

The Role of Microbiome in Regenerative Medicine: A New Frontier

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I. Introduction

Tissue engineering or regenerative medicine is an upcoming therapeutic, scientific discipline that encompasses great potential in shaping the future of the healthcare industry. It is based on the concept that organs and organ function can be repaired or replaced by influencing cells, tissues, and organs to heal themselves (Sipe, 2002). This type of regenerative medicine, being an inter-disciplinary area, derives from stem cell therapy, tissue engineering, gene therapy, and immunomodulation, which, in other words, is a direct attempt to trigger the inherent self-healing in the body for tissue repair as well as regain functional losses. The application of regenerative medicine is diverse, with potential uses ranging from injuries and ulcers to osteoarthritis and other neurodegenerative diseases. In recent times, the field of regenerative medicine has increased the capacity to develop new therapies for organ failure that were simply unthinkable previously (Tandon et al., 2024). With few exceptions, regenerative medicine entails new therapies for increasingly common diseases and illnesses with the objective of enhancing the patient's lifestyle. Among the perspective directions of modern regenerative medicine, it is possible to distinguish a new branch of regenerative medicine, the microbiome that unites all microorganisms inhabiting the human organism. To date, the microbiome is defined as the aggregate of microorganisms, such as bacteria, viruses, fungi, and other microorganisms, that inhabit and interact within and on the exterior of the human body and is estimated to host at least 10^{12} microorganisms (Wilson, 2018). The consistencies of microbiota, mainly the gut and skin-associated microbiota, have been shown to control several physiological functions, including metabolism, the immune system, and the brain and central nervous system (Malaviya et al., 2022). New data that became known in recent years showed that microbiota directly influences tissue repair, which means that these bacteria are involved in the regulation of the organism's inherent reparative capabilities (Xu & Hsia, 2018). This has led several researchers in the area of regenerative medicine to start emphasizing the use of microbiome and how it may be fitted into the area of regenerative medicine to enhance tissue repair, increase the healing rate, and reciprocally, the rate of success in regenerative medicine therapies. The microbiome influences tissue regeneration through various mechanisms, including in this context, the microbiome plays a part in tissue regeneration through the following processes:

Modulation of Immune Responses: The immune system has the task of balancing the ability of the cells to repair and regenerate the tissues, while the microbiome can manage the immunity network (Shavandi et al., 2020). The availability of useful microorganisms is the ability to activate constructive inflammation, which is to suppress pathological inflammation to create opportunities for tissue repair. On the other hand, dysbiosis- an unstable microbial community may result in inflammation and remodeling of the tissues' regenerative potential.

Promotion of Angiogenesis: Thus, the microbiome field exerts an influence on angiogenesis, which represents a significant form of tissue repair or the generation of new blood vessels. Based on the increase in VEGF, a product of the gene that regulates angiogenesis, some of the SCFAs'

effects on endothelial cells were shown to be positive (Gomes et al., 2023).

Influence on Stem Cell Function: The microbiome communicates/interacts with stem cells; these are undifferentiated cells that depend on signals to develop into various cells to form tissues for repair. To the realization that the bacteria of the gut are already capable of producing signaling factors that relate to stem cell activation, differentiation, and migration, therefore forming a basis for replacing dead or sick tissues (Oncel & Basson, 2022). The researchers build a new division of progressive scholarly works by applying microbiome elements to regenerative medicine. Hence, unraveling the complex interconnection of the microbiome with the regenerative processes is the key to the therapeutic strategies that unlock the full potential of the microbiome for healing and enhancing tissue repair, faster recovery, and better patient prognosis. This chapter is devoted to the description of the newest findings in this rapidly progressing field and the following topics will be discussed in detail.

2. Understanding the Microbiome

The understand the role of the microbiome in the approach of regenerative medicine, it is necessary to study its evolution, characteristics, and significance to the organism, with the additional consideration of factors that impact the intricate system of the microbiome.

2. 1 Composition and Diversity of the Human Microbiome

The human microbiome is a dynamic and complex individuals that care for trillions of microorganisms, of which sixty percent consist of bacteria, viruses, Fungi, and archaea (Nazir et al., 2024). This population interacts with various body surfaces, and these include skin, oral mucosa, respiratory system, and urogenital system. However, the highest microbial density and the research emphasis is on the gastro-intestinal tract, which contains trillions of microbes thus, the formation of the gut microbiota. These organisms comprise thousands of various bacterial species, the bacteria detected in the gut are almost similar to the total number of human body cells. Thus, although human gut microbiota is rather heterogeneous and is influenced by heredity, food intake, age, and the person’s geographical position (Pulipati et al., 2020) the typical bacterial phyla in healthy individuals involve Firmicutes, Bacteroidetes, Actinobacteria, and Proteobacteria. This diversity is very essential for establishing a proper microbiota, which has the capability of synthesizing many products relevant to human beings (Table 1).

Table 1: Microbiome Composition in Health and Disease

Bacterial Group	Healthy Gut	Inflammatory Bowel Disease (IBD)	Diabetes	References
Firmicutes	Abundant	Reduced	Increased	(Stojanov et al., 2020)
Bacteroidetes	Abundant	Reduced	Reduced	(Labbé et al., 2014)
Actinobacteria	Present	Variable	Variable	(Xu et al., 2022)
Proteobacteria	Present	Increased	Increased	(Salem et al., 2019)
Bifidobacterium	Abundant	Reduced	Reduced	(Das et al., 2021)
Lactobacillus	Abundant	Reduced	Reduced	(Salem et al., 2019)
Faecalibacterium prausnitzii	Abundant	Reduced	Reduced	(Remely et al., 2016)
Akkermansia muciniphila	Present	Reduced	Reduced	(Zheng et al., 2023)

2.2 Role of Microbiota in Health and Disease

The microbiome could not be regarded as just being there in the human (and organs of the human body) but is rather a sort of co-participant that, in a way, defines human health or disease. Healthy and balanced gut microbiotas are today established as a component of the physiological stability of the body and aspects such as digestion, immune system, and protection against diseases (Hajiagha et al., 2022).

Digestion and Metabolism: The microbes that exist in each of us are, at the very least, capable of helping with the digestion of complex carbohydrates, absorption of vitamins, and metabolism of several nutrients (Ofoedu et al., 2021). They also are involved in strengthening the most critical line of defense, namely the barrier that has formed in the intestine, which many pathogenic substances must not penetrate.

Immune Function: This is because the immunity of any organism depends on the digestive system, and therefore, due to this, the connection between the two is great. This, in turn, helps to enhance the immunity of the persons to be treated to be able to differentiate between and reject non-pathogenic substances and organisms. Immunomodulation relates to the alteration within the normal function of the immune system due to dysbiosis, bringing about continual inflammation leading to autoimmune diseases (Balakrishnan & Taneja, 2018).

Neurological Function: For the sake of clarity, the gut microbiota has been shown to have an interaction with the central nervous system with the help of the gut-brain axis that acts as a moderator of mood, behavior, and cognition. Some of the neurological conditions that they have linked to shifts in the gut microbiome include Parkinsonism, Alzheimers, and autism, according to some of the literature available (Stopińska et al., 2021).

2.3 Factors Influencing Microbiome Composition

The composition and function of the microbiome are not fixed but are constantly shaped by a multitude of intrinsic and extrinsic factors: It is urgent to realize that microbiome composition, as well as its functioning, can be continuously influenced by numerous intrinsic and extrinsic factors:

Diet: It should be noted that consumption patterns are one of the most significant factors determining the features of the composition of the gut microbiota. Consumption of fiber, fruits, vegetables, and whole grains gives the Microbiome in one's stool a healthy, diversified eating plan (Jawhara, 2023). However, a diet that complements processed food, refined sugars, and unhealthy fats increases dysbiosis, which is characterized by significantly low rates of beneficial bacteria and high rates of risk bacteria.

Antibiotics: Antibiotics are strong agents that change the balance of the population in the gut. They are good at cleaning out bacterial infections; however, they are potent on all bacteria, and their use destroys the many beneficial bacteria that may have future benefits for a person's health (Bloomfield et al., 2006).

Age: Considering this fact the gut microbiome is not a constant system during people's lifetime as it is ecosystems that are home to trillions of microbes (Fasano & Flaherty, 2021). There are relatively few kinds of microorganisms in the body of a baby at birth, but as the age of the baby the variety and the complicated nature of microorganisms increases. However, with time, the variety of the microbiota and its stability are in danger, and it has something to do with some of the troubles that are associated with age.

Genetics: Host genetics are also necessary for regulating the sensibility of the gut microbiome; however, this factor remains, to some extent, undefined (Patrignani et al., 2014). SNP is valuable as it influences the functions of genes, which in turn manage to turn on the immune reactivity, nutrients, and microbiome, among other functions.

Environmental Factors: Different kinds of negative influences, such as toxins, pollutants, stress, and others, alter the concentration of the gut microbiota and its action (Bhardwaj et al., 2024). These factors alter the homeostasis of the microbial community, which, if disrupted, leads to dysbiosis and the development of disease. These aspects must be understood to develop specific approaches towards manipulating the microbiota for a therapeutic end.

3. Basics of Regenerative Medicine

Regenerative medicine is defined as the new direction in healthcare management. The main goal of this field is to restore damaged or failed tissues and organs by activating the organism's self-change processes. This field involves a wide range of strategies, and despite its different mechanisms of operation and general functions, it is mostly aimed at enhancing the wound-healing process (Figure 1).

Tissue Engineering: In this case, tissue engineering is a broad area of study that is concerned with the development of functional tissues or organs using cells, scaffolds, and signals (Abdollahiyan et al., 2021). These cells are then harvested directly from the patient, which is then cultured on the scaffold that also defines the formation of the tissues. At first, a positive effect on cell metabolism is applied with basic proteins; later, for cell proliferation and formation of functional tissues, growth factors, and cytokines are used (Deuel & Chang, 2014).

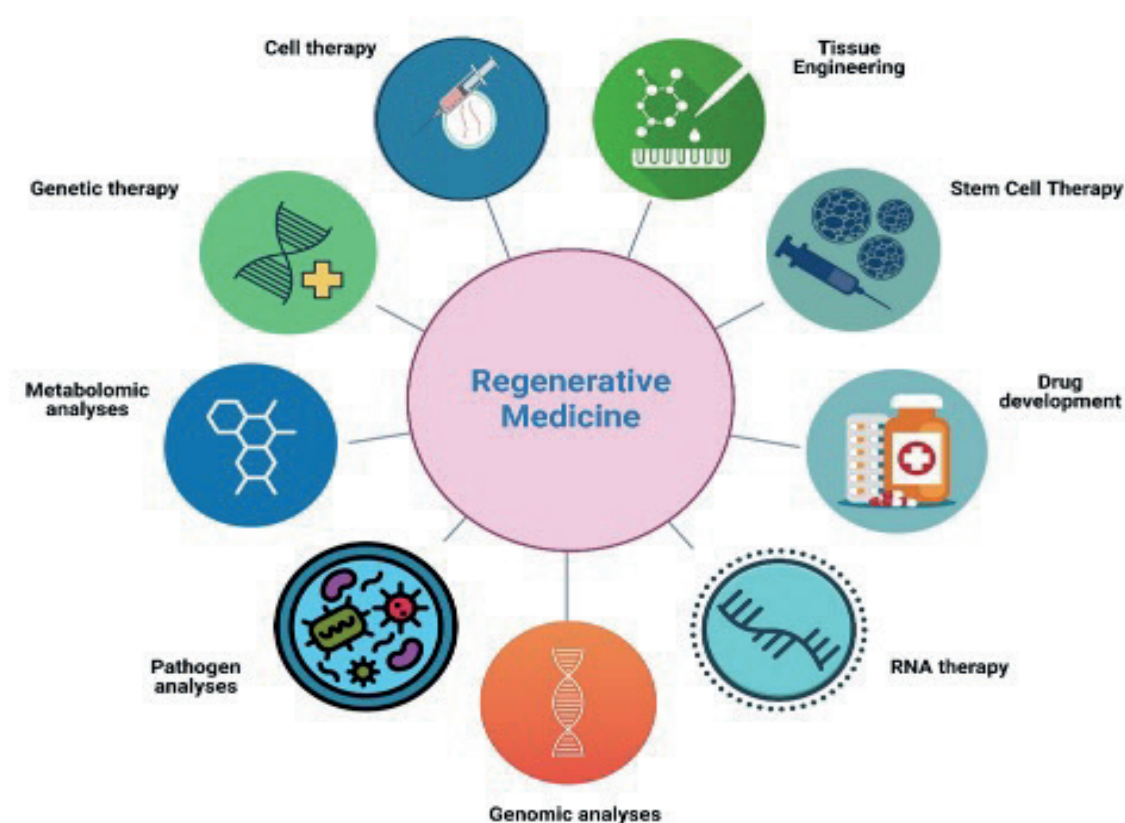


Figure 1. Basics of Regenerative Medicine

Stem Cell Therapy: Stem cells are the cells that still retain the ability to divide and produce more stem cells and other specialized cell types; they constitute part of the foundation of regenerative medicine (Suman et al., 2019). They can be derived directly from embryonic stem cells; they can also be derived from adult stem cells and also from the creation of human somatic cells to pluripotent stem cells known as iPSC. Stem cell therapy involves the master donor of these cells and infusing them into tissues where they can differentiate into such kinds of cells, plug up the gaps in tissues,

and help in the repair of damaged tissues (Mafruchati, 2023). The experimental application of stem cells is widely implemented in the treatment of various illnesses: Cardiovascular and vascular, neurological and neurosensory, and musculoskeletal diseases and injuries.

Biomaterials: Biomaterials can be described as the biological or synthetic components that are laid down with the specific task of performing a particular function in the body of a living organism (Lakes & Park, 2012). They are essential in all segments of tissue engineering, drug delivery systems, and implantation materials that substitute damaged tissues. The NBM and any other components of regenerative medicine must comprise biocompatibility and bioactivity in order not to cause negative impacts in the human body but at the same time, they should be able to offer the desired effect. In light of the structure of the composite biomaterials, at least one of the components in the composite material replicates the extracellular matrix, which is the natural environment of cells and tissues and directs their formation (De Santis et al., 2019).

3.2 Current Application and Case Studies

Regenerative medicine has already achieved remarkable success in various clinical applications, demonstrating its potential to transform healthcare: This young branch of medicine has already provided numerous outstanding results in numerous clinical uses, proving the viability of applying regenerative medicine for the improvement of healthcare services:

Skin Regeneration: Cultured skin cells and biomaterials have also been used to manage burns and chronic ulcers and improve wound healing rates with minimum keloid scar formation (Elfawy et al., 2023). The mentioned grafts can serve as either the temporary or definitive layer of the wound, promoting tissue repair and preventing infection.

Cartilage Repair: MSC therapy seems to hold impressive expectations in regenerating the impaired cartilage in joints thereby reducing the frequency of total joint replacement surgeries (Vigano, 2017). This therapy involves the use of the patient's cartilage cells or MSCs harvesting and expansion, and reconstructed cells are implanted, leading to cartilage restoration of the arthritic joint.

Bone Regeneration: Since time immemorial, bone grafts, whether autografts where the graft is derived from the recipient's body or allografts where the donor is different from the recipient have been employed to improve bone fracture and nonunion healing. New ones are bone tissue engineering, which employs the use of autografts combined with growth factors and stem cells in bone regeneration and remodeling (Nassif & El Sabban, 2011).

Corneal Regeneration: One of the procedures that has been used successfully to treat patients with corneal blindness due to limbal stem cell deficiency has emerged as autologous limbal stem cell transplantation (Selver et al., 2017). This involves moving normal stem cells from another donor or the patient's healthy eye or affected eye to encourage the growth of the cornea.

3.3 Challenges and Limitations in Regenerative Medicine

Despite the significant progress and promising results, regenerative medicine still faces several challenges and limitations: There are many drawbacks and limitations in the development of regenerative medicine, but it continues to show promising results and a lot of progress. The biggest challenges are the following:

Complexity of Tissue and Organ Regeneration: Despite all these advances, tissue engineering is still in front of several major technical issues. In creating the methodologies for the formation of the tissues and organs containing several types of cells and organized in the multi-functional 3D constructs. It is thus crucial to be able to control the differentiation process of the cells in space and time, tissue organization, and vascularization for tissue biomimicry (Carotenuto et al., 2022).

Immune Rejection: Immunological rejection of the transplanted tissue is always an increasing factor and can be more emphasized in the case of allogeneic tissue (González-Molina et al., 2016). The presumption regarding the risk of GvHD is still a mystery, but immunosuppressive medications or a generation of hypoallergenic cell sources are possibilities.

Long-Term Efficacy and Safety: The helpful and safe effects of regenerative medicine cannot skip the research review of clinical trials and literature. This entails assessing the capacity of cell therapy to revive tumorigenicity, differentiate abnormally, and any other effect that might develop after some time (Carvalho, 2020).

Regulatory and Ethical Considerations: The realization and advancement of regenerative medicine therapies entail qualities or matters that relate to regulation and ethical standards (Yamada et al., 2021). For example, matters concerning the safety and quality of cell and tissue products and issues regarding the use of hESC and avoiding unethical stem cell research and clinical application. Thus, it is possible to overcome these challenges and limitations and continue regenerative medicine's development with its incredible opportunities for creating a new future for medicine and the lives of many patients.

4. Mechanisms of Microbiome Influence on Regeneration

Therefore, relating microbes with their host and the host's tissues is a process, and the use of the microbiome in regenerative medicine is analogous to a well-coordinated ballet. These interactions include direct and indirect communication, altering the immune response, regulation of inflammation, and biosynthesis of bioactive compounds (Caffaratti et al., 2021). Understanding these mechanisms is necessary to evaluate and enhance the microbiome's potential in the therapeutic process and tissue regeneration.

4.1 Microbiome-Host Interactions

The microbiome and its host are two entities continually sending signals to each other, and each can impact the other's function through infinitely many molecular messengers.

Direct Cell-to-Cell Communication: According to parts of the microbiota, they may directly come into contact with the host cells or release compounds capable of binding to host cell receptors (Krasulova & Illes, 2021). For example, certain bacteria in this place are known to adhere to the mucosa of the small bowels through intricate intracellular signaling, frequently used in the stimulation of cell division and differentiation required in tissue healing.

Indirect Signaling via Metabolites: These are propionate, acetate, and butyrate of SCFAs, cobalamin, niacin, and folate of vitamins, tryptophan, histidine, and cysteine of amino acids, and u bowel of secondary bile acids. These metabolites can act as soluble mediators of the host and gene system's state or modulate the corresponding system (McCarville et al., 2020). For instance, SCFAs can bind to GPCRs on the surface of the host cells to modulate the immune response, promote angiogenesis, and regain the integrity of the intestinal barrier (Fock & Parnova, 2023).

Immune System Modulation: In the immune system the gut microbiome plays a crucial role in both the innate and adaptive immune system since they are part of the body's development. This interaction is relevant to help avoid a constant inflammatory status that does not allow tissues to heal (Wilson et al., 2001).

4.2 Role of Microbiota in Immune Modulation

The microbiome impact on immune modulation is multifaceted and involves several key mechanisms: Thus, immune modulation is just one of the microbiome functions, and there are several ways it is realized:

Promotion of Immune Tolerance: From these points of view, a capacity to stimulate the immune or hosting system's tolerance to harmless antigens such as a food particle and environmental allergens relates largely to commensal bacteria as the most crucial element or resident as a component of the host gut habitat. This tolerance is very crucial in preventing over-activation of the immune cells that are likely to destroy tissues while arresting their healing process (Tu & Li, 2023).

Regulation of Inflammation: The SCFAs and PSA are some of the inflammation inhibitory spectra that gut bacteria produce. They act to block the pro-inflammatory processes in the body and, at the same time, promote the differentiation of Treg cells (Dwivedi et al., 2016). Treg cells are also involved in shifting the equilibrium of immune responses and implementing the anti-inflammatory processes, resulting in tissue repair and regeneration.

Protection Against Pathogens: Symbiotic microorganisms are present to counter the colonization of tissues by the pathogens of the host and to envelop them (Ganesan et al., 2022). This protective function is achieved through competitive exclusion, the production of antibiotics, and the role of giving signals to the host's immune system.

4.3 Impact on Inflammation and Healing Processes

Inflammation is a biological process and can be described as being multistage and its major function is to help repair tissue. Hence, acute inflammation is vital in initiating the healing process. However, chronic inflammation is dreadful in tissue healing since it upregulates fibrosis and scarring reactions. The targets of the microbiome suggest its capacity to reduce inflammation and tissue healing (Laing et al., 2018). Stereochemical fecal acids, which are products of the gut microbes, can exhibit efficient anti-inflammatory qualities. Consequently, SCFAs can act as ligands of certain receptors on immune cells: Thus, they can inhibit the production of pro-inflammatory cytokines and stimulate the production of anti-inflammatory Treg cells (Rasouli-Saravani et al., 2023). All that has been said and depicted above indicates the anti-inflammatory property of the adipose tissue-derived stem cells that could facilitate tissue repair and regeneration by minimizing the degree of tissue inflammation, providing the formation of new blood vessels (or angiogenesis), and activating the stem cells for proliferation and differentiation.

4.4 Production of Bioactive Compounds and Metabolites

There are many papers on bioactive compounds and metabolites of gut bacteria that impact host physiology and tissue regeneration. These include:

Short-chain fatty acids (SCFAs): Dietary fibers are fermented in the gut by bacteria, and SCFAs are produced, where butyrate, propionate, and a minor amount of acetate are obtained (Vinelli et al., 2022). SCFAs were related to the up-regulated proliferation genes and anti-tissue repair actions in neovascularization, reformation of the epithelial barrier, decreasing inflammation, and providing energy to intestinal cells.

Vitamins: Gut bacteria can also synthesize some vitamins, including vitamin K and vitamin B, which are involved in cell metabolism, DNA synthesis, energy generation, and cellular redox state regulation (Hossain et al., 2022). These vitamins play essential roles in the healing process or even the regrowth of tissues in the body.

Bile Acids: The bacterial flora in the gut can convert the first bile from the liver to the secondary bile, which has many activities. Some secondary bile acids enhance the TGF- β and Smad signaling pathway involved in tissue remodeling and enhance stem cell differentiation to maturation besides stimulating angiogenesis (Wiercinska, 2005).

Neurotransmitters: Microbiota can produce some neurotransmitters, such as serotonin and dopamine, which impact the brain and its functions and behavior (Ignatova, 2019). These neurotransmitters can also act on the gut and regulate the transport of nutrients and the immune

status of the intestinal tissues.

5. The Microbiome in Wound Healing and Tissue Repair

The relations between skin microbiota and wound healing are considered a relatively new field of knowledge (Canesso et al., 2014). Although studies coming to the very center of the concept regarding the microbial societies living symbiotically with us play a complex role in regulating the sequence of events that make up the process of wound healing. Such knowledge could build therapies that would boost the capacity of the microbiome to restore sinuses and, therefore, the patient's state.

5.1 Skin Regeneration Impact

The epidermis or skin, which is the largest organ of the human body and acts as the primary barrier against pathogens, has a complex and constantly changing population of microorganisms that reside there, collectively referred to as the skin microbiota (Pistone et al., 2021). This skin microbiome plays many roles in the health of the skin, control of pathogens, regulation of the immune system, and healing of skin injury. Recent studies have shed light on the specific mechanisms by which the skin microbiome impacts skin regeneration (Figure 2). Recent studies have helped identify how the skin microbiome influences skin regeneration through skin biology's various mechanisms (Patel et al., 2022).

Inflammation Modulation: The skin microbiome plays a role in the intention of inflammation, particularly due to skin injury (Nørreslet et al., 2020). On a similar note, *Staphylococcus epidermidis*, a blow-seen bacterium responsible for human skin, acts against pathogenic bacteria and additionally produces antimicrobial peptides that hinder the intrusion of pathogenic organisms and can prevent infections. In addition, these bacteria can regulate the functions of inflammatory and anti-inflammatory cytokines that define the level of inflammation and cell tissue repair (Steen et al., 2020).

Re-epithelialization Enhancement: Re-epithelialization refers to the process of movement and replication of tissues that results in the wound bed being covered and is considered a standard component of the phases of healing. For instance, *Staphylococcus epidermidis* is regarded as a healing-promoting bacteria and should enhance cutaneous wound healing and the pan of the keratinocyte to form the scar faster (Stoica et al., 2020). Also, these bacteria stimulate the synthesis of growth factors, including KGF, which aids the re-epithelialization processes in addition.

Angiogenesis Stimulation: An example of the latter is angiogenesis. New blood vessels are formed to support the formation of blood vessels to heal a given wound. Angiogenesis can also be affected by chemicals released from the skin microbiome, among them being the vascular endothelial growth factor (VEGF) and the platelet-derived growth factor (PDGF), among others (Zielińska et al., 2023). They produce positive effects that enhance the motility of the endothelial cells; thus, the formation of blood vessels and improved blood flow in the tissues is enhanced.

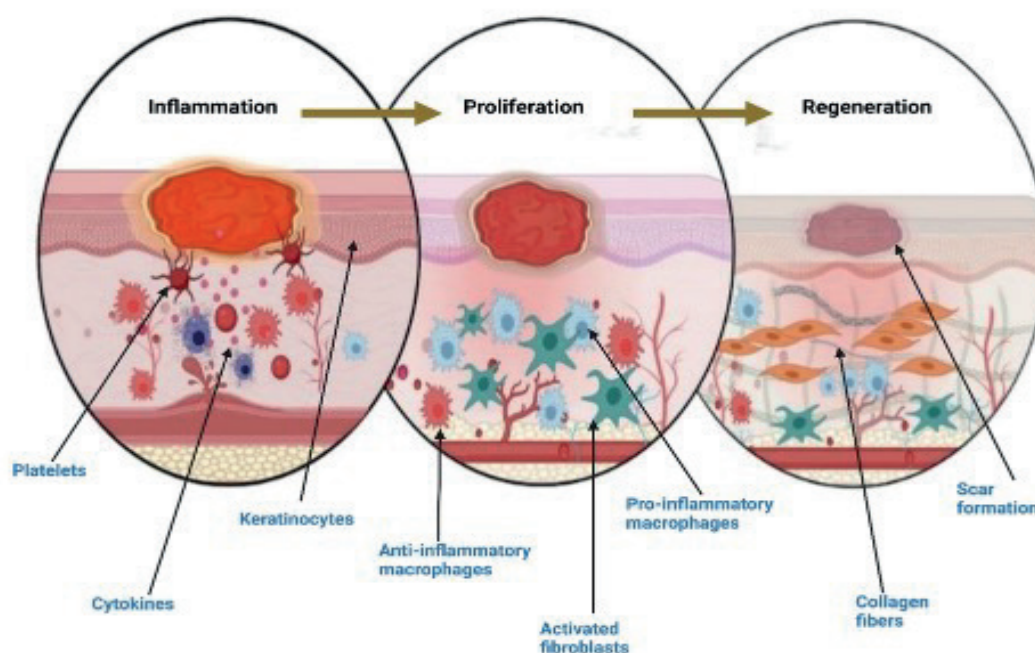


Figure 2. Stages of Wound Healing: A Dynamic Journey of Repair and Regeneration

Scar Formation Modulation: It also plays a role in scar tissue formation, the last process in wound healing, which is a complicated pathological process. Skin dysbiosis describes the skin microbial imbalance and is linked with hypertrophic scarring, which entails the accumulation of collagen and other ECM proteins (Fernandes et al., 2023). Conversely, an appropriately functioning microbial community will encourage scarless healing by regulating the activity of the fibroblasts, the cells that synthesize collagen.

5.2 Microbiome in Chronic Wound and Ulcer

It affects mid and elderly-aged masses; a special type of lesions is chronic non-healing ulcers; diabetic foot ulcers, pressure ulcers, and venous leg ulcers. These are significant health burdens worldwide characterized by long-healing time, recurrent infection, and impaired quality of life (Probst et al., 2022). The composition of the microbiome contributes significantly to the development and treatment process of chronic wounds. Thus, chronic wounds, the majority of the time, can be associated with dysbiosis indicated by a decrease in microbial richness and an increase in pathogenic load (Tang et al., 2023). This imbalance continues inflammation within the chronic wound, limits the body's ability to heal damaged tissues, and sets the optimal stage for biofilm development, a bacterial colony protected by a slimy matrix that eludes conventional treatments and the body's defenses. Another issue that aggravates chronic wound healing is the formation of biofilms because they reduce the ability of topical agents, including antibiotics, to penetrate through the wound site and may contribute to the delay in the healing process (Razdan et al., 2022).

5.3 Probiotics and Prebiotics Applied in Therapy

The health-related uses of probiotics and prebiotics, especially in wound healing and tissue repair, have been considered for further studies. Among nutraceuticals, probiotics are live microorganisms that possess health benefits, and prebiotics are non-digestible food ingredients (Table 2). It stimulates the growth of beneficial bacteria, which have been considered to effectively alter the skin microbiome as well as improve the healing rate of the skin (Canchy et al., 2023). Some of the beneficial effects demonstrated by the use of topical probiotics are the decrease in inflammation, acceleration of the re-epithelialization process, angiogenesis in the granulation

issues, and the inhibition of biofilm formation, although these effects were studied in animals only (Bădăluță et al., 2024).

Table 2: Therapeutic Interventions for Wound Healing Using Probiotics and Prebiotics

Intervention	Mechanism of Action	Effectiveness	Potential Applications	References
Probiotics	Introduce beneficial bacteria to restore microbial balance and promote healing.	Varies depending on strain and application	Chronic wounds, burns, diabetic ulcers, pressure sores	(Fijan et al., 2019)
Prebiotics	Provide nourishment for beneficial bacteria, promoting their growth and activity.	It is promising, but more research is needed	Same as probiotics, also in preventive skincare	(França, 2021)
Synbiotics	Combination of probiotics and prebiotics for synergistic effects.	Potentially enhanced effectiveness	It is the same as probiotics and prebiotics	(Simon et al., 2021)
Topical Probiotics	Direct application of beneficial bacteria to the wound site.	Limited evidence	Minor cuts, abrasions, skin infections	(Mohammed-saeed, 2015)

Thus, probiotics can cause these effects through the direct production of bacteriocins and other antimicrobial peptides, alteration in cytokine secretion, or the activation of growth factors. FOS and GOS used in the diet can also reduce bacterial infection and enhance their positive effect on bacterial metabolites, such as SCFAs (Zhang et al., 2022). These metabolites can improve wound healing by increasing new blood vessel formation, regulating the immune system, and preventing bacterial growth. The findings of existing studies regarding probiotics and prebiotics in wound healing have not been well researched and, therefore, are promising. The mentioned therapies are considered as a potential organic solution to regular measures taken while treating the wound, thus minimizing the probability of receiving adverse effects.

6. Effects of Microbiome and Stem Cell Therapy

The correlation between the microbiome and stem cell therapy has recently become an extensive and complex field of study, the findings of which open a fresh world of possibilities for stem cell therapy in regenerative medicine (Tu et al., 2022). The specific interest are the roles of the gut microbiome in stem cell biology and its relation with stem cell function and differentiation, as well as the interaction between stem cells and the surrounding microenvironment, locally referred to as the stem cell niche.

6.1 Enhancing Stem Cell Function and Differentiation

Recent findings indicate that the gut microbiota affects the function and differentiation of stem cells both directly at the site of the gut microbiota niche and indirectly to other tissues. This modulation is regulated by several processes, chiefly through the synthesis of active metabolites by the gut microbiome.

Short-Chain Fatty Acids (SCFAs): Gut microbiota-derived metabolites, SCFAs, are the most significant modulators of stem cells' properties generated from dietary fiber fermentation. The role played by Butyrate, an SCFA, as one of the most effective factors was to increase the number of intestinal stem cells (ISCs), which are important in maintaining acceptable levels of Epithelial layer integrity. That occurs through activating G protein-coupled receptor 43 (GPR43) on ISCs, promoting Wnt signaling, a critical pathway for stem cell division (Ma et al., 2022). Butyrate has also been reported to affect the regulation of colonic Tregs, which is important for immune regulation and the overall health status in the gut (Silva et al., 2018).

Microbiome-Derived Factors and Stem Cell Migration: The gut microbiome can synthesize numerous factors that affect stem cell migration and homing. For instance, some bacteria are in a position to release chemoattractants that direct stem cells to areas of damaged tissue or inflammation (Ratajczak et al., 2013). This can promote tissue repair by producing a pool of cells that will replace the damaged or dying tissues.

Regulation of Epigenetic Modifications: Microbiota can affect gene regulation by altering the epigenetic marks like DNA methylation and histone acetylation of stem cells, thus changing their fate (Lorzadeh et al., 2021). The described epigenetic changes can be brought by microbial metabolites or through the microbiome's interaction with immune systems and may affect stem cells' ability to differentiate and tissues to regenerate.

6.2 Modulation of Stem Cell Niches by Microbiota

Stem cells are located in a specific structure known as a niche, which is responsible for their quiescence, renewal, and distinction. The availability and function of SCNs involved in stem cells are highly influenced by the gut microbiome, which alters the functions of various stem cells and tissue repair.

Gut Microbiome and Intestinal Stem Cell Niche: Gut microbiota is also known for its important function in protecting the stem cells of the small intestine situated in the crypt base (Nigro & Sansonetti, 2015). Dysbiosis can be defined as the adjustment of this niche, which contributes to the decline in the functionality of stem cells, changes in the differentiation patterns, as well as to compromised tissue regeneration. For instance, antibiotics' action on dysbiosis restrains the proliferation of the normal cellular parts, which are Lgr5 + stem cells and Paneth cells that are vital in the regulation of intestinal epithelium's homeostasis (Wallaey et al., 2023).

Microbiome and Bone Marrow Stem Cell Niche: Among the current research works that have been conducted, it is possible to point out such a correlation that was not expected between the gut microbiome and the BMSC niche that enabled it to be determined (Gavin, 2019). It has also been noted that the relative signals of the gut microbiota can control the formation and productivity of hematopoietic stem cells (HSCs) that are believed to be liable for the production of all kinds of blood cells. This will logically lead to the fact that SCFAs that stem from gut metabolism either enhance or decrease the functional ability of the HSCs residing in the bone marrow. It is mainly responsible for the general immunological capacity and the general potential of the marrow on which a second layer of coating can be applied (Li et al., 2021).

6.3 Case Studies: Gut Microbiota and Bone Marrow Transplantation

The gut microbiota's influence on MSC-based treatment is most pronounced in the context of bone marrow transplantation (BMT), which is a lifesaving intervention for patients with hematologic cancers and other blood dyscrasias. However, BMT is often complicated by various side effects such as graft versus host disease, infection, and immune reconstitution disorders (Barrett, 1987).

It was also identified that obesity also affects the complexity of the gut microbiome and the risk of development and severity of these complications. It has also been observed that the gut microbiota of patients with low Bacterial and fungal diversity with pathogenic bacteria overgrowth are at a higher risk of getting GVHDs and infections (Kumari et al., 2019). On the other hand, a pathogenic and imbalanced gut microbiota has been associated with the above-mentioned complications and hinders the engraftment of the transplanted stem cells. Recent studies indicate that manipulating gut microbiota via the administration of probiotics, prebiotics, or FMT might enhance the treatment results in patients receiving BMT (Yu et al., 2020). The guidelines for these interventions are as follows: interventions that can assist in reconstructing a microbiome, decrease inflammation, improve immune reconstitution, and lower the risk of developing GVHD.

7. Gut Microbiota and Organ Regeneration

Though mostly associated with the intestines, the gut microbiome critically impacts the renewal of different organs in the human body. Recent studies have elaborated on the relationship between microbiota and organ regeneration and are thus in a position to explore the microbiome's regenerative capabilities for acting as a therapeutic tool.

7.1 Liver Regeneration and Microbiome

The organ most sensitive to gut microbiota is the liver, which is recognized for its excellent ability to regenerate. The gut-liver axis, as a two-way communication channel, consists of the metabolites, bacteria, immune cells, and signaling molecules that influence liver performance and regeneration (Huang et al., 2024).

Gut Microbiota and Liver Injury: Pro-inflammatory dysbiosis involving disruption of the gut microbiota is posited to be involved in NAFLD, ALD, and cirrhosis patients, respectively (Giraud & Saleh, 2021). These conditions are defined as chronic inflammation, high levels of oxidants, and defective hepatocyte proliferation. Both basic studies and clinical trials have demonstrated that the changes in the gut microbiome by using probiotics, prebiotics, or FMT can decrease hepatotoxicity and inflammation and enhance liver regeneration in animal experiments and clinical research (Xue et al., 2019).

Microbiome-Derived Metabolites and Liver Regeneration: Liver regeneration is mainly regulated by gut bacteria metabolites that directly impact this body's function. The fermentation products of proteins and fibrous constituents of diet, referred to as SCFAs, have been demonstrated to induce the proliferation of liver cells, referred to as hepatocytes, as well as stimulate the metabolic activity of those cells (Visekruna & Luu, 2021). Also, SCFAs regulate immune responses, decrease inflammation, and enhance the gut barrier function, which is significant for the liver and its regeneration process.

Gut Microbiota and Liver Transplantation: Therefore, the gut microbiota significantly influences liver transplantation outcomes. Studies has revealed that McMaster has adverse effects on the recipient, such as infection, rejection, and GVHD, whereas, on the other hand, a healthy, diverse MAC increases the chances of graft survival and immunological acceptance (Yao, 2022). Hence, interventions aimed at altering the gut microbiota through prebiotics, probiotics, or FMT might help to enhance the prognosis among liver transplant patients.

7.2 Role in Intestinal and Colonic repair

The gut microbiome plays critical functions for the remodeling and healing of the epithelium which is a monolayer of cells that forms a layer of protection in our gut from certain compounds. Intestinal epithelium is self-renewable due to the presence of a small nutrient supply containing Isc associated with the bottom of the crypts (De Francesco et al., 2016).

Microbiome-Derived Factors and ISC Proliferation: These bacteria generate several metabolites that can impact ISC proliferation and IEF directly or without any interference. For example, butyrate, which is a kind of SCFAs that derive from some host bacteria, has been verified to facilitate the expansion of ISC and defend against intestinal injury (Sphyris et al., 2021). Other microbial metabolites affect ISC functionality, the differentiation of ISC, and the overall epithelial homeostasis of the intestine. This is through tryptophan metabolites and bile acids.

Microbiome and Inflammatory Bowel Disease: Crohn's disease and ulcerative colitis are subtypes of IBD; it is defined by the presence of chronic inflammation and compromised mucosal healing of the gut (Zonderman & Vender, 2009). The imbalance of gut microbiota, commonly described as dysbiosis, is a characteristic feature of IBD associated with the decrease in anti-inflammatory and the increase in pro-inflammatory bacteria. Fecal microbiota transplantation, as well as the use

of probiotics, have been advocated in the amelioration of IBD and have demonstrated the ability to induce remission and heal the mucosa in such patients (Imdad et al., 2023).

7.3 Cardiac Regeneration: Insights from the Gut-Heart Axis

As bidirectional communication, the gut-heart axis showed that the aim of the microbiome can be concerned with cardiac regeneration. Some observations made recently are the findings that gut microbiota seems to lead to a lifelong change in the functional properties of the cardiac tissue (Lippi et al., 2017). It also the adaptation and repair of the tissue by influencing the process of inflammation, production of reactive oxygen species, and metabolic engineering of cardiac muscle (Figure 3).

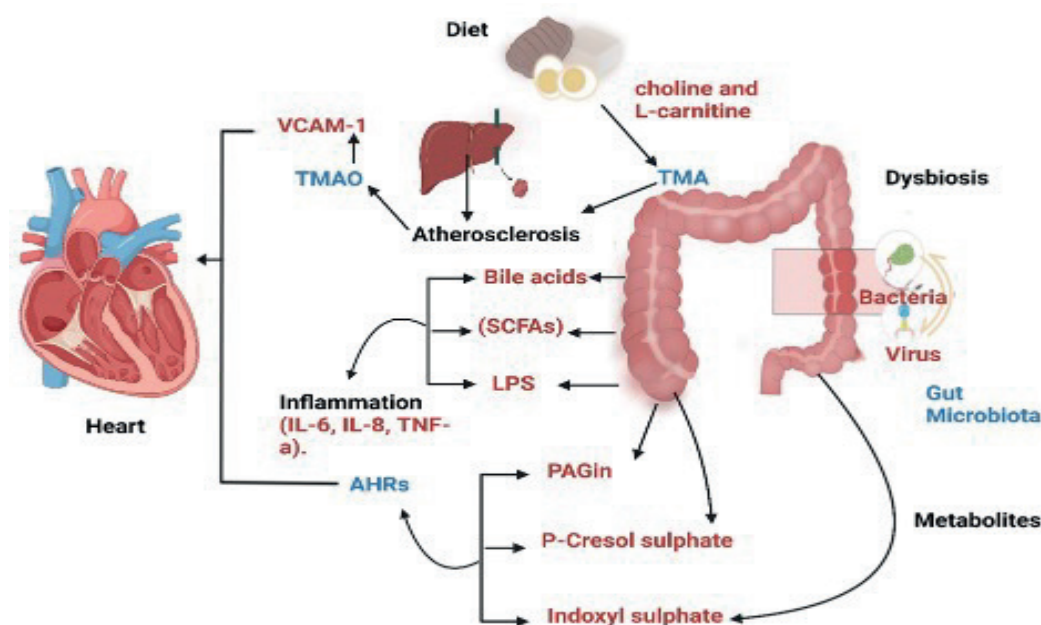


Figure 3. Gut-Heart Axis: Microbiota's Influence on Cardiac Regeneration

Microbiome and Myocardial Infarction: An example of an Acute condition is an acute myocardial infarction, also known as heart attack, in which there is death of cardiac muscles. The specific type of bacteria within the GI tract may also affect inflammation and tissue healing after an MI, which may affect the heart's performance and self-repair (Zhu et al., 2020). Several studies showed that the change in the gut microbial composition that was induced by the probiotics leads to a reduction of the range of cardiac damage. It also has protective effects on the worsening of the contractile dysfunction of the myocardial cells in animal models of MI (Chen et al., 2019).

Microbiome-Derived Metabolites and Cardiac Repair: What is clear to all of us is that there are gut bacteria that produce certain metabolites, and all these metabolites can influence the state and the recovery of the heart. Among the newly identified human gut metabolites termed Trimethylamine N-oxide or TMAO, the cardiovascular consequences were unfavorable (Wang et al., 2021). But other metabolites have, for instance, been classified under SCFAs, which Scientific studies claim have the potential to offer cardioprotection through the processes that assist in combating inflammation and enhancing endothelial function and angiogenesis.

8. Microbiome-Based Therapies in Regenerative Medicine

The symbiotic relationship between bacteria and their host regarding the host's ability to regenerate its tissues has created new horizons in treatment; microbiome therapies might serve as supplements for the body's inherent ability to fix itself. These advanced strategies utilize microbial interactions to influence immune reactions, blood vessel formation, and stem cell activity and, as a result, improve tissue healing and regeneration processes.

8.1 Fecal Microbiota Transplantation (FMT) and Tissue Repair

FMT, a procedure in which stool from a healthy individual is introduced into the gastrointestinal system of a disorder recipient with pathological gut microbiota, has been identified as a strong technique for re-establishing the relation and complexity of the gut microbiome. Although it was initially applied to patients with recurrent *C. difficile* infection, FMT has derived a positive result for various diseases, such as IBD and IBS (Borody et al., 2019). However, the potential roles of this effect have recently expanded over and above the newly discovered inflammatory diseases and encompassed tissue repair and regeneration.

FMT and Wound Healing: Diabetic foot ulcers, pressure ulcers, and venous ulcers are some common types of CRWs that affect the healthcare systems globally. Some of these injuries are qualified as dysbiosis, which means that there are disruptions in the composition of the microbial community, which can cause the wound not to heal. There are indications that FMT can be applied in chronic wound infection; researchers have found that it can alter, dampen, increase, and expedite wound healing in the GI microbiota, inflammation, and angiogenesis, respectively (Bangs, 2020).

FMT and Organ Regeneration: The studies that were carried out earlier in the recent indicated that FMT might be used in the regenerative medicine of vital organs. For instance, certain techniques, such as Fecal Microbiota Transplantation, have been identified to help regain liver function and further assist in the regeneration of liver tissues in patients with cirrhosis, a severe liver disease. The introduced microbiome is believed to suppress inflammation and/or directly alter the gut microbiota to facilitate organ regeneration. Further, FMT has been considered for application in stem cell transplantation, where it would help improve their engraftment and functioning by shaping up the gut microbiota (Zama et al., 2020).

8.2 Development of Microbiome Derived Bioactive Molecules

The microbiota synthesizes numerous bioactive metabolites, of which SCFAs, vitamins, amino acids, and secondary bile acids can be expected to have tissue repair activities (Debnath et al., 2021). To present these molecules from the microbiome to treat the above-said person is now the field of regenerative medicine.

SCFAs as Therapeutic Agents: Therefore, SCFAs, especially butyrate, have been disclosed to be the promoters of the tissue repair and regeneration process (Hajjar et al., 2021). These metabolites can affect stem cell division and differentiation and may participate in forming new blood vessels, regulating immune cells, and reducing inflammation. While butyrate is supplied for IBD, it is also used in such experimentations to elicit the formation of genes required for wound healing, any process associated with necrosis stated, or any impaired tissue repair.

Microbiome-derived Antimicrobial Peptides (AMPs): AMPs are small molecules produced by bacteria inhabitant the intestinal tract that has a direct impact on pathogens by killing them (Furci & Secchi, 2018). They can kill or restrict the growth of pathogenic bacteria, thus showing prospects of being used in the treatment of infections and the promotion of wound healing. Emergent work has been done to discover and classify the new AMPs from the gut microbiome and their additional role in regenerative therapy.

8.3 Synthetic Biology and Engineered Microbes

Biologically inspired engineering and system techniques within synthetic biology pave the way for microbiome-based therapeutic approaches. In creating the microbial solution, the scientists hope for the achievement of site-specific therapies that will address the regenerative processes.

Engineered Probiotics: Thus, researchers are selecting and modifying probiotic strains to have various custom features, including the synthesis of certain metabolites or the expression of therapeutic proteins (Singh et al., 2018). These purposefully constructed bacteria could be utilized

to carry therapeutic compounds directly to the particular area of tissue damage or disease, thus improving tissue remodeling and regeneration.

Microbial Consortia: Another promising strategy in synthetic biology is the construction of microbial communities and multiple bacterial strains (Rodríguez Amor & Dal Bello, 2019). These consortia could also work harmoniously to enhance the yield of specific desirable metabolites and have a greater impact on tissues than a single strain.

Targeted Drug Delivery: The engineered microbes can thus be used as carriers of drugs or any other therapeutic molecules, with a preference towards a particular tissue or organ (Wu & Liu, 2022). They can also increase the efficiency of the drugs and diminish the overall toxicity of the system; they can also help increase the regenerative capacity of the established remedies.

9. Challenges and Future Directions

The prospectus of microbiome-based therapies in regenerative medicine is profound. However, multiple complexities and concerns have to be met to effectively and safely transport these promising treatments into the clinic.

9.1 Technical and Scientific Problems

The microbiome is a multifaceted and constantly changing system, and the involvement of the microbiome in regenerative medicine is an area of distinctive study. Several technical and scientific challenges remain to be addressed:

Identifying Key Microbial Players: The microbiome contains an incredible number of microorganisms, and it is difficult to pinpoint the exact species or even strains that are so important for tissue regeneration (DeSalle & Perkins, 2015). Novel sequencing and computational biology techniques are being discovered to catalog the microbiome and discover possible drugs for treatment.

Understanding Mechanisms of Action: Although it is clear that the microbiome does indeed dictate the means of tissue regeneration, the exact ways in which this process is regulated are still not quite understood. More work should be conducted on the various parts and pathways of bacterial metabolites, the signaling of bacteria with host tissues, and the immune response to bacterial repair of injured tissues (Yang & Chiu, 2017).

Developing Standardized Therapies: The challenge then emerges as to how to standardize and reproduce post-rigor microbiome-based therapies like probiotics and Fecal Microbiota Transplant. Microbial communities also have different structures and functions in different people, which makes it impossible to talk about individual universals in the use of therapies (Moran et al., 2019). Dietary recommendations and the intensity of treatments may have to be chosen depending on the results of an individual's microbiota analysis for optimized therapeutic outcomes.

9.2 Policy and Process Implications

The use of microbiome-based therapies raises several ethical, legal, and social considerations that need to be carefully addressed: The use of microbiome-based therapies raises several ethical, legal, and social considerations that need to be carefully addressed:

Safety and Long-Term Effects: The consequences of adjusting this microbiome, especially from sanitation or pharmacologic research, including FMT, are not the subject to good comprehension today (König et al., 2017). However, these therapies must be proven safe and effective with the applicable double-blind studies first.

Informed Consent and Autonomy: Patients' conditions must be explained to ensure that they understand the consequences such as the probability of contracting other diseases, side effects, and the long-term impact of microbiome therapies (Ribeiro et al., 2020). Although it may be impossible

to avoid conflicts of interest in healthcare, the patient's right to decide and be protected must be upheld by acquiring informed consent.

Access and Equity: Some micro-biome-based treatments, like FMT, are expensive and, therefore, not affordable to all people. It remains a major ethical issue to ensure that people in need and who could benefit from these types of interventions get equal chances and opportunities (Hoggett et al., 2008).

Regulatory Oversight: The existing legal framework of microbiome-based therapies is also continuously shifting (Manrique et al., 2024). Therefore, measures, requirements, policies, and objectives regarding the production and use of these therapies need to be developed and established.

9.3 Regulatory Factor and Approval Process

Approving these microbiome-based therapies requires particular concern because the microbiome is large and variable.

Classification of Microbiome-Based Products: It is, therefore, possible to categorize microbiome-based therapies as drugs, biologics, or medical devices depending on their intended usage and composition, creating more regulatory issues (Manrique et al., 2024). More specific regulations are missing or lacking details that could help in launching and approving these treatments.

Clinical Trial Design: Considering important aspects like the microbiome's complexity, the inter-individual response, or the outcomes of microbiota-targeted therapies, clinical trials for microbiota-based approaches should be specifically designed (Favaron et al., 2023). The study designs should be strong, following globally established guidelines to produce evidence that fits the acceptance criteria of regulatory agencies.

Post-Market Surveillance: Due to the immense process of constant change of the microbiome, after-approval monitoring or post-market surveillance becomes a necessity to assess the safety and effectiveness of microbiome-based therapies. This can help identify an adverse effect, follow the evolution of the microbiome, and estimate the impact of these therapies in patient management (Vázquez-Baeza et al., 2018).

9.4 The Possibility of Patient-Specific Regenerative Medicine

The convergence of microbiome with regenerative medicine can be seen as the key to the future of the field because it makes it possible to create the individual's regenerative approach (Williams et al., 2023).

Microbiome Profiling: It has been found that by looking at an individual's microbiome, which is the microorganisms living in the body, clinicians can determine if there is dysbiosis or imbalances in the body that would prevent essential tissue repair. These details can help to design individual treatment plans; for example, the client can take probiotics, prebiotics, or receive an FMT to restore a healthy microbiota and achieve the best regenerative result (Ugwu et al., 2024).

Targeted Therapies: Microbiome-based therapies can be designed to modulate the pathways contributing to tissue healing and regeneration (Lee, 2021). This specific procedure can improve the effectiveness of regenerative treatments while reducing side effects.

Predictive Biomarkers: Thus, expanding the understanding of the relationship between microbiome and an individual's response to regenerative therapies offers the potential for treatment optimization and better patient outcomes (Van Lier et al., 2021).

9.5 Directions for Collaboration Between Microbiome and Regenerative Medicine Investigators

It is here important to link microbiome investigators with regenerative medicine to hasten the possibility of a cure undertaking. This collaborative approach can be facilitated through several key strategies. Thus, several strategies may be employed to enhance this kind of collaborative approach:

Joint Research Projects: Therefore, the representatives of the microbiome and regenerative medicine can produce a positive interaction that will offer an opportunity to develop and perform intricate investigations. That will help in conceiving and displaying the processes, which would improve knowledge of the microbiome and the niches of tissue regeneration. Such projects can focus on such objectives as the identification of microbial genera or bioactive compounds that are engaged in the healing process, the identification of the signaling networks of such processes, or the new therapeutic approaches that regulate the interaction with host microbiota (Pires et al., 2024).

Data Sharing and Integration: Clinicians and microbiome-inspired researchers need to share data so that new knowledge that is created needs to be applied (Tomasulo et al., 2024). Microbiome collections might be merged with clinical data to identify correlations and connections that are hard to ascertain in studies involving individuals at given time points. Thus, it helps define new biomarkers for the potential assessment of the patient's response to therapies, identification of potential beneficiaries of certain treatments, and, all in all, the assessment of the long-term outcomes driven by microbiome interventions (Elhag et al., 2022).

Multidisciplinary Teams: It is important to identify various teams containing particular specially microbiome researchers' immunologists, senior bioinformaticians, and other special individuals belonging to a similar subject treatment. Such teams could advise their specialist and provide the required knowledge on the aspects concerning the growth of microbial consortia and the development of the delivery system to achieve the goal the paper aims for, namely, standardization of FMT (Fitzpatrick et al., 2024).

9.6 Empirical Process and Clinical Trails

Many healthcare providers want microbiome-based therapies to become standard clinical practice. However, this is only possible if well controlled trials are conducted.

Well-Designed Studies: Clinical trials must be designed according to certain research questions and appropriate endpoints and methodological stringency (Provencher et al., 2018). Due to the complexity of the microbiome and persons' responses to the administered treatments, this position is understandable. For example, the current level of the microbiome characterization means that patients need to be segmented based on characteristics of the microbiome to identify the population that will benefit based on the changes to be made to its structure through various interventions.

Standardized Protocols: Therefore, there is a need to capture the comparability of the various Microbiome interventions; Fecal Microbiota Transplantation FMT, Probiotics, and Prebiotics for repeatability of the studies involved (Yadegar et al., 2024). Proselytization of such protocols should include information about the choice of the donors, preparation of the material, its delivery, the doses to be used, and the length of the treatment. Standardization is also necessary, especially when it comes to the safety and quality of the products developed from microbiomes such as FMT.

Long-Term Follow-Up: Due to the described consequences and the complexity, one should control the patients' outcomes after microbiota manipulation by using microbiome-based therapies with definite prolonged intervals (Abdul Rahman et al., 2021). It can assist in assessing the sustainability of the therapeutic interventions' gains for side effects and other factors that may influence the treatment outcome. In addition, with the help of long-term research, it is possible to define the effectiveness of microbiome interventions in preventing cancer relapse or progression.

Continuing Medical Education: Thus, it might be advisable for healthcare providers to engage in relevant CME programs to familiarize themselves with the existing state of the studies and clinical guidelines regarding the utilization of the microbiome in treatment. This can furnish them with the knowledge and skills that they need to practice these therapies and also handle patients in the same (Gonzalez et al., 1990).

Patient Education: The patients that have to be administered the microbiome treatment would have to understand what the microbiome is, how it works, and such things as the microbiome therapy is beneficial or hazardous to the human body (Nayak & Turnbaugh, 2016). This may help them make proper decisions on their health and make them participate in their treatment. Referral materials, including brochures, sources of information on the internet, and support groups from the patients, could be vital in the general process of educating the patients.

10. Conclusion

Microbiome or microbial symbionts, which are a prolonged identity of people, are at the forefront of new regenerative medicine. It plays some appreciable role in the process of tissue repair and regeneration, involving in part the regulation of immune cells and angiogenesis, influence on the stem cells, and last but not least, the process of differentiation. Now that the role of the concept of the microbiome was viewed from other points as the support of the healing process of different tissues together with the Bioluminescent technology a new area was opened in the treatment of many illnesses and injuries. Some of the existing and known treatments cover FMT, the combination of probiotics with prebiotics, and producing active molecules originating from microorganisms that efficiently accelerate the regeneration and skin repair process. The ability to build functional and controlled communities or from certain residents who ensure the right environment for tissue renovation is a new approach that addresses the challenges of chronic ulcers, biomatrix damage, and degeneration among the population. However, there are several problems related to using microbiome research in regenerative medicine. Difficulties in isolation and delineation of such microorganisms and their niches and ways of operation, as well as logical, juridical, and ethically considerate problems, demand additional research and passingly navigated paths. Therefore, the task of building a common and personal, at the same time, highly effective and reproducible microbiota-directed therapy remains a tough one, and, accordingly, it is hoped that it will be solved by people of various fields only. However, microbiome-based regenerative medicine has a great future based on the following factors. Novel techniques, including single-cell sequencing, and new insights into the bioinformatics tools, are helping them expand the horizon for the perspective of deciphering the trends of the microbiota and the host tissues. For such reasons, in light of opportunities to use genetic manipulations of microbial cells and targeted delivery systems, the prospects of the application of microbes in the treatment of diseases are much broader. As researchers study further the microbiome's roles in aiding the regeneration of tissue, improved therapies should be developed because of this energy source for healing. It is a new overcoming paradigm in the field of regenerative medicine that possesses an excellent opportunity to revolutionize the present system of health care by offering new concepts, ideas, and strategies in the management of chronic non-healing ulcer wounds, organ failure and degenerative diseases with the overall improvement in the quality of life of the patients.

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