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Wnt signaling in bone, kidney, intestine, and adipose tissue and inter-organ interaction in aging

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Abstract

Over the last two decades, it has become increasingly apparent that Wnt signaling plays a critical role in development and adult tissue homeostasis in multiple organs and in the pathogenesis of many diseases. In particular, a crucial role for Wnt signaling in bone development and bone tissue homeostasis has been well recognized. Numerous genome-wide association studies (GWASs) confirmed the importance of Wnt signaling in controlling bone mass. Moreover, ample evidence suggests that Wnt signaling is essential for kidney, intestine, and adipose tissue development and homeostasis. Recent emerging evidence demonstrates that Wnt signaling may play a fundamental role in the aging process of those organs. New discoveries show that bone is not only the major reservoir for calcium and phosphate storage, but also the largest organ with multiple functions, including mineral and energy metabolism. The interactions among bone, kidney, intestine, and adipose tissue are controlled and regulated by several endocrine signals, including FGF23, klotho, sclerostin (SOST), osteocalcin, vitamin D, and leptin. Since the aging process is characterized by structural and functional decline in almost all tissues and organs, understanding the Wnt signaling-related interactions among bone, kidney, intestine, and adipose tissue in aging may shed light on the pathogenesis of age-related diseases.

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Competing interests

The author declare no competing interests.

Graphical abstract

Wnt signaling plays a crucial role in the development and homeostasis of bone tissue, as well as kidney, intestine, and adipose tissue, and it may play a fundamental role in the aging process of those organs. This review discusses recent progress in understanding the role of Wnt signaling in aging bone and other organs and tissues, with an emphasis on the interaction between inter-organ regulation and aging bone.

Keywords

Wnt/ β -catenin signaling; bone; FGF23-klotho; sclerostin; aging

Introduction

Wnt signaling is one of a handful of highly conserved signaling pathways that play crucial roles in multiple aspects of embryonic development and adult homeostasis throughout the animal kingdom. Wnt signaling is initiated by Wnt ligands (Wnts). Wnts are evolutionarily conserved secreted cysteine-rich glycoproteins, and there are 19 genes that encode Wnts in the mouse and human genomes. Wnts can activate several intracellular signaling pathways, including the canonical Wnt/ β -catenin pathway and non-canonical Wnt pathways. The non-canonical Wnt pathways include the Wnt/planar cell polarity (PCP) and Wnt/ Ca^{2+} pathways as well as the β -catenin-independent Wnt/LRP6 pathways, related to Wnt/stabilization of proteins (STOP) signaling and Wnt/target of rapamycin (TOR) signaling.^{1,2} The canonical Wnt/ β -catenin signaling is evolutionarily highly conserved and is the best understood pathway. We will therefore focus on Wnt/ β -catenin signaling in this review article.

The key element in the canonical Wnt/ β -catenin pathway is the regulation of protein stability of β -catenin, which acts as a transcription co-factor. β -catenin has dual functions and is also involved in cell adhesion by forming a stable complex with the cell adhesion molecules of the cadherin family. In the absence of Wnt ligands, cytosolic β -catenin interacts with other components of the destruction complex, including Axin1, adenomatous polyposis coli (APC), glycogen synthase kinase-3 (GSK-3), casein kinase-1 (CK1), protein phosphatase 2A (PP2A), and the E3-ubiquitin ligase β -transducin repeat containing protein (β -TrCP).² Axin1 is a central scaffold protein of the destruction complex and directly interacts with all other core components of the destruction complex, such as APC, GSK-3, CK1, and β -catenin. It has been reported that Axin1 is the rate-limiting factor of the β -catenin destruction complex.³ β -catenin is phosphorylated by two kinases of the destruction complex, GSK-3 and CK1. The destruction complex creates a β -TrCP recognition site on β -catenin. After phosphorylation and ubiquitination, β -catenin is degraded by the proteasome. When Wnt ligands bind to their coreceptors Frizzled (FZD) and low-density lipoprotein-receptor-related protein-5 or -6 (LRP5/6), the destruction complex is dissociated through phosphorylation of LRP5/6, which then binds Axin1. β -catenin, released from the destruction complex can enter the nucleus, where it binds to the transcription factors LEF/TCF and activates downstream target genes.⁴

Considering the pivotal role of Wnt signaling in embryonic development and adult tissue homeostasis, it is not surprising that the signaling is tightly controlled. Wnt/ β -catenin signaling is regulated at many levels by a number of conserved inhibitors and activators. Several extracellular Wnt inhibitors are able to directly bind to Wnt ligands, such as secreted Frizzled-related proteins (sFRPs),⁵ Wnt inhibitory factor (WIF),⁶ and klotho.⁷ Other Wnt inhibitors include proteins of the Dickkopf (DKK),^{8,9} and the sclerostin (SOST) family members.¹⁰ These Wnt antagonists block Wnt signaling through interaction with membrane-associated LRP5/6.¹¹ Adenomatosis polyposis down-regulated 1 (APCDD1) is a membrane-bound glycoprotein that inhibits Wnt signaling by binding to both Wnt and LRP.¹² Conversely, the Wnt activators Norrin and R-spondins (Rspo) enhance the signal strength of canonical Wnt signaling by binding to Wnt receptors¹³ or releasing a Wnt-inhibitory step.¹⁴ Recently, two highly homologous Wnt target genes, zinc and ring finger 3 (ZNR3) and ring finger protein 43 (RNF43) were identified as potent negative-feedback regulators of Wnt signaling.^{15,16}

Population aging is a public health problem throughout the developed world. By 2030, the population aged 65 and over is projected to be 72 million, accounting for approximately 20% of the United States population. Aging is characterized by progressive decline in tissue and organ function and increased risk of mortality, but its causes remain one of the central challenges of biology and medicine. Although there is no single mechanistic description of organ aging, due to the complex nature of the aging process, common hallmarks of aging have been proposed,¹⁷ including systemic inflammation, macromolecular damage leading to genomic instability, telomere attrition, epigenetic alteration, loss of proteostasis, deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, and altered intercellular communication. The aging process is characterized by structural and functional changes affecting almost all tissues and organs. A defined feature of the process of aging is the decline in regenerative capacity associated with reduced adult stem cell function. Despite the role of Wnt signaling, which has been intensively studied in the development and cancer, relatively few studies have looked at the function of Wnt signaling pathways during aging. Due to the critical roles that Wnt/ β -catenin signaling plays in development and tissue homeostasis, mutations of the Wnt signaling pathway components could lead to severe diseases, such as many hereditary disorders, osteoporosis, diabetes and cancer.⁴ The dysregulation of Wnt signaling has also been implicated in fibrosis¹⁸, chronic kidney disease (CKD),¹⁹ and in age-related neurodegenerative diseases, including Parkinson disease²⁰ and Alzheimer disease²¹.

A number of studies suggest that Wnt signaling has positive effects on health during aging, delaying the aged phenotype.²² However, Wnt signaling is augmented in a mouse model of accelerated aging,⁸ and inhibition of Wnt pathway signaling reverses the aging-associated impairment of skeletal muscle regeneration.²³ These contradictory results indicate that the role of Wnt signaling in aging may change with age in different organs, as we explore further below. Since aging is a major risk factor for most late-onset diseases, such as osteoporosis, osteoarthritis, intervertebral disc degeneration, diabetes, cardiovascular disease, neurodegenerative diseases, and cancer,¹⁷ a greater understanding of the relationship between aging and Wnt signaling would be valuable to prevent or delay aging-related diseases. In this review, we will discuss recent progress in understanding the role of

Wnt signaling in aging bone and other organs and tissues, with an emphasis on the interaction between inter-organ regulation and aging bone.

Wnt signaling in aging bones

Genetic evidence from both humans and mice indicates that Wnt/ β -catenin signaling plays crucial roles in controlling multiple aspects of bone development and homeostasis. The adult skeleton contains three major cell types: osteoblasts, osteoclasts, and osteocytes. Osteoblasts are differentiated from mesenchymal stem cells (MSCs), whereas osteoclasts are derived from hematopoietic progenitor cells. Osteoblasts form bone, while osteoclasts resorb bone. Osteocytes, terminally differentiated osteoblasts, maintain bone and contribute to the regulation of osteoblasts and osteoclasts during bone modeling and remodeling.¹

Wnt signaling has crucial roles in regulating osteoblast differentiation. Lack of β -catenin in mesenchymal progenitor cells inhibits osteoblast differentiation, suggesting that Wnt signaling is essential for early osteoblast specification. Wnt signaling is also involved in the regulation of bone homeostasis.^{24,25} Deletion of both *Lrp5* and *Lrp6* in mouse mesenchymal progenitors results in loss of osteoblasts.²⁶ In human, loss-of-function (LOF) mutations in *LRP5* cause osteoporosis pseudoglioma syndrome (OPPG),²⁷ a form of juvenile-onset osteoporosis. In contrast, gain-of-function autosomal-dominant mutations of *LRP5* lead to high bone mass and enhanced bone strength.^{28–31} Loss-of-function mutations in *LRP6* lead to coronary artery disease associated with osteoporosis, an autosomal-dominant familial disease.³² In addition, loss-of-function or loss-of-expression mutations in sclerostin (*SOST*), the secreted Wnt/ β -catenin signaling antagonist, cause high bone mass in sclerosteosis and Van Buchem disease.^{33–35} Notably, the high bone mass mutations in *LRP5* decrease the binding of *SOST* and dickkopf1 (*DKK1*), another WNT inhibitor.^{28,31,36–37} Furthermore, mice with a global deficiency of *Lrp5*³⁸ exhibit postnatal low bone mass, and *Lrp6* haploinsufficiency further decreases bone mass in *Lrp5*-null mice.³⁹ In contrast, mice with the gain-of-function mutations in *Lrp5* in osteoblasts display a high bone mass phenotype.^{40,41} Mouse models with deletion of the Wnt antagonists *Dkk1* and *SOST* show high bone mass. Both our *Axin2* KO⁴² and *Axin1* conditional KO mice (unpublished data) show a high bone mass phenotype. Thus, there is ample evidence showing that Wnt signaling plays crucial roles in postnatal bone formation.

Analysis of *Lrp5* mutant mice revealed that these mice have reduced osteoblast numbers and activity without obvious changes in osteoclast formation.^{38,40,41} Surprisingly, activation or deletion of β -catenin in mature osteoblasts or *Col2*-expressing progenitor cells results in decreased or increased osteoclast numbers and bone resorption,^{43–46} failing to recapitulate the phenotypes of *Lrp5* mutant mice. Thus, how *LRP5* regulates bone mass is currently unclear.^{1,47}

Osteocytes are terminally differentiated cells of the osteoblast lineage. They make up 90–95% of all bone cells within the matrix or on bone surfaces. Accumulating evidence demonstrates that osteocytes are master regulators of bone homeostasis by controlling osteoblast and osteoclast activity through sclerostin and receptor-activator of NF- κ B ligand (RANKL). Deletion of β -catenin in osteocytes increases osteoclast activity and bone

resorption, without changes in bone formation⁴⁵. However, it has been reported that constitutive activation of β -catenin in osteocytes increases both osteoblasts and osteoclasts, leading to increased bone mass.⁴⁸ Also, osteocytes are the principal sensors for mechanical loading of bone. Several reports have revealed that Wnt signaling plays an essential role in osteocytes for sensing changes in mechanical loading. Deletion of a single allele of β -catenin in osteocytes has been shown to abrogate the anabolic response to mechanical loading.⁴⁹ Deletion of sclerostin protects mice from mechanical unloading-induced bone loss.⁵⁰ In *Lrp5*^{-/-} mice, mechanoresponsiveness is dramatically reduced.⁵¹ Furthermore, osteocytes are the major source of the Wnt inhibitor sclerostin⁵² and fibroblast growth factor 23 (FGF23).⁵³

It has been reported that Wnt signaling is significantly downregulated in the bones of aged women.⁵⁴ Recent GWASs of age-related osteoporosis suggest that *LRP5*, *DKK1*, *SOST* and other Wnt pathway components contribute to the development of osteoporosis.⁵⁵ A GWAS of individuals of European descent has shown that nonsynonymous single nucleotide polymorphisms in *LRP4* and *SOST* are associated with bone mineral density (BMD).^{56,57} *Wnt16* and *Wnt4* have been identified as BMD and fracture risk-associated genes.^{58,59} Mice with a deletion of *Wnt16* in osteoblasts showed increased fracture susceptibility.⁶⁰ Also, osteoblast-derived WNT16 has been revealed to inhibit osteoclast formation by inhibiting RANK signals.⁶⁰ Furthermore, the transgenic mice expressing WNT4 in osteoblasts have been shown to promote bone formation and inhibit osteoclast formation and inflammation.⁶¹ Other Wnt signaling members, such as *WNT10b*, *SFRP1*, *SFRP4* and *CTNNB1* (encoding for β -catenin) have been identified as osteoporosis susceptibility candidate genes.^{62,63} Secreted frizzled related protein 4 (SFRP4) is a soluble Wnt antagonist that binds Wnt ligands and thus regulates both canonical and noncanonical Wnt signaling. Deletion of *Sfrp4* in mice increased amounts of the trabecular bone, but lead to thinning of cortical bone.⁶⁴ The largest meta-analysis on lumbar spine and femoral neck BMD, including 17 GWASs and over 30,000 individuals of European and Asian ancestry, confirmed the association of *LRP4*, *LRP5*, *SOST* and *MEF2C* (myocyte enhancer factor 2C) with BMD.⁶⁵ This convergence of multiple analyses of very large cohorts of human populations of different genetic backgrounds strongly suggests that Wnt signaling may indeed be the most dominant regulator of bone mass in humans. Importantly, an antibody targeting SOST has yielded encouraging results in clinical trials.⁶⁶ Taken together, mounting evidence suggests that Wnt signaling plays crucial roles in aging bones.

Bone plays important functions in the body, including structural support for the mechanical action of soft tissues, such as the contraction of muscles and the expansion of lungs; support and protection of soft tissues; harboring of bone marrow; and calcium and phosphate storage.⁶⁷ Indeed, more than 99% of calcium in the body is stored in the bone as hydroxyapatite, which provides skeletal strength and is a source of calcium for the multiple calcium-mediated functions. Also, over 85% of the total body phosphate is stored in bone in both mineralized matrix and exchangeable pools.⁶⁸ Bone is the major site for the long-term storage and short-term buffering of calcium and phosphate. Outside of the bone, the kidney and intestine are the two main organs that regulate calcium and phosphate homeostasis in the body.⁶⁹ Importantly, new discoveries demonstrate that bone is also an endocrine organ. Fibroblast growth factor 23 (FGF23) is an endocrine hormone secreted by osteocytes and

osteoblasts that regulates serum phosphate levels.⁶⁹ Osteocalcin is another endocrine hormone produced by osteoblasts that plays a major role in energy homeostasis and glucose metabolism.⁷⁰ Recently, sclerostin (SOST) produced by osteocytes and osteoblasts has emerged as an endocrine factor that regulates glucose and fat metabolism (Fig. 1).⁷¹

Wnt signaling in the aging kidney

Wnt signaling has an essential role in kidney development as well as homeostasis and injury repair. Wnt signaling is a crucial regulator of kidney morphogenesis. Kidney development is dependent upon the interaction of three main cell types: the ureteric epithelium, the metanephric mesenchyme, and the renal stroma. Wnt signaling plays essential roles in ureteric epithelia branch morphogenesis.⁷² Wnt signaling also plays a role in the induction of the condensed mesenchyme.^{73,74} It has been demonstrated that the tight control of β -catenin activity is essential for balancing self-renewal of the nephrogenic progenitors and induction of nephrogenesis.^{75,76} Several studies shown that Wnt signaling also plays essential roles in the renal stroma.^{77–79} Taken together, Wnt signaling is a central player in kidney development.

Although Wnt signaling has an essential role in kidney development, its activity is relatively low in adult kidney.⁸⁰ However, Wnt signaling is upregulated in virtually every experimental animal model ranging from acute kidney injury (AKI) to various forms of chronic kidney disease (CKD), suggesting that Wnt signaling may have a crucial role in the subsequent repair or disease development after a wide variety of injuries in the adult kidney.⁸¹ Although adult mammalian kidney has been regarded as a static organ with limited cellular turnover and regenerative capacity,⁸² Wnt-responsive stem cells have been identified in adult kidney.⁸³ It has been reported that Wnt signaling is increased in aged kidney.⁸⁴ And Wnt signaling increases in the kidney in accelerated aging models.⁸⁵ Patients with CKD have a common premature aging phenotype, including hypogonadism, skin atrophy, osteopenia, and cognitive impairment.⁸⁶ Importantly, Wnt signaling is up-regulated in all animal models of CKD and human kidney disorders.⁸⁷ This suggests that Wnt signaling may play an essential role in kidney aging that may be shared with CKD. As described above, bone not only functions as a frame for muscle attachment for the purpose of locomotion, it is also the major storage site for minerals in the body, such as calcium and phosphate. Recently, bone has been identified as an active endocrine organ that communicates with other organs involved in mineral and energy metabolism.⁸⁸

Klotho is an antiaging gene encoding a single-pass transmembrane protein that forms a complex with multiple FGF receptors and functions as a co-receptor for FGF23. *Klotho* mutant mice display an extremely shortened life span with multiple disorders resembling human aging, including hypogonadism, growth retardation, osteoporosis, skin atrophy, vascular calcification, accelerated thymic involution, hearing loss, and auditory syndromes.⁸⁹ In contrast, transgenic mice that overexpress *klotho* have a 20–30% increase in life span.⁹⁰ Emerging evidence reveals that *klotho* deficiency is an early biomarker for CKD, and replacement of soluble *klotho* or forced overexpression of *klotho* protects the kidney from renal injuries.⁹¹ *Klotho* is expressed mainly in the kidney and parathyroid gland. Since the phenotype of mice with a kidney-specific ablation of *klotho* recapitulates the phenotype of

global *klotho* KO mice, it suggests that the kidney is the principal contributor of *klotho* and *klotho*-induced antiaging traits.⁹²

FGF23, along with FGF19 and FGF21, is a member of the FGF19 subfamily of endocrine FGFs. FGF23 is predominantly expressed and secreted from osteocytes and osteoblasts. The major target for FGF23 is the kidney, where FGF23 suppresses renal phosphate reabsorption by decreasing the expression and membrane insertion of the sodium-dependent phosphate co-transporters NPT2a and NPT2c, demonstrating that FGF23 is a long range endocrine hormone.⁹³ In the kidney, excess FGF23 reduces circulating levels of 1,25-dihydroxyvitamin D₃ (1,25(OH)₂D₃, the active form of vitamin D) by inhibiting CYP27B1, the enzyme that converts 25-(OH)D₃ to 1,25(OH)₂D₃, and stimulating CYP24A1, a mitochondrial enzyme responsible for inactivating 1,25(OH)₂D₃ through the C-24 oxidation pathway.⁹⁴

Unexpectedly, *Fgf23* KO mice develop multiple aging-like phenotypes that are almost identical with those observed in *klotho*-deficient mice.⁹⁵ These observations strongly suggest that *klotho* and FGF23 may function in a common signal transduction pathway. Thus, the kidney-bone endocrine axis mediated by *klotho* and FGF23 has emerged as a primary mechanism for regulation of phosphate and vitamin D metabolism. The aging-like phenotype observed in *klotho* and *Fgf23* KO mice may be caused by toxicity resulting from excess phosphate and/or vitamin D. Of note, a universal characteristic of patients with CKD is high serum phosphate levels. And patients with CKD have high serum FGF23 levels with decreased *klotho* expression in the kidney. While *klotho* has been reported to function as a secreted Wnt antagonist⁸ and it has been reported that loss of *klotho* contributes to CKD through increased Wnt signaling,⁹⁶ it remains to be determined what the role of Wnt signaling is in regulating the *klotho*-FGF23 axis in the kidney-bone network (Fig. 1). Dysregulation of mineral metabolism exacerbates the severity and progression of renal failure. A deeper understanding of mineral metabolism is pivotal for the prevention and treatment of CKD.

Wnt signaling in aging intestine

During intestinal development, Wnt signaling plays a crucial role in endoderm specification and gut tube patterning, as well as in intestinal stem cell (ISC) maintenance and intestinal epithelial homeostasis.⁹⁷ The intestinal epithelium is renewed every 3–5 days and is one of the fastest self-renewed tissues among all mammalian tissues.⁹⁸ This rapid turnover is fueled by dedicated, mitotically active ISCs at the bottom of the intestinal crypts.^{99,100} After many years of searching, a landmark 2007 study identified LGR5 as a marker for these rapidly cycling ISCs at the base of each intestinal crypt.¹⁰¹ LGR5 is a receptor for R-spondins, noted earlier as Wnt-related ligands that enhance Wnt/β-catenin signaling.¹⁰² The LGR5⁺ ISCs continually generate the cells that differentiate into either the secretory lineage (Paneth, enteroendocrine, and goblet) or the absorptive lineage (enterocytes) cells of the intestinal epithelium.¹⁰³ Wnt signaling is critical and required for this process.¹⁰⁴ The relative balance of Wnt versus Notch pathway signaling in these LGR5⁺ ISCs determines the epithelial cell fate to become either secretory lineage (high Wnt/low Notch signaling) or absorptive lineage (low Wnt/high Notch signaling).¹⁰⁵ Loss of Wnt signaling in these cells results in loss of secretory lineage epithelial cells and loss of epithelial and crypt structure.¹⁰⁶ Disruption of the Wnt/Notch signaling balance in the ISC results in abnormal changes in stem cell fate

ratios and loss of intestinal barrier function (leaky gut).^{107,108} Targeted loss of LGR5 results in loss of crypt ISCs and loss of intestinal epithelial renewal.¹⁰⁹ Inhibiting Wnt signaling in adult mice with an inducible Wnt antagonist, DKK1, blocks proliferation within crypts and results in crypt loss.^{110,111} Targeted complete deletion of *β-catenin* in the intestinal crypt also results in loss of ISCs and intestinal barrier function, causing intestinal hyperpermeability (leaky gut).¹¹² Paneth cells in the small intestinal crypts are major producers of WNT2B and WNT3A that promote ISC health.¹¹³ Wnt signaling from surrounding mesodermal fibroblasts and possibly immune cells also plays an essential role in establishing the small intestinal and colonic crypt niche.¹¹⁴ These results demonstrate that Wnt signaling is required not only to form crypts but also to maintain intestinal homeostasis, including barrier function, throughout adult life. Significantly, a key recent study has shown that aging results in loss of Wnt/β-catenin signaling in the LGR5⁺ crypt ISCs in mice and humans.¹¹⁵ This loss of ISC Wnt signaling is also associated with loss of Notch signaling and loss of another key ISC stem cell marker, ASCL2 (also a Wnt signaling target gene).¹¹⁶ Importantly, culture of intestinal organoids from aged mice and aged humans *ex vivo* with additional WNT3 was able to restore the gene expression pattern to that of young ISCs.¹¹⁵ Other investigators have proposed loss of Wnt signaling is a key feature driving ISC aging. This has potential therapeutic implications for the aging intestine (and bone, see below) by restoring Wnt signaling. For example, the Wnt/β-catenin agonist lithium has been shown to promote repair of the intestinal epithelium and barrier function.¹¹⁷

Remarkably, most (>80%) sporadic colorectal cancer cases are the result of loss of both APC alleles.¹¹⁸ Since intestinal stem cells are dependent on Wnt activity, it is not surprising that components of the Wnt pathway are frequently mutated in colorectal carcinomas.^{118–121} Studies have shown that the LGR5⁺ ISCs are the source of abnormally proliferating cells in colon polyps and colon cancer.¹²² Stimulation of Wnt/β-catenin signaling in intestinal epithelium via the removal of the Wnt pathway antagonist APC results in abnormal proliferation and ectopic crypt development that leads to polyp formation and can become colon cancer.^{97, 123,124} Production of short chain fatty acids (SCFA), especially butyrate, by the intestinal microbiota is associated with reduced colon cancer risk in part through suppression of excessive Wnt/β-catenin signaling.¹²⁵

Much recent interest in bone metabolism, especially in aging, has focused on the role of the intestinal tract, especially the role of dysregulated intestinal epithelial barrier function, resulting in hyperpermeability (leaky gut), and the intestinal microbiome.¹²⁶ Leaky gut increases with aging in species from *Drosophila* to humans,^{127–129} and can promote systemic inflammation via LPS and other microbial products.¹³⁰ Several studies have shown significant effects of the microbiome on bone health, resulting in a new area of study termed osteomicrobiology.¹³¹ So called inflammaging (systemic inflammation characteristic of aging) has been thought to contribute to aging bone loss by stimulation of osteoclast activity while inhibiting osteoblasts.^{132,133} A key recent study showed that inflammaging in aging mice was the result of changes in the intestinal microbiome that result in leaky gut.¹³⁴ When transplanted with microbiome from young mice, the leaky gut and systemic inflammation in old mice were prevented. In support of this model, ovariectomy is used to model age-related bone loss, and recent studies have shown that treatment of ovariectomized mice with probiotics can prevent bone loss, at least in part by preventing leaky gut and systemic

inflammation.^{135,136} Probiotics are well established for ameliorating leaky gut and promoting intestinal barrier function.¹³⁷ Significantly, many of these microbiome effects may all be related to ISC Wnt signaling (needed for a healthy gut barrier, see above) because recent studies also show that both probiotics and the microbiome regulate Wnt signaling in bone and ISCs.^{138,139} The intestinal microbiome has significant effects on Wnt signaling in the crypt ISCs. Reduced ISC Wnt/ β -catenin activity and decreased *Wnt5a* and *Wnt11* expression were observed in mice lacking commensal bacteria.¹⁴⁰ Several studies have also shown a clear link between Toll-like receptor (TLR) signaling by the microbiome and ISC Wnt signaling.¹⁴¹ Thus, an abnormal microbiome may disrupt ISC Wnt signaling required to maintain normal intestinal crypt cell fate and barrier function and may be a critical cause of inflammaging resulting in aging-associated bone loss, as seen in the ovariectomized mouse model.^{142,143}

As we have mentioned above, although genetic evidence has shown that LRP5 has crucial roles in regulating bone mass, the mechanisms by which LRP5 controls bone formation remain unclear. Unexpectedly, based on mouse genetic studies, a model was developed in which LRP5 regulates bone mass by suppressing serotonin synthesis in the duodenum.⁴⁰ It was suggested that intestinally derived circulating serotonin plays critical roles in controlling bone formation and bone mass. However, contradictory results have been reported.^{26,41} These studies favor a model in which LRP5 functions occur within osteoblast lineage cells, mostly in osteocytes. There has been a public debate about these discrepancies.^{144,145} Therefore, the mechanisms through which LRP5 regulates bone mass need to be further investigated. Of note, the intestinal tract is also one of the principal organs that control the dietary balance of calcium and phosphate so important for bone health.

Wnt signaling in aging adipose tissue

Adipose tissue is a loose connective tissue consisting mainly of adipocytes. Mammals have two different types of adipose tissue: white adipose tissue (WAT) and brown adipose tissue (BAT). The primary purpose for white adipose tissue is to store lipids and release fatty acids when fuel is required. Brown adipose tissue has a metabolic and thermogenic role and is more prominent in neonates and infants. Wnt signaling suppresses adipogenesis by blocking induction of PPAR γ and CEBP α , the master regulators of adipogenesis. Conversely, disruption of extracellular or intracellular Wnt signaling with recombinant sFRP1/2 or through constitutive expression of *Axin* lead to spontaneous adipocyte differentiation.^{146,147} LRP5 has been reported to inhibit adipogenesis and enhance osteoblastogenesis.^{148–150} Bone marrow adipose tissue (BMAT) has emerged as a unique adipose depot that has been recently recognized as an important endocrine tissue. This fat depot makes up 50–70% of the marrow space in healthy adult humans. BMAT accumulates with aging and in diverse clinical conditions such as osteoporosis, diabetes, anorexia nervosa and obesity.^{151,152} Interestingly, it has been recently demonstrated that BMAT differentiation is modulated by sclerostin, which inhibits Wnt signaling in pre-adipocytes and promotes BMAT formation.¹⁵³

Wnt signaling plays critical role in regulating mesenchymal stem cell (MSC) fate. Activation of Wnt signaling stimulates myogenesis and inhibits adipogenesis.^{154–157} It has been

reported that Wnt signaling promotes the differentiation of adipose progenitor cells into fibroblastic cells rather than adipocytes.¹¹⁶ Leptin is synthesized by mature adipocytes in response to changes in body fat mass and nutritional status. Leptin regulates bone mass through the central nervous system (Fig. 1).¹⁵⁸ Interestingly, leptin increases osteoblast secretion of FGF23, with a consequent reduction in phosphate resorption.¹⁵⁹

As described above, sclerostin has emerged as an endocrine factor that regulates glucose and fat metabolism.⁷¹ Outside of the skeleton, sclerostin is present in the serum, supporting a circulating endocrine role.^{160,161} Circulating sclerostin increases progressively with age and the higher serum sclerostin levels found in elderly post-menopausal women are associated with a greater risk of hip fractures.^{162–164} More recently, circulating sclerostin has been reported to be associated with glucose and adipose tissue metabolism.^{71,165–167} *Sclerostin* KO mice have reduced adipogenesis, increased insulin sensitivity, and are similar to the mice treated with a sclerostin antibody. These mice are resistant to obesogenic diet-induced disturbances in metabolism. Those effects are due to the action of sclerostin on white adipose tissue.^{71,149} Since adipocytes do not produce sclerostin, these findings suggest an endocrine function for sclerostin that facilitates communication between the bone and adipose tissue. Taken together, these results support the existence of a novel endocrine regulatory loop through which sclerostin, produced by bone cells, contributes to the regulation of glucose and adipose tissue metabolism while affecting the skeleton.

Conclusions

As one of a handful of highly conserved signaling pathways, Wnt is expressed repeatedly during development to regulate many cellular processes. Indeed, Wnt signaling plays essential roles during bone, kidney, intestine, and adipose tissue development and homeostasis. Emerging evidence suggests that Wnt signaling may play a fundamental role in the aging process of those organs as well.¹⁶⁸ Bone is not only the major reservoir for calcium and phosphate, but also the largest organ serving multiple physiologic functions, including mineral and energy metabolism. The interaction among bone, kidney, intestine, and adipose tissue may be controlled and regulated by many endocrine signals among these organs, such as FGF23, klotho, SOST, osteocalcin, vitamin D, and leptin (Fig. 1). Since the aging process is characterized by structural and functional decline in almost all tissues and organs, understanding the role of Wnt signaling in the interactions among bone, kidney, intestine, adipose tissue, and other organs in aging may shed light on the pathogenesis of age-related diseases.

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Figure 1.

Interactions among bone, kidney, intestine, and adipose tissue are controlled and regulated by endocrine signals. Wnt signaling may play a fundamental role in the aging of those organs as well. Bone is not only the major reservoir for calcium and phosphate storage, but also the largest organ with multiple functions, including mineral and energy metabolism. FGF23, klotho, SOST, osteocalcin, vitamin D, and leptin play crucial roles in coordinating and regulating the interactions among bone, kidney, intestine, and adipose tissue.