transfer of microbiota during birth fostering regulation of the first birth reaction. The maternal gamma delta T cells shape the offspring pulmonary type2 immunity in a microbiota dependent manner .The offsprings of gamma delta T cell deficient dams displayed enhanced lung type 2 immunity .TCR delta deficient dams displayed deficient both in AMP levels and microbiota composition of the skin (Papotto et al., 2023). Rabbits gut microbiome is important in regulating trait and played a key role in immune system development. As well as it could be related to longevity and resilience (Biada et al., 2020). Incorporation of probiotic with rabbits diet supplementation increased the splenic and thymic index, levels of IgM, C3 and C4. Hence,probiotics supplement in diet could effectively improve immune organ index and immune function (Zhang et al., 2020, Salvo-Romero et al., 2020). Rabbits gut bacteria can modulate gut resident immune cells and brain resident immune cells Studies on gut-brain axis have shown that gut microbiome modulate brain development and function in presence of immune system cooperation (Li et al., 2020).

7.5 Mice Microbiome-Immune Axis

In an experimental settings mice microbiome arrested Such arrestment lead to stunting in the immune system maturation with few peripheral regulatory T cells and decreased levels of IgA and increased susceptibility to Salmonella infection (Lubin et al., 2023). Neonatal mouse gut is enriched with neuro-transimittors and with specific bacteria produce serotonin directly while down regulating mono-amin oxidase A to limit the serotonin breakdown .Serotonin inhibit mTOR activation to promote regulatory T cells and suppress T cell responses both in ex-vivo and in-vivo in the neonatal intestines .Oral gavage of serotonin into the neonatal mice lead to long term tolerance toward diet antigens and commensal bacteria as well as gut microbiome dysbiosis (Sanidad et al., 2023, Sanders et al., 2023).

8. COMPARATIVE VIEW

There were significant co-diversification with ten gut bacterial phyla including Firmicutes, Actinobacteriota. Strikingly around 44% of co-diversifying clades detect in African apes were absent from microbiome data of man and 54% were absent from industrialized human population (Salvo-Romero et al., 2020). Gut microbial taxa, microbial gene family contents of the great ape and human are more related by life

Table 3. Comparative translation approach in human primate, non-human primate and small mammals

Model	Microbiome homeostasis	Alteration	Matchability to human	References
Monkey	Gut	Dysbiosis	Immune impairment	(Li et al., 2020)
Rabbit/Rhinosinsusitis	Nasal	Dysbiosis	Matchable	(Rowe et al., 2018)
/Cystic fibrosis	Gut	Dysbiosis	Matchable	(Liang et al., 2021)
Mice/Obesity	Gut	Dysbiosis	Matchable	(Maue and Lundberg, 2017)

style than geography (Campbell et al., 2020). Human gut microbiome composition and potentials are more similar to those of old world monkeys, the baboons than African apes. Though there were inter-individual variation in the functional potentials of gut microbiome with in human species. Such variations suggest that human gut microbiome may exhibit more plasticity in response to environmental variation (Amato et al., 2019). Antibiotic treatment of rhesus monkey model induced gut microbiome dysbiosis and impair the peripheral cellular immunity (Li et al., 2020).

Results of rabbit microbiome studies can be translated to that matching human being as in the case of rhinosinusitis accompanied by sinus microbiome dysbiosis (Rowe et al., 2018). In addition to the young rabbits cystic fibrosis model that was associated with gut microbiome dysbiosis simulating that of human being cystic fibrosis (Liang et al., 2021).

Mouse gut microbiome composition contains 85% of bacterial genera different from that of human gut microbiome. The remaining 15 % of the mouse gut bacterial flora were similar to that of man. This fraction of mouse gut microbiome includes 80 genera shared with human gut microbiome. Therefore it is essential for the researchers tempting translation of mouse experimental results to human being to have a clear understanding of the benefits and limitations of their model system if they wish to translate their finding to man. Mouse obesity and IBD are the most models for microbiome studies both of which associated with microbiome dysbiosis (Maue and Lundberg, 2017), Table 3.

9. HOMEOSTASIS VERSUS DYSBIOSIS MICROBIOMES

Homeostasis, is a state of normal functional balance of the influence of microbiota on health and disease depends onto; quality, quantity, proportion of each of microbiota component. Homeostasis is in line with functional balance between the component of the microbiome. Which indicate normal state of each of the components. Such balance plays important roles in maintenance and development of human immune system (Ogunrinol et al., 2020). Dysbiosis, is any alteration in human or animal microbiota is associated with a disease state. Alteration in the microbiota immune axis results in immune mediated diseases such as; intestinal infection, inflammatory bowel disease, autoimmunity, hypersensitivity and cancer (Campbell et al., 2023, Ogunrinol et al., 2020).

10. SUGGESTION ONE

"Human gut microbiome and the innate immunity levels in neonates, children under five years and adolescents".

Elect 50 male and female normal; neonates, child under five years and adolescent. Collect feces and blood from each group. Test the phagocytic activity, acute phase proteins, C3 and C4 levels. Fecal sample will be processed for the detection of gut microbiome by the use of either DNA or 16SRNA kits. Gut microbiome results concerning diversity, composition, similarity, enterotype and differences in each group in relation to the levels of innate immune parameters.

11. SUGGESTION TWO

"Dysbiosis of human gut microbiome in typhoid patients".

A plane for gut microbiome dysbiosis in normal and typhoid patients will be planed. Normal subjects, untreated and treated typhoid patients will be the test groups. Fecal samples from each group will be collected and processed for gut microbiome dysbiosis using either DNA or 16S RNA kits. Results analyzed for; composition, diversity, and enterotypes for each group.

12. CONCLUSION

Microbiome is important for human normal immune system development from neonates till ageing. Human gut microbiome acts as a signaling hub that integrate exposome with genome and metabolic pathways. Dysbiosis to the microbiome is mostly in line with disease state. Monkey , rabbit ,and mice microbiomes may simulate but not reach the limits of identicality to human being microbiome ,there are advantages and some limitations for each of which both in structural and functional aspects .Rabbit (Rhinosinusitis, cystic fibrosis) and mice(Obesity, IBD) microbiota were tempted for translation to human beings .As a suggestion monkey microbiome is expected to be more similar to human than rabbit and mice but apparently no tempts for translation to human till now so far current information indicated. Two suggested programs for human gut microbiome studies were made.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author hereby declare that NO generative AI technologies such as Lage Language Models(ChatGPT ,COPILOT ,etc…) and text to image generators have been used during writing or editing of this manuscript.

CONSENT AND ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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