Vitamin D Signaling in Gastro-Rheumatology

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Vitamin D has been recently pointed out, and abnormalities of the vitamin D axis have been described in both in vitro and in vivo models of inflammatory bowel diseases (IBD) and arthritis.

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1. Introduction

Bone metabolism is a complex and dynamic process that tightly regulates the composition of the skeleton of human body. Besides their structural function, the bones play a fundamental role for hosting, in the bone marrow, hematopoietic cells (HSCs), myeloid and lymphoid progenitors, and mature cell of the immune system. Those cells share the same milieu of the cells regulating the bone metabolism (e.g., osteoblasts, osteoclasts, and osteocytes) and are closely connected by reciprocal interactions mediated by multiple molecular mediators, such as cytokines, chemokines, transcription factors, and signaling molecules [1]. The potential relation between osteogenesis and immune system has been highlighted since the 1970s in studies regarding periodontitis [2]. In 2000, the term “osteoimmunology” was coined to define the complex interwoven link between these two systems, particularly evident in T-cells mediated regulation of osteoclastogenesis observed in autoimmune arthritis [3]. Multiple molecular mediators have shown a potential role in the osteoimmune network [4]. Osteoblasts progenitors produce stem cell factors and CXC-chemokine ligand 12 (CXCL12) that are crucial for HSC maintenance and differentiation, and mature osteoblasts produce interleukin-7 (IL-7) that has an important role in the regulation of the lymphoid lineage. Osteoclasts produce proteolytic enzymes, such as matrix-metallopeptidase 9 and cathepsin K, that contribute to the HSC mobilization. Moreover, the bone reabsorption process is essential for the bone marrow cavity formation as well as for the increase in calcium level and the release of some factors, e.g., transforming growth factor (TGF)-β), that have a role in HSC regulation. Osteocytes regulate lymphoid and myeloid differentiation through the production of sclerostin and granulocyte colony-stimulating factor (G-CSF). Conversely, the activated immune system and the aberrant inflammation may affect osteosynthesis through the production of IL-17 by Th17 cells and the induction of the receptor activator of nuclear factor-κB ligand (RANKL) further amplified by the pro-inflammatory cytokines IL-1, IL-6, and tumor necrosis factor (TNF), which promote osteoclastogenesis. In line with this vision, the bone alterations observed in several immune diseases are no longer considered related merely to malnutrition or steroids use, and the common osteoimmune molecular pathway has been proposed as a novel potential target for therapeutic strategies.

2. Vitamin D and Intestinal Permeability

Vitamin D is a dietary nutrient with demonstrated anti-inflammatory and immunomodulating functions. Recent data suggest that the intestinal mucosal barrier is a possible *trait d'union* between vitamin D, immune system, and gut microbiota. The intestinal mucosa is both an absorption site that allows entry of food-derived metabolites and a physical barrier that blocks pathogens translocation, thus protecting against infection with enteropathogenic microorganisms and intestinal inflammation. The intestinal epithelium is composed by enterocytes and specialized epithelial cells, such as Goblet and Paneth cells. Goblet cells produce mucus that forms a layer between the epithelium and the luminal contents, whereas Paneth cells release antibacterial molecules (e.g., α- and β-defensins, cathelicidin) [5]. Sub-mucosal cells of the innate immunity, such as macrophages and dendritic cells (DCs), clear microorganisms and luminal particles that penetrate the first line of defense of the epithelial/mucus layer, thus containing the immune inflammatory reaction. The presence of different structures between adjacent epithelial cells, such as tight junctions (occludin, proteins of the zonula occludens, and claudins), adherens junctions (E-cadherin, catenins, nectin), and desmosomes, is also essential in maintaining the resistance of the intestinal mucosa [6].

In view of the above, it is not surprising that dysregulation in these components, such as defective expression of defensins, upregulation of claudin-2, or increased apoptosis of epithelial cells, can contribute to the disruption of the mucosal barrier, as reported in IBD and SpA patients [7][8][9][10][11]. In particular, it has been hypothesized that, in SpA patients, the increased intestinal permeability, probably induced by genetic factors (HLA-B27), could induce a disruption of the basal membrane, hyperplasia of goblet cells, and activation of Paneth cells producing high levels of anti-microbial peptides (AMPs) and IL-23, leading to exaggerated antigenic stimulation and activation of effector T-cells of the intestinal mucosa [12][13][14][15][16][17].

Vitamin D/VDR signaling can modulate the number and the functionality of tight junction proteins in both in vitro and in vivo studies on transgenic mice. VDR knockout and vitamin D-deficient mice displayed epithelial barrier dysfunction with hyperfunction of claudin-2, decreased transepithelial resistance, and increased susceptibility to invasive bacteria colonization and colitis [18][19][20][21]. Conversely, transgenic mice overexpressing VDR in the gut epithelium have resistance to colitis with decreased mucosal inflammation and apoptosis of epithelial cells [22]. In addition, vitamin D supplementation has been shown to ameliorate the clinical symptoms and the histologic findings in Dextran sulphate sodium (DSS) treated mice by preserving the expression of E-cadherin, claudin, and zonula occludens in Caco-2 cells [23].

3. Vitamin D and Gut Microbiota Homeostasis

The gut microbiota is a complex ecosystem of archaea, bacteria, fungi, and viruses that is essential for digestion of complex carbohydrates as well as absorption and supply of vitamins, but it exerts also immunomodulatory, metabolic, and anti-infective functions. Any imbalance in the gut microbiota resulting in a loss or overgrowth of a species and/or reduction in microbial diversity is defined as dysbiosis. In the last two decades, dysbiosis of the gut microbiota has been described in different pathologies such as depression, IBD, RA, and SpA [24][25][26].

The impact of diet and nutrients on the gut microbiota is suggested by the differences in its composition/variety between geographically and life-style distant populations [27]. It is known, indeed, that a western diet rich in animal proteins, simple sugars, and saturated fats is characterized by a reduction in the variety of microbiomes and is associated with the *Bacteroides* enterotype, whereas a diet habit rich in fruits and vegetables leads to a prevalence of *Prevotella* [28]. Dietary intervention can also impact the gut microbiota composition and richness. Foods rich in fibers, such as those present in the Mediterranean diet (MD), indeed, are degraded by Firmicutes and Bacteroidetes into SCFA, such as butyrate [29][30], which can have a protective role on the gut barrier by reducing its permeability. We have recently found that RA patients with high adherence to MD have a lower disease activity joined to a healthier gut microbiota composition with a significant decrease in *Lactobacillaceae* and an almost complete absence of *Prevotella copri* in comparison with the low/moderate adherence patients [31].

It has been also shown that vitamin D can also influence the composition of the gut microbiome in animal models [32][33]. VDR KO mice with defective autophagy have consequent gut dysbiosis with depletion of *Lactobacillus* and *Bacteroides.* Moreover, administration of butyrate can increase intestinal VDR expression and suppress inflammation in an experimental colitis model [34].

Results on human studies have been recently summarized in a systematic review by Waterhouse et al. [35]. Most of the fourteen analyzed studies evaluated both microbiota diversity and composition and reported significant association between vitamin D and specific changes in gut microbiota. However, there was scarce consistency in the taxa affected and the direction of effect. Indeed, results are hard to compare due to several variables, in particular the heterogeneity in study designs (e.g., cross-sectional vs. prospective, randomized trials vs. observational study), the differences in the assessment of vitamin D (e.g., self-reported dietary, nutritional supplement vitamin D i6ntake, serum 25(OH)D administration), and in the population setting (e.g., healthy people, IBD, cystic fibrosis, multiple sclerosis, infants, pregnant women). Moreover, most of the studies were conducted on very limited samples, and only some of them adjusted for confounding factors such as body mass index, smoking, physical activity, comorbidity, and therapy. Three studies evaluated the effect of vitamin D on the gut microbiota in UC and CD patients. Administration of vitamin D demonstrated a positive effect in modulating the intestinal bacterial composition in both CD and UC patients, leading to a reduced intestinal inflammation in patients with active UC, with a concomitant increase in *Enterobacteriaceae* without changes in microbial diversity [36][37][38]. An additional study published in 2020 was in contrast with these results. In fact, the authors found that reduced levels of vitamin D observed in winter/spring were associated with more balanced microbiome composition both in UC and CD. In particular, they identified lower level of *Escherichia/Shigella* in stool of UC patients and increased level of Bacteroidetes in the stool of CD patients accompanied by lower proportion of *Clostridium spp*. and higher proportion of Firmicutes in the mucosa [39]. Another study that evaluated samples of the intestinal mucosa found a decrease in gammaproteobacteria and increased Bacteroidetes in the microbiome of the upper gastrointestinal tract of patients receiving vitamin D supplementation without significant effects on terminal ileum, ascending colon, sigmoid colon, and stools [40]. Of note, the only GWAS study demonstrated that the VDR gene variation correlated with beta diversity in both humans and mice [41].

Assuming that microbiota and vitamin D have a bidirectional and possible feedback interaction, few studies have evaluated the role of bacteria in modulating vitamin D levels. In fact, it is known that both commensal and pathogenic bacteria can regulate VDR expression and location in mice [42]; some bacteria have enzymes involved in the hydroxylation of steroids and can process and activate vitamin D [43]. Butyrate produced by some gut microorganisms such as Firmicutes and Bacteroidetes can increase VDR expression in the epithelial cells of mice models [21]. In addition, the microbiota can influence vitamin D metabolism through the fibroblast growth factor (FGF)-23 (the protein that regulates the 1,25(OH)2D3 hydroxylating enzyme, CYP27B1). Germ free mice, indeed, have low levels of vitamin D and high FGF-23, and their colonization with bacteria leads to normalization of vitamin D levels and reduced FGF-23 [44].

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