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# Gut microbiome: a balancing act between degeneration and regeneration

**Nitin Saksena*, Matt Keon**

In a symbiotic and mutualistic manner, the gut microbiota strongly influences many vital aspects of host physiology, biology, repair, and regeneration. The role of microbiota in many areas of regenerative medicine is just beginning to emerge, but it is under-recognized because of its complexity. As we remove the barriers that impede our understanding of this complex entity, we will uncover some of the most vital facets of our microbiome that make us who we are, its intrinsic connection with not only our wellbeing, but also with regeneration within. This will subsequently define its utility in regenerative medicine.

As the human microbiota is constantly exposed to extraneous forces, it has been dubbed as one of the most vital unclassified epigenetic forces because the metabolites they secrete can regulate immune cells and cytokines via epigenomic modifications (Chen et al., 2017). This process is akin to the non-coding RNAs, methylation, and chromatin/histone modulation, which help communicate the message between the gut and brain in regulating the immune system and carrying out regenerative functions. Microbiota, thus, regulates every single physiological process directly or indirectly. Thus, any alterations in the equilibrium between gut microbial compositions can lead to disequilibrium in the production of microbial metabolites needed for communication, leading to wide-ranging diseases afflicting humans. This perspective highlights the possible regenerative roles microbiota plays in neurodegenerative diseases, stem cell transplantation, cancers, in addition to defining clinical outcomes of diseases. Microbiota is a new paradigm in regenerative medicine; therefore, it is essential to provide a discussion on several fronts that will stimulate our understanding of its full clinical implementation in regenerative medicine.

**Degeneration to regeneration:** According to the current literature, there is no doubt about the human microbiome's vital role in neurodegeneration and neuro-regeneration. It is a matter of homeostatic equilibrium, tightly maintained between microbial species at the genus level. Any imbalance in this equilibrium (dysbiosis), defined by microbial diversity, tilts the balance in favor of disease. The main mantra is- higher the microbial diversity better the health outcome, which is akin to higher diversity in antibodies to fight pathogens during infectious disease.

**Microbial control of the regenerative potential of stem cells:** The gut microbiota is a powerful innate sensor, and the gut microbial products are known to serve as a source of microbe-associated molecular patterns. These, in turn, bind to pattern recognition receptors on innate cells (monocytes/macrophages and natural killer cells). Thus, epigenetic and metabolic reprogramming accompany cell activation leading to a rise in cytokines and immune responses upon pathogen exposure. It is thus essential to mention that the microbial ligands that reach the bone marrow through blood circulation also condition the hematopoietic progenitors, induce long-term memory traits, and enhance myelopoiesis to achieve a beneficial outcome against an infectious modality.

Given the proximity gut microbiota maintains with the intestinal epithelial cells, it is vital to understand the underlying mechanisms that regulate signals the gut microbiota conveys to the epithelial cells. Furthermore, this proximity also points to the role played by intestinal stem cells in epithelial regeneration and homeostasis and repair post-damage. Thus, this barrier and the proximity between the intestinal epithelium and microbiota serve as the primary gateway for potential interactions that play vital roles in immune, developmental, metabolic, regenerative, and repair functions.

To name a few, the stem cells are a vital part of the skin, hair, bone marrow, joints, muscles, and more importantly, brain and gut, although they are rare cells in these organs. Moreover, these cells have a regenerative function in generating new tissue during the growth period and repairing damaged tissues during the aging process. Thus, the utility of stem cells in treating human diseases (cancer, spinal cord injuries, neurodegenerative diseases, diabetes, and heart diseases) and injuries (spinal cord and sport-related injuries) remains the top priority in medicine and in defining precision treatments. Of fundamental importance is the relationship the stem cells maintain with gut microbiota, which, if clearly understood, can help treat injuries, facilitate the durability of organ transplant, and treatment of various diseases that involve stem cell transplant.

**Allogeneic hematopoietic stem cell transplantation (HSCT) and gut microbiome:** Metabolic changes in stem cell niches could be attributed to the microbiota and its derived metabolites. A recent report has linked microbiota and hematopoietic stem cells differentiation via alteration of metabolic stress. Thus, the microbiota is essential in microbial homeostasis, metabolism alterations, and regulating the innate and adaptive immune systems. Furthermore, evidence suggests that dysbiosis-driven compositional changes in the gut microbiota are linked to the aging of stem cells in terms of dysregulations of metabolism, aberrant activation of the immune system, and epigenetic instability of stem cells (Tan et al., 2019).

The omnipresence of microbiome and stem cells *in vivo* indicates an intrinsic association that these two entities maintain at all times with both regenerative and degenerative processes. The homeostatic imbalance of these two entities drives disease development. Thus, the host-microbe interactions play a significant role in patients receiving allogeneic HSCT, and such a relationship is inseparable. Moreover, it is apparent from the complications observed in patients receiving allogeneic HSCT, which is influenced by the gut microbiota (Liu et al., 2017) that impacts the overall survival.

Currently, HSCT is commonly used as curative immunotherapy for several non-malignant and malignant hematologic conditions, including various cancers. However, such a transplantation procedure comes with severe side effects, including infections, acute graft-versus-host disease (aGvHD), and mortality. Although the post-transplantation complications are intrinsically associated with the host's immune system, a seamless interaction exists between gut microbiota and the immune system (Wang et al., 2015). The elevated concentrations of antimicrobial peptide human beta-defensin 2 are present before the transplantation in patients with a high abundance of Lactobacillaceae, who later developed moderate or severe aGvHD and exhibited high mortality. In contrast, rapid reconstitution of natural killer and B cells was seen in patients with a high abundance of obligate anaerobes such as Ruminococcaceae, who displayed no or mild aGvHD accompanied by low mortality. Notably, the high inflammation in patients, as evident from C-reactive protein levels, coincided with the high abundance of facultative anaerobes in Enterobacteriaceae.

It is to be cautioned that the changes in the stem cell niches during HSCT could only be partially explained by microbiota composition. However, a large part of the damage is accounted for by the high doses of chemotherapy patients receive. In this case the evidence suggests that the gut microbiome is more likely to shape the maturation of the immune system developing from the transplanted hematopoietic stem cells and the onset of transplant-related complications. In the study of Peled et al. (2020), the impact of gut microbiota was seen only in T-replete HSCT, suggesting the microbiota influences the outcomes only with an active immune reaction. Thus, it is important to iterate that some metabolites secreted by the microbiome are also crucial in the success and failure of HSCT (Masetti et al., 2021).

Pulmonary complications upon allogeneic HSCT have been seen. This is of fundamental importance because of the intrinsic control the gut microbiome maintains with other bodily systems and their regulatory control. Intestinal permeability may permit the translocation of bacteria or their metabolites (liposaccharides) to the lung, causing acute respiratory distress syndrome and sepsis post engraftment, thereby compromising patient outcomes. Investigation of the role of the microbiome in the gut–lung crosstalk post-HSCT (Harris et al., 2016) showed not only the parenchymal abnormalities and associated mortality but also the dominance of Gamma-proteobacteria of gut microbiome that were significantly associated with pulmonary complications. Thus, the identification of multivariate associations between specific microbial taxa, Host immune markers, immune cell reconstitution, and clinical outcomes concerning HSCT are significant and point to profiling the intestinal microbiome and establishing its longitudinal surveillance concerning relevant immune markers, such as human beta-defensin 2, particularly HSCT patients. This may not only help define the success of HSCT transplant but may also open doors to developing a

prognostic tool for identifying reasons for poor immune reconstitution and adverse outcomes (aGvHD and death), which can guide precision treatment in the right direction with robust clinical outcomes. In addition, this may highlight the possible therapeutic implications and value of the gut microbiome, during HSCT, in a rational design for effective intervention and therapeutic strategies.

**Gut–the second brain: implications in human neurodegenerative disorders and behavior:** In recent times, the gut is often referred to as the "second brain", or as the "enteric nervous system" owing to comparable levels of neurons present in the gut and spinal cord (Hadhazy, 2010), thereby exerting extensive influence on numerous body systems and processes, in addition to regulatory control of these aspects. Recent studies have suggested a close relationship between the diversity of host-microbiota the aging and aging-related diseases (Carabotti et al., 2015). The gut-brain axis comprises bidirectional communication between the central and the enteric nervous system, which links both the emotional and cognitive centers of the brain with peripheral intestinal functions. Thus, the gut-brain axis mediates health as it maintains firm control over human behavior, sense of taste, smell, appetite, social interaction, stress, and pain sensations. The regulation of behavior occurs via the influence of local gastrointestinal hormone release or bacterial fragments and metabolites that communicate with the central nervous system (CNS) and directly affect the hypothalamus (Carabotti et al., 2015). Gut microbiota has also been shown to regulate the permeability of the blood-brain barrier and the release of serotonin. Moreover, the production of polyunsaturated fatty acids and short-chain fatty acids (SCFAs) by the gut microbiota may also regulate levels of neurotransmitters in the CNS, in addition to regulating mechanisms underlying processes such as myelination, neurogenesis, energy metabolism, and neuron survival, growth, and differentiation. Thus, the microbial SCFAs have a significant role in the maturation and function of the microglia.

Given the commonalities between the CNS and enteric nervous system, drugs for treating CNS disorders, such as depression and anxiety that target the mind, can unintentionally affect the gut. There are more than 30 neurotransmitters in the enteric nervous system, which is akin to the brain. Surprisingly, > 95 percent of the body's serotonin is found in the bowel. In this case, it is essential to mention that bowel problems, significantly reduced bowel movement or constipation, are prevalent in Parkinson's, which arises due to slowness of movement (bradykinesia) and muscle rigidity, both of which are visible symptoms of the condition. Problem with motility of the gut is a major source of difficulty which persists throughout the disease course, and more so in advanced Parkinson's disease. Concerning Serotonin, there is progressive and non-linear loss of serotonergic terminals in Parkinson's disease, which is slower than the dopaminergic loss.

Further, stressing the role of SCFAs, propionic acid has been used as a potential regenerative treatment, as the SCFAs are known for their influence on immune reactions in the gut (Mulak, 2018) and eliciting a direct effect on neurons after crossing the blood-brain barrier (Silva et al., 2020). Furthermore, propionates are produced from dietary substrates by colonic bacteria, and they stimulate intestinal gluconeogenesis, which is associated with reduced stress behavior. More importantly, the SCFAs are depleted in the feces of patients with Parkinson's disease. With this, a recent study from Johns Hopkins University suggests that the origins of Parkinson's disease may lie in the gut (John's Hopkins, 2019).

In the more global context, various studies suggest that intestinal health significantly impacts neurodegeneration despite the anatomical distance between the gut and the brain. Neurodegenerative diseases like Alzheimer's disease and amyotrophic lateral sclerosis may have underpinnings in the gut. Here, it is important to mention that in the amyotrophic lateral sclerosis mouse model, disease-specific damage to intestinal tight junctions, increased gut permeability, and reduced levels of the butyrate-producing bacteria Butyrivibrio fibrisolvens were the main features (Boddy et al., 2021).

In the case of autism, gastrointestinal problems are often associated with many autism cases, suggesting that it is not just a psychiatric disorder but may also have underpinnings in the gut. Thus, alleviating the gastrointestinal problems could help alleviate the symptoms leading to successive improvement.

In the context of autism as discussed in the previous sections, serotonin seeping from the enteric nervous system can play a part in autism. Moreover, the genes involved in synapse formation between neurons in the brain also involve alimentary synapse formation. These are the genes affected in autism and could explain why some kids with autism have GI motor abnormalities" in addition to elevated levels of gut-produced serotonin in their blood. Supporting this argument, sustainable beneficial effects have been demonstrated in children diagnosed with autism spectrum disorder through Microbiota Transfer Therapy or Fecal Matter Transplant. Remarkably, improvements in gut health and autism symptoms appear to persist long after the treatment with a slow, steady reduction of autism spectrum disorder symptoms during treatment and over the next two years. For example, there was a 45% reduction in core autism spectrum disorder symptoms (language, social interaction, and behavior) at two years post-treatment compared to pre-treatment, which could be attributed to the augmentation in microbial diversity and the introduction of beneficial bacteria (Bifidobacteria and Prevotella), which help boosting the overall health.

**Conclusions:** Understanding the dysbiosis pre- and post-disease manifestation could bring about not only the resolution to some of these diseases but may also unveil the regenerative potential of the gut microbiome across diseases that afflict humans.

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