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Mikrobiyata ve Kök Hücre ile Kemik İlişkisi Birlikteliği

The Relationship of Microbiota with Stem Cell and Bone

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ÖZ

Mikrobiyota, deneysel verileri son zamanlarda artan ve klinik uygulamaları olacak şekilde gelişen, bir ürün olma potansiyelindedir. Etkilerini özellikle kök hücre olmak üzere hücre davranışını değiştirerek göstermektedir. Patolojide olan bu değişikliğin anlaşılması, tedavide kullanılmalarının önünü açmaktadır. Barsak mikrobiyotasının en önemli etki gösterdiği ve yaşam kalitesini olumsuz etkileyen hastalıkların başında kemik ile ilgili patolojiler gelmektedir. Bu derlemede mikrobiyota ile kemik ilişkisinin detayları literatürdeki kaynaklar kullanılarak açıklandı. Son yılların mikrobiyota ve kemik ile ilişkili makaleleri incelenerek önemli görülen bilgiler birleştirildi. Barsak mikrobiyotası değişik etkenlere maruz kaldığında, hücrelerin kendileri ve salgıladıkları faktörler de değişerek hemostazın bozulmasına neden olmaktadır. Özellikle biyoinformatik veriler üzerinden alınan bilgilerin deneysel verilerle birleşmesi, mikrobiyatanın kemik patolojilerinde tedavi amaçlı kullanılabileceklerini göstermektedir. Gelişen teknoloji, mikrobiyata gibi maliyetleri düşük, tedavi etkinliği yüksek klinik kullanımı olabilecek ürünlerin oluşmasını sağlayacaktır. Üç boyutlu organoid modelinde olduğu gibi çok daha kolay incelenip ve anlaşılabilecek mikrobiyota etkisi yine kolaylıkla aynı modelle tedavinin etkinliğinde gösterebilecektir. Bunların sonucu olarak yaşam kalitesi düşmüş hastalara yeni umutlar sunabilecektir.

Anahtar kelimeler: Mikrobiata, Kemik, Kök Hücre, Tedavi, İmmünoloji,

ABSTRACT

The microbiota is a potential product which experimental data and clinical applications have increased recently. The microbiota shows its effects by changing cell behaviors, particularly those of the stem cells. Understanding of these changes in pathology opens the way for their use in treatment. Changes in intestinal microbiota related to bone diseases which also have a negative impact on patient life quality. In this review, the relationship of microbiota with stem cell and bone was explained based on the literature. Microbiota and bone-related articles of the recent years were reviewed, and the information considered important was collected. When the intestinal microbiota is exposed to various factors, stem cells themselves and the factors they secrete change, which causes hemostasis to deteriorate. The combination of experimental and bioinformatics data shows the possible use of microbiota for the treatment of bone pathologies. Developing technology will make it possible to produce products with significant efficiency and low costs in clinical applications. Using three-dimensional organoid model, it will be much easier to understand the effect of microbiota and similar model can be used for the effectiveness of the treatment. As a result, it may offer new hopes to patients with reduced quality of life.

Keywords: Microbiota, Bone, Stem Cell, Treatment, Immunology,

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INTRODUCTION

Mammals contain many bacteria, viruses and eukaryotic cells, which are called microbiota. In humans, the number of microbiotas is 10 times that of human cells. Microbiota is known to affect blood formation, immune system factors, and the reconstruction of the metabolism and bone in the tissues and the environment they form. Bone marrow-derived Mesenchymal Stem Cells (BMSCs) have not only multipotent differentiation capabilities but also a significant immune-modulating capacity (1, 2). The effect of the microbiota on the immune system and metabolism are well known and the effects of microbiota-induced changes on bone have been demonstrated in many studies (3, 4, 5). It has been shown that the impact of the microbiota in the intestine occur through epigenome and gene expression. It has been found that microbiota induces the transcriptional process in the cells through its microbial bioactive compound production-related effects. It is known that intestinal microbiota interacts with the cell epigenome using the RNAs, DNA methylation and histone modification. Understanding of this process and examining of the mechanisms will make it possible to use them more effective in clinic application (2, 7).

Microbiota and related factors effects in the regulation of bowel behavior by the stem cells and their secreted factors as a niche. Through these effects, nutrient absorption, endocrine signal, energy balance, immune response and healthy hemostasis occur (3). The deterioration of this balance is associated with some important pathologies ranging from obesity to inflammatory bowel diseases and cancer. Correcting these negative changes in the intestinal stem cells through microbiota will have a significant place in the medicine of the future (4).

MICROBIOTA AND STEM CELL FOR BONE

In a previous study, MSCs from the germ-free and pathogen-free mice were isolated. There were no bacteria in their feces which shown by Polymerase Chain Reaction (PCR). Stem cell (SC) characterization of both groups performed with flow cytometry demonstrated that they were positive for surface markers such as CD73, CD90, CD166, CD105 and stem cell antigene-1, and that they were negative for hematopoietic cell markers such as CD34 and 45. Colony formation was significantly higher in both types of mice. On the other hand, colony formation in microbiota-added cultures significantly decreased in the SPF-derived stem cells. It was found that GF-derived MSCs had higher growth capacity than SPF-derived MSCs, which was confirmed by the cell cycle analysis that demonstrated more G2 and S-phase cell percentage in GF-derived MSCs than that in SPF-derived MSCs. The cell cycle analysis also showed fewer apoptotic cells in GF-derived MSCs. Adipogenic differentiation of MSCs with microbiota analyzed by O red oil staining was lower in GF mice, and osteogenic differentiation of MSCs analyzed by Alizarin Red staining was higher in GF mice, which was confirmed by Western blotting for the Osteocalcin capacity (OCN) and by the Run-related transcription factor2 (Runx2) for the osteogenic capacity. When these cells were used in bone defects in the rat mandible, MSCs obtained from GF mice showed a more successful healing. Increased bone mineral density and decreased osteoclast activity were similar to bone resorption in mice. They were also increased adipogenesis and osteogenesis in GF mice even treating with antibiotics (5, 6).

Improvement of osteogenic capacity in bone with probiotic and prebiotic therapies shows that intestinal microbiota plays a crucial role in bone metabolism and bone health. Because of this effect in bone marrow, stem cell behavior in these two different mouse models was investigated in terms of immunomodulation. Flow cytometry analysis of the T cell apoptosis for MSCs was found to be significantly less compared to MSCs in GF mice. In addition, cytokine analysis revealed that chemokine C–C motif ligand 5 (CCL5) and interleukin (IL) 23 pro-inflammatory cytokines secretion increased in GF mice. In the next step, a significant decrease was determined in the body weight in the experimental colitis mouse model performed with 3% dextran sulfate sodium 3 days later. Significant diarrhea and bleeding occurred in mice with colitis. At this stage, GF mouse MSC treatment was not effective in MSC infusion with 9-day-old mice, whereas SPF mouse MSC treatment partially corrected body weight. Diarrhea and bleeding symptoms reduced as well, which suggests that the intestinal microbiota can be affected by MSC modulation (5).

MICROBIOTA AND BONE PATHOLOGY

The 30% mortality risk in the first year in patients with postmenopausal osteoporosis, especially in those with hip fractures shows the importance of microbiota treatment. Both estrogen and androgen deficiency are characterized by significantly increased osteoclast formation in the cortical part of the skeleton. This hormone deficiency causes not only osteoclast formation but also an increase in T and B cells secreting Receptor Activator NF kB Ligand (RANKL) and Tumor Necrosis Factor (TNF). This is also related to IL-1. TNF simulation is known to increase RANK activity and T helper 17 cells (Th17). Th17 cells also secrete IL-17, 1 and 6, and IL-17 is found in high amounts, especially in patients with postmenopausal osteoporosis. TNF function produced by T cells has been shown to be associated with bone loss in patients with postmenopausal osteoporosis. Microbiota application regulates the systemic immune response by activating T cells in cases with hormone insufficiency-induced bone loss. Briefly, microbiota had a significant effect on menopausal bone loss through the TNF and RANK IL-17 secretion by T and T17 cells (6, 12).

MICROBIOTA AND TREATMENT

Another condition associated with bone loss is and changes in intestinal permeability and epithelial submucosa. Hormone insufficiency increases inflammatory markers by increasing intestinal permeability and bacterial transmission. In the increase of this transition, gap junction protein, claudin deteriorates the barrier integrity by affecting 2, 3, 15 and JAM3. Thus, antigen loading activates the immune system and induces local osteoclastic cytokine release. Therefore, osteoclastic cytokines secreted by immune cells are critical for bone balance.

The fact that the treatment of osteoporosis is inadequate despite the use of many drugs, and that drugs such as bisphosphonates has side effects have led to the use of probiotics. When used in appropriate amounts, probiotics, which are live microorganisms, regulate metabolic activity and immune response, and thus protect the epithelial barrier function. Administration of probiotics has been shown to increase bone mass in chickens and reduce alveolar bone loss in rats. The efficacy of probiotic administration has been shown to be as successful as the administration of bisphosphonate in ovariectomized rats. Lactobacilli exert this protective

effect through IL-1 and TNF. It has also been shown that microbiota also increases regulatory T cells (Treg) decreased due to ovariectomy. Moreover, microbiota decreases CD4 T cells where there was increase due to ovariectomy and increases the anti TNF factor. The bacteria-mediated effect is achieved by tightening the epithelial barrier in the intestine and reducing the tight junction protein (6,12,13).

It is known that microbiota affects stem cell transformation and wound healing and regulates cell proliferation and migration in the intestine. It has been shown that microbiota exerts these effects not only through junction proteins but also through the mitogen-activated Protein Kinase (MAPK) and Phosphoinositol 3 Kinase (PI3K) signaling pathways. Intestinal Endoplasmic Reticulum expressed by intestinal epithelial cells is known to increase MAPK signaling.

Bone weakness begins when the continuity of intestinal epithelium is impaired in case of hormone deficiency. Probiotics, such as *Lactobacillus rhamnosus* GG (LGG) and VSL3 (a commercial product which is a mixture of 4 *Lactobacyl* strains) have been shown to reduce hormone deficiency-related bone loss by correcting the reduced microbiota. This has been clinically demonstrated, and it has been determined that prebiotics and probiotics maintain intestinal barrier integrity and limit the production of osteoclastogenic cytokines (14, 15).

Prebiotics are non-digestible fermented ingredients which increase the beneficial effect of the microbiome. They maintain their effectiveness by metabolizing bacteria. Another important effect of probiotics is the absorption of calcium in healthy people. They are also effective in postmenopausal women through the absorption of calcium. For example, it has been demonstrated that inulin increases cortical bone volume and structure in healthy mice.

They also increase bone mineral density in young women and decrease bone loss in postmenopausal women. However, their mechanism of action on the bone is not known.

The first view was that with the fermentation of dietary fibers, short-chain fatty acids (SCFA) are formed, which increases the calcium absorption in the intestine by decreasing the pH with SCFAs formed in the intestine. An important effect is that these fatty acids induce cytokine production and increase Treg cells.

Similar to these effects on the bone, there is microbiota related to dental diseases and implant applications in the dentistry (7).

MICROBIOTA AND FUTURE

In the human body, the place where the effect of microbiota is best recognized and that information related to this effect is available is the intestine. The mucosal barrier integrity maintained by microbiota and especially the regulation of the immune system by microbiota affects many organs. For example, cytokines secreted as a result of the activation of lymphoid cells and macrophages protect the organism from diseases by activating hemostasis (8).

The relationship between microbiota and bone and tooth cells and directing the regenerative capacity of the stem cell will take important part in future clinical applications (9, 10, 16, 17). Three-dimensional

organoid disease model will provide guidance for clinical applications by making it possible to understand the effects of microbiota on bone and tooth (11). Not only will enhance the data on this issue but will also provide much healthier data (18, 19).

Developing technology and pharmacological industry have improved the efficiency of treatment to increase the quality of patient life but have led to significant increases in costs. Microbiota showing promise to be a successful product due to its significant efficiency and low costs is gaining value every passing day. Evidence-based scientific studies suggest that microbiota will play an important role in future clinical application.

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