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Review Article

A Stem Cells and Intestinal Microbiome

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Abstract

We carry out an in-depth analysis of the importance of stem cells and intestinal microbiota through the evaluation of their interactions, highlighting their significance through their central objective, both isolated and united, and reviewing the impacts that these entities have on the intestinal microbiota in people who have undergone stem cell transplants and confirm the conditions in which they have been successfully applied. We also focus on the advantages and disadvantages of each procedure, in order to provide appropriate application percentages and rationalization of their use.

Keywords: *Stem Cells (SCs); Intestinal Stem Cell (ISC); Microbiome (M); Intestinal Microbiota (IM); Acute Graft Versus Host Disease (AGHD); Intestinal Microbiota Transplant (IMT); Fecal Microbiota Transplant (FMT)*

Introduction

Stem cells

Undifferentiated cells of a multicellular organism capable of generating more cells of the same type indefinitely, and from other types of cells which arise by differentiation [1]. They can divide into new stem cells that are specialized (new tissues and organs). They are of great interest and can be used to treat diabetes, heart disease, parkinson's disease, and others [2]. Are there two types of stem cells (SCs): embryonic and adult (tissue stem cells).

Among the latter are the hematopoietic and neural SCs; hematopoietic SCs are located in the blood and bone marrow, whereas neural SCs are located in the spinal cord and brain [3].

Mouse embryonic cells are among the most studied. If cultured embryonic cells are injected into the blastocyst, cells that can mimic almost any tissue will be generated. These cells are called pluripotent due to their unique ability to produce any type of cell [4].

The use of human embryonic SCs raises ethical concerns because blastocyst-stage embryos are destroyed in the process of obtaining them. Their use is prohibited in some countries and accepted in others [5]. The FDA (Food & Drug Administration) approved them in 2009, but due to their limited federal funding in the United States of America, many scientists prefer using the mouse model [6].

Adult SCs, which can be located in the epidermis, the lining of the small intestine, and the bone marrow, usually persist indefinitely [7].

Bone marrow contains hematopoietic SCs, which generate all types of blood cells and cells in the immune system. They are found in small quantities in peripheral blood, while in large quantities in umbilical cord blood [8].

Neural SCs are localized in the brain and can be cultured *in vitro* as neurospheres [9]. They have been used in cell therapy to treat Parkinson's disease and other forms of neurodegenerative or traumatic damage to the central nervous system [10].

The multipotent SCs found in the bone marrow are the best known, after being used therapeutically since 1960 to treat leukemia, myeloma, and lymphoma [11]. Their use requires immunosuppressive drugs during engraftment, whereas the use of multipotent autologous SCs (self-stem cells) does not require these drugs, since they have specific surface proteins and are accepted by the host's immune system [12].

In animals, patches of cardiac myocytes derived from human embryonic SCs can form viable human myocardium [13]. The use of SCs still has to overcome many obstacles [14].

What is the human microbiome?

Joshua Lederberg on April 1, 2001 introduced the word Microbiome (M), defining it as the ecological community of commensal, symbiotic, and pathogenic microorganisms that literally share our body space and have been ignored as determinants of health or disease [15]. Currently, M refers to the total number of microorganisms and their genetic material. It has been referred to in many ways since 2001, including: The Last Human Organ [16]. Our second genome [17]. New Systemic Organ [18]. Human Organ in Research [19]. Invisible Organ of the Body [20]. Forgotten Organ [21]. And Super-Organ or Super-Organism [22].

Intestinal microbiota

Microbiota is a set of microorganisms: bacteria, eukaryotes, viruses, and archaea present in a defined environment, in the intestine we find intestinal microbiota (IM) [23]. IM, the largest immune organ, provides more vital genes than our own genome and carries out a series of vital functions that prevent deadly infections in the mucous membranes, in the skin, or by pathogens that cannot normally proliferate [24]. With over 40 functions performed by the IM, the most important are: Collaborate with neurological function through the "gut-brain axis", neurological development assistant, promote endocrine functions, protection, determining intestinal homeostasis, inhibit opportunistic pathogen diseases, produce short-chain fatty acids (SCFA), and prevent the development of neoplasms [25-27].

Interactions between stem cells and gut microbiota

One of the ways of knowing what the interaction is between them is by visualizing what happens in allogeneic SCs transplants. In them, it has been observed that one of the most significant policies to follow is the analysis of the diversity of IM, since it is associated with acute graft-versus-host disease (AGHD) [28].

These interactions involving the host's innate and adaptive intestinal and extraintestinal immunity, in some cases lead to serious health effects [29]. AGHD, produced by the activation of various immune cells, especially donor T cells and causing inflammation of the liver, lungs, intestine, and skin, occurs in 40% to 50% of patients undergoing allogeneic hematopoietic SCs transplantation [30] and produces significant post-transplant mortality [31]. IM has been predicted to have the potential to prevent or ameliorate this acute reaction [32].

Although M bacteria have been largely investigated, the mycobiome and virome are much less understood [33]. Like bacteria, fungi and viruses are highly diverse in the gut, showing evidence that they interact with the host's immunity [34]. In addition to producing immunomodulatory metabolites, IM confers resistance to colonization against pathogens [35], by preventing them from invading the intestine

[36]. The immune response as inflammatory cytokines tend to inflammation, infections, and sepsis (bacteremia and fungemia) [37], generally caused by *Escherichia coli, Pseudomonas aeruginosa*, and *Candida albicans*, which, when treated with broad-spectrum antibiotics, lead to severe resistance conditions and death [38].

It has been observed that administering 17 butyrate-producing *Clostridia* strains improve the integrity of the intestinal epithelium, reduces specific damage, and improves survival after allogeneic SCs transplantation, in a murine model [39].

Considering IM signatures have a high probability of becoming criteria for therapy follow-up, research focused on the generators of infectious processes should be intensified and categorized before stem cell transplantation [40]. A large cohort retrospective study linked the presence of Gram-positive SCFA producing *Eubacterium limosum* with reduced risk of disease relapse [41].

Urine metabolomics is another non-invasive way of locating biomarkers for bacterial metabolites. Recently, the importance of indoxyl sulfate (produced predominantly by beneficial intestinal microorganisms) was brought to light [42]. The decreased concentration of this metabolite was associated with a poor prognosis in patients with allogeneic SCs transplants [43]. In the near future, manipulation of the IM will be beneficial in reducing morbidity and mortality related to allogeneic SCs transplantation [44]. Likewise, the determination of inflammation, indicated by high levels of C-reactive protein, in patients with an abundance of anaerobic bacteria such as *Enterobacteriaceae* [45] will also become beneficiary.

Increased human beta-defensin 2 has been observed in moderate to severe cases of AGHD and high mortality. In these patients, NK and B cell reconstitution was slow compared to patients with low mortality rates [46]. The effect of the interaction between IM and transplanted patients with SCs can be diverse. For this reason, recent studies indicate that specific anaerobic intestinal microorganisms may be particularly important in allogeneic transplantation [47], showing evidence of resistance to colonization and impact on significant clinical outcomes such as overall survival and transplant-related mortality [48]. These benefits can lead to lower transplant-related complications, such as infection and acute graft-versus-host disease [49].

Currently, it is unknown exactly how beneficial gut microorganisms are at enhancing defense against transplant complications in allogeneic recipients [50]. An increase in knowledge can enable the use of antibiotics intelligently, accompanied with the maintenance of important bacterial groups such as *Bacteroidetes, Lachnospiracaeae* and *Ruminococcaceae* [51].

Advantages and disadvantages of stem cells and gut microbiota

The SCs of intestinal niches implement various devices to process the environment with constant changes [52], like having to respond to regulatory factors of the intestinal barrier, especially the elements of diet, obesity, cancer, inflammatory bowel disease, and IM [53]. The latter exert actions through their effects on metabolism, nutrition, and the integrity of the intestinal barrier [54]. Similarly, the intestinal epithelium through pattern recognition receptors [55] communicates with bacteria *in situ* [56]. And by means of Toll-like receptors, it detects the presence of pathogens [57] with immediate responses from NoD2 receptors [58]. Toll-like receptor signals have been shown to alter intestinal homeostasis, affecting proliferation and apoptosis rates in the crypt [59]. In it, Lgr5 + stem cells generate high levels of the cytosolic innate immune sensor (NoD2), –even higher than that of Paneth cells [60], protecting the survival of SCs, mediated by oxidative stress [61]. The replacement of the intestinal epithelium responds to NoD2 (muramil dipeptide), through molecules originating in IM [62].

All of the above determines whether there is a close interaction between intestinal stem cells (ISCs) and IM [63]. With this, we can conclude that rather than defining who has the most advantages, our observation is that both are closely complemented. More evidence supporting this is the intestinal epithelium's contact with commensal intestinal bacteria resulting in the production of ROS (Reactive Oxygen Species), which signal molecules that modulate the innate immune response, motility, and cell proliferation [64]. Physiologically generated ROS act as signaling molecules to mediate increased cell proliferation and motility to modulate innate immune signaling [65].

It is probable that the elevation of ROS impacts intestinal infections, acting against commensals and pathogens [66]. Redox homeostasis (oxidation-reduction reactions) is essential in regulating the characterization of ISCs, while ROS modulate their neo-generation [67].

An immune response was discovered two decades ago in the gut of the genetic model system in *Drosophila melanogaster*, used to further our understanding of intestinal pathophysiology in humans [68], numerous discoveries to follow will bring us closer to the truth when it comes to IM relationship with ISCs.

Diet, probiotics, prebiotics, symbiotics, transbiotics and paraprobiotics

Diet. Hippocrates used to say "Let food be your medicine and medicine be your food", with this rationing we enter into a topic centuries-old [69]. Breast milk and formulas favorably modulate IM early in life [70]. Therefore, both IM and M are altered by elements of one's diet [71].

We must not forget the incidence of poor dietary habits in inflammation [72], as well as the involvement of the inflammatory process in various diseases, including cardiovascular disorders and cancer [73]. The high administration of meat generates an inflammatory process [74]. If a Mediterranean ketogenic diet is accepted, we can improve countless diseases [75]. Critiques change when it comes to managing patients with allogeneic SCs transplants [76] where the inflammation generated by dietary processes also plays a significant role in its modulation [77], and uncontrolled self-renewal would increase the risk of tumor processes [78]. Demonstrated by several studies, where the appearance of colorectal cancer due to inflammatory conditions is the most significant [79].

Intermittent fasting and caloric restriction prompt beneficial impacts on aging tissue functions, demonstrated by health in eukaryotes [80]. Whereas a high-fat diet or overnutrition usually disrupts IM and bacterial load, although the effect on ISCs is temporary [81]. In any case, there is a significant increase in enteroendocrine cells [82] with an exposure of ISCs to toxic metabolites [83]. Fasting produces an increase in circulating SCFA, with the consequent positive modulation of ISCs [84].

Stress also impacts CSIs, causing them to multiply repeatedly [85]. If we correct intestinal dysbiosis, symptoms of various diseases can be improved, through the introduction of new therapeutic approaches [86].

Probiotics: Live microorganisms that, after ingestion in specified amounts, exert health benefits beyond those of inherent basic nutrition [87]. Its use improves gastrointestinal disorders in the elderly, when using: *Saccharomyces boulardii, Lactobacillus acidophilus, paracasei* and *reuteri*.

The most widely used probiotics are *Lactobacillus* spp and *Bifidobacterium* spp. [88]. IM, like *Lactobacillus,* interacts with ISCs both directly and indirectly to regulate their proliferation and differentiation [89]. *Barnesiella* generates resistance to pathogens through the occupation of intestinal niches, including those of ISCs, incitement of host immunity, and nutrient competition [90]. *Lactobacilli* elaborate indole-3-aldehyde from tryptophan, which is a known AhR ligand [91]; in this process, the protection of intestinal mucosa is carried out [92].

What probiotics are used in hematopoietic stem cell transplantation?

Although the use of steroids and antibiotics is the first thing to be carried out, unfortunately, they have a series of added phenomena, which is the reason we consider probiotics in hematopoietic stem cell transplantation, as well as in AGHD [93]. *Lactobacillus* has been administered before and after transplantation, reducing AGHD [94].

Prebiotics: Glenn Gibson and Marcel Roberfroid define the probiotic as an "indigestible food ingredient, which beneficially affects the host, by selectively stimulating the activity or growth of a limited number of bacteria, thereby improving their health" [95]. Nondigestible

plant oligosaccharides and polysaccharides are fermented in the colon by commensal bacteria, resulting in the production of SCFA that serve as an energy source for the colonocytes [96].

By minimizing the transfer of *Enterococcus*, there is a decrease in mortality in patients with AGHD [97]. SCFA feed and impact the enterocytes giving energy and disrupting the antiapoptotic effect [98]. Exogenous butyrate has been shown to renew barrier integrity, preserve enterocytes, and enhance AGHD [99], carrying out the SCFA central role in the anti-inflammatory pathways through the induction of Tregs, anti-inflammatory cytokines generated as part of a bidirectional process [100]. This change in the balance of anti-inflammatory cytokines can modulate the incidence and severity of AGHD [101]. A study demonstrated a reduction in *Enterococcus* translocation and decreased mortality in AGHD patients who were administered fiber, glutamine, and oligosaccharides [102].

Symbiotic: A mixture of probiotics and prebiotics administered simultaneously, often beneficial to IM [103]. They can be consumed as raw fruits or vegetables, fermented dairy or pickles, or as pharmaceutical formulas [104]. Its effect on metabolic health is linked to the mixture of probiotic-prebiotic [105]. The most commonly used combination is that containing *Bifidobacterium* or *Lactobacillus* with fructooligosaccharides [106], as they can generate reduced concentrations of undesirable metabolites, and inactivation of carcinogens and nitrosamines [107]. Symbiotics are used in the same processes as probiotics, only it has been reported that they have a better effect [108].

What are the best symbiotics?

The first thing to take into account to answer this question is that symbiotics hold great resistance to pathogens. Among the best symbiotics: *Bifidobacterium bifidum, Lactobacillus plantarum*, *Lactobacillus rhamnosus*, and *Saccharomyces boulardii* stand out, mixed with prebiotics (fructooligosaccharides, galactooligosaccharides, xylose oligosaccharides, and inulin) [109]. Lastly, risks should be evaluated such as bacteremia, sepsis or endocarditis, and cholangitis. Systemic infections risk probiotic infections, fungal sepsis, and septic shock [110].

Postbiotics: Functional bioactive compounds, generated in a matrix during fermentation, can be used to promote health [111]. They can be considered components of microbial fermentation. They include SCFA, metabolites, functional proteins, microbial cell fractions, and extracellular polysaccharides [112]. It is worth investigating in older people, as they also have immunomodulatory effects [113].

Some examples of Postbiotics: Those that come from *Lactobacilli* and *Bifidobacteria*, for example, *L. plantarum* RG14, RG11, and TL1 have antioxidant activity [114].

Paraprobiotics: Nonviable microorganisms could produce health benefits similar to those generated by live probiotics [115].

Bacteriophages as therapy (Phages): They have been known since Frederik Twort [116] and Felix d´Hérelle [117] discovered bacterial viruses. They infect bacteria, not eukaryotic cells [118]. Several countries use them like Georgia, Russia, and Poland [119]. Lytic bacteriophages are being reborn, especially in multi-resistant infections [120]. They are generally used in cocktails [121]. Its use has minimized the impact of *Escherichia, Klebsiella, Proteus, Pseudomonas*, and *Staphylococcus*, in eastern countries [122]. Phage-encoded proteins (endolysins, exopolysaccharidases, and holins) are promising antibacterials [123].

Intestinal microbiota transplant (IMT): Also known as fecal microbiota transplantation (FMT), bacteriotherapy, fecal transplantation, etc. [124]. Being a second genome and including proteins, genomic DNA and metabolites have real efficiency in multiple diseases, especially the multi-mentioned *Clostridioides difficile* [125]. Improved results of IMT in patients with Acute Host vs Graft Disease suggest that the procedure is a new tool to control symptoms. Furthermore, no complications have been found [126], and repopulation could be carried out through bacterial consortia [127]. Three out of four patients achieved complete remission of the AGHD [128].

FMT has been considered the best probiotic for restoring bacterial diversity in the gut [129]. In patients undergoing intestinal stem cell transplantation, with a history of antibiotic-resistant *C. difficile*, FMT can be performed before stem cell application [130].

Although the IMT is being addressed at the end, we consider it one of the tools that should be used at the beginning of intestinal stem cells transplant procedures, we should also only consider the recommendations of the FDA regarding the convenience of taking COVID-19 into account [131].

Conclusion

- The interaction between intestinal stem cells and the intestinal microbiome is a reality, beneficial for the former.
- Among the components to be used in stem cell transplants and their complications we have diet, probiotics, prebiotics, symbiotics, transbiotics, and paraprobiotics, with the most benign being the symbiotics.
- Phage therapy and fecal microbiota transplantation can be used, but in the West FMT is the most beneficial.
- We should not ignore the FDA's recommendations when using FMT.

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