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REVIEW

LRP5 and bone mass regulation: Where are we now?

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The discovery of causal mutations in the low-density lipoprotein receptor-related protein 5 (*LRP5*) gene underlying conditions of altered bone mass ushered in a new era in bone research. Since those original publications, the role of Lrp5 and the Wnt/β-catenin signaling pathway controlled by Lrp5 and its homologs, Lrp6 and Lrp4, in bone mass regulation has been an intense area of investigation. Studies to date have implicated this pathway in skeletal development, osteoblast differentiation and proliferation, osteoblast/osteocyte apoptosis, regulation of the balance between osteogenesis–chondrogenesis–adipogenesis, regulation of osteoclastogenesis and the response of bone to mechanical loading. Interestingly, the data from knockout and transgenic mice involving Lrp4/5/6 and/or their regulators, as well as β-catenin signaling pathway components, and *in vitro* studies have sometimes yielded conflicting results. Adding to the complexity of the system are the studies that suggested Lrp5 regulated bone mass through a gut-bone endocrine signaling system involving Lrp5 mediated control of gut serotonin synthesis. However, recent studies have called this into question and so this provocative concept remains an open question. Clearly, the manipulation of Lrp5/Wnt/β-catenin pathway presents as a major target for drug development to treat diseases of low bone mass such as osteoporosis and these new therapies are in full progress. At present, although it is clear that Lrp5 has a role in bone mass regulation, much of the details remain to be elucidated and this is a major and exciting challenge for future studies.

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The Story Unfolds

What began as a simple gene discovery involving two rare and seemingly unrelated genetic disorders, the autosomal recessive osteoporosis-pseudoglioma syndrome (OPPG) and the autosomal dominant high bone mass (HBM) kindred, has evolved into a profound, paradigm shifting impact on the field of bone biology. Early genetic studies on these two traits that defined overlapping linkage intervals for the gene underlying these two traits[1,2] suggested the possibility that these two traits might be caused by allelic variants of the same gene.[2] This was borne out in December 2001 and January 2002 when Warman and co-workers[3] and Johnson and co-workers[4] published the identification of mutations in the low-density lipoprotein receptor-related protein 5 (*LRP5*) that caused the altered bone mass in their families. Shortly after the publication of the identification of *LRP5* mutations that caused OPPG and HBM, Boyden *et al.*[5] reported an identical G171V mutation in an unrelated family that had an even higher bone mass on average compared with the HBM family.[2] Since those original publications, numerous reports of other *LRP5* mutations that give rise to altered bone mass phenotypes have been described.[6–19]

The first clue about the function of LRP5 in bone came from the 'experiments of nature' illustrated by the phenotypes evident in families that carry mutations. The OPPG homozygous recessive affected members had a bone mineral density (BMD) *Z*-score of −4.7 (4.4 s.d. below the mean of sex- and age-matched normal individuals) and heterozygote carries had a mean BMD *Z*-score of −1.4, whereas the two G171V HBM kindreds had BMD *Z*-scores ranging between +3 and +8 depending upon affected member and bone site measured. The OPPG also had an associated progressive loss of vision leading to blindness by the age of 20. Boyden *et al.* also reported an associated torus pallatinus/mandibularis, which they suggested was due to the *LRP5 G171V* mutation,[5] but in the original HBM family these tori were uncommon and also found in unaffected members (unpublished data).

Following the studies reported in humans, mouse models were developed that shed further insight into the role of LRP5 in bone. Kato *et al.*[20] described the mouse with a global knockout of *Lrp5* (*Lrp5*$^{-/-}$). These mice developed a low bone mass similar to the human OPPG phenotype and displayed a failure to regress the hyaloids vessels during embryonic development

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of the eye, which might mechanistically explain the progressive blindness in those affected individuals. At the bone cell level, Kato *et al.*[20] demonstrated that *Lrp5*$^{-/-}$ mice had decreased bone formation rates due solely to a decreased mineral apposition rate determined by dynamic histomorphometry. Although they noted a mild delay in osteogenesis in the *Lrp5*$^{-/-}$ mice, the major effect was shown to be on osteoblast proliferation. No defect in osteoclastogenesis was detected, indicating that altered bone resorption was not contributing to the decreased BMD in the knockout mice. Babij *et al.*[21] created a transgenic mouse line carrying the human *LRP5 G171V* complementary DNA under the expression of the 3.6 Col 1a1 promoter. This HBM mouse model recapitulates the human phenotype in terms of increased bone mass and the studies by Babij *et al.* also revealed decreased osteoblast and osteocyte apoptosis as a result of the mutation. Collectively, these mouse studies suggest that Lrp5 functions in the osteoblast lineage of cells to control proliferation and apoptosis, but has little or no effect on osteoclasts.

Interestingly, it has been suggested that because neonatal calvarial osteoblasts isolated from *Lrp5*$^{-/-}$ mice proliferate in culture identical to wild-type (WT) neonatal calvarial osteoblasts, Lrp5 loss-of-function affects osteoblasts through extracellular signals rather than from the osteoblasts themselves.[22,23] However, at the 31st Annual Meeting of the ASBMR, Javaheri *et al.* presented an abstract (Poster), in which they demonstrated that osteoblastic cells isolated from the long bones of adult (19-week-old) *Lrp5*$^{-/-}$ mice grew slower in culture than WT cells and that the *LRP5*^{G171V} cells grew faster than both.[24] Publication of this data is anxiously awaited as this apparent contrast between neonatal- and adult-isolated cells has important implications for both cell culture studies using primary osteoblasts in general, but also for understanding Lrp5 function.

Lrp5 has a close homolog, Lrp6, which has also been implicated to have an important role in the skeleton. Global deletion of *Lrp6* results in an early neonatal lethal phenotype, but mice with a heterozygous loss of *Lrp6* have skeletal patterning defects.[25] A homozygous hypomorphic *Lrp6* mouse allele known as *ringleschwanz* results in multiple dysmorphologies of the skeleton and neural tube defects, as well as delayed ossification at birth and low bone mass in adults.[26] Holmen *et al.*[27] have also shown that Lrp6 contributes an increment of adult bone mass by comparing the phenotypes of *Lrp5* and *Lrp6* single and double mutant mice. Kubota *et al.*[28] went on to demonstrate that the *Lrp6 rs* allele results in increased receptor activator of nuclear factor κβ ligand (RANKL) expression and a concomitant increase in osteoclastogenesis without any impairment of osteoblast function. Thus, it seems clear that Lrp5 and Lrp6 have some overlapping functions in bone, but do not represent redundant entities in that each has distinctly separate functions as well as loss of one is not compensated by the other. Understanding the distinct roles of Lrp5 versus Lrp6 is a major gap in our knowledge at this time.

Recently, Lrp4/Megf7, another member of the low density lipoprotein receptor family to which Lrp5 and Lrp6 belong, has been implicated as having a role in skeletal development and bone mass regulation. Lrp4 was first shown to be expressed in the apical ectodermal ridge and its deletion in mice resulted in polysyndactyly.[29,30] Subsequent studies in mice also demonstrated that Lrp4 is expressed in osteoblasts and binds Dkk1 and sclerostin.[31] They also demonstrated that *Lrp4* knockout mice had reduced femoral bone mineral content and BMD as well as other parameters consistent with a role in bone mass regulation. An *Lrp4* mutation in humans that causes Cenani-Lenz syndrome, which has associated limb malformation and kidney anomalies, has been reported[32] and a recent study involving two Swedish cohorts identified Lrp4 and interaction between Lrp4 and other genes in the Wnt and BMP signaling pathways as contributing to peak bone mass and fracture incidence.[33] Two mutations in humans have also been identified in Lrp4 that demonstrated it is required for the inhibitory action of sclerostin on bone formation through its binding of sclerostin.[34] In tooth development, Lrp4 has also been shown to bind the protein Wise.[35] Collectively, these data suggest that Lrp4 may be another important player in the modulation of Lrp5/6, perhaps as a docking protein for molecules, such as Dkk1, sclerostin and Wise, and presenting these important regulators to Lrp5/6, thereby preventing activation of the Wnt/β-catenin signaling, although Lrp5/6-independent functions cannot be ruled out at this time.

A major unresolved question is why mutations in Lrp5 or Lrp6 or Lrp4 are not compensated by the presence of the other homologs? This implies some level of distinct function for these receptors. Although skeletal patterning seems to be primarily a function of Lrp6 during embryonic development and it appears that Lrp5 functions most importantly in postnatal bone acquisition and homeostasis (perhaps through its role in the response of bone to mechanical loading, see below), these do not appear to be exclusive. Sorting out the distinctive and overlapping roles of these receptors is critical to the development of new agents to modulate bone mass.

One cannot fully understand the role of LRP5 without also considering its important function in regulating the Wnt/β-catenin signaling pathway. LRP5 and its close homolog LRP6 are co-receptors, along with the frizzled family of proteins, for the Wnt protein family of signaling molecules. LRP5/6 functions in the regulation Wnt/β-catenin signaling, the details of this pathway have been described extensively (http://www.stanford.edu/group/nusselab/cgi-bin/wnt/). The key component of this pathway is β-catenin, which through binding to specific transcription factors, primarily the Tcf/lef and FoxO family members, regulates the transcriptional activity of several genes.[36–39] The specific Wnt ligand responsible for bone mass regulation is still unknown, although Wnt 10b is known to promote mesenchymal stem cell differentiation along the osteogenesis pathway versus adipogenesis[40] and a role for Wnt7b in regulating osteoblastogenesis has been suggested.[41] *In vitro* studies routinely use Wnt3a or Wnt1 as ligands to activate β-catenin signaling. Global deletion of Wnt3a in the mouse results in an embryonically lethal phenotype because of early-disrupted somitogenesis.[42–44]

Given the importance of β-catenin as the downstream signaling molecule from Lrp5 (and Lrp6/4), several investigators have studied the role of this signaling molecule in bone cell function and bone mass regulation. Greatly aiding these studies has been the genetic manipulation of β-catenin using conditional deletion and gain-of-function models,[45] specifically combined with Cre mouse lines designed to target bone cells. Several groups have clearly established an essential role for β-catenin in osteoblast differentiation and controlling the balance between osteoblastogenesis and chondrogenesis. Hu *et al.*[41] conditionally deleted β-catenin using a cross with the *Dermo1-Cre* mouse, which deletes β-catenin in skeletal early progenitor cells.

Using this strategy they showed that β-catenin signaling acted downstream of hedgehog signaling in osteoblast differentiation. Hill *et al.*[46] used the *Prx1-Cre* mouse to conditionally delete in limb and head mesenchyme and demonstrated that loss of β-catenin blocked osteoblast lineage differentiation and that instead osteoblast precursors develop into chondrocytes. Day *et al.*[47] used crosses to the *Dermo1-Cre* and *Col2a1-Cre* mice to also show the important role of β-catenin in osteoblast differentiation and the balance between osteoblastogenesis and chondrogenesis.

While those studies focused on early differentiation events, others have investigated the role of β-catenin in the later stages of osteoblast differentiation. Holmen *et al.*[27] used the *osteocalcin (OC)-Cre* mouse to delete β-catenin at a later stage in the osteoblast differentiation pathway and observed early onset of severe bone loss in both trabecular and cortical compartments, growth retardation and premature death by 5 weeks of age. Using the OC-Cre mouse to conditionally delete *adenomatous polyposis coli*, a key component of the degradation complex and therefore its loss will increase β-catenin levels, resulted in a nearly complete filling in of the marrow space with bone, which likely compromised hematopoiesis and resulted in even earlier lethality than the OC-Cre-deleted β-catenin mice. Deletion of both β-catenin and adenomatous polyposis coli resulted in a phenotype that was nearly identical to the loss of β-catenin alone. Mechanistically, loss of β-catenin resulted in markedly increased osteoclast numbers, whereas loss of adenomatous polyposis coli resulted in the absence of osteoclasts. Glass *et al.*[48] also demonstrated that in differentiated osteoblasts, β-catenin was important for the regulation of osteoclast differentiation by osteoblasts. They demonstrated that β-catenin regulated osteoblast expression of osteoprotegerin (OPG), important for the inhibition of osteoclastogenesis.

Moving even further down the osteoblast differentiation pathway, Kramer *et al.*[49] deleted β-catenin in osteocytes. The homozygous deletion in osteocytes resulted in a bone phenotype that included significant reduction in bone mineral content and BMD, almost absent trabecular bone and decreased cortical thickness, the bone loss was progressive with aging and the mice developed cortical porosity and died prematurely, with females more severely affected than male mice. The reduced bone mass was due to increased osteoclast number and activity, while osteoblast function and number was unaffected. The increased osteoclastic activity correlated with decreased OPG expression and an increased RANKL/OPG ratio. The heterozygous knockout in osteocytes had a much milder phenotype that was observed in the cancellous bone compartment. Interestingly, the phenotype showed an age and sex difference in severity with females being worse than males at a younger age.

A comparison of the phenotypes caused by Lrp5 versus their β-catenin mutation counterparts is both interesting and informative as to the role of Lrp5 in the skeleton. In humans, loss of Lrp5 causes early onset of juvenile osteoporosis and progressive blindness, which is mimicked in *Lrp5* knockout mice. The major underlying cause of the low bone mass appears to be reduced osteoblast proliferation and decreased mineral deposition. In the case of the *HBM G171V* mutation in *LRP5* (*LRP5*^{G171V}), there is decreased osteoblast (and osteocyte) apoptosis, with the longer life span presumably enabling greater mineral deposition, as well as decreased inhibition of Lrp5 by Dkk1 and/or sclerostin, which could result in increased signaling through the Wnt/β-catenin pathway. The HBM mutation also results in an increased OPG/RANKL ratio in response to mechanical loading,[50] which reduces osteoclastogenesis. In the case of the β-catenin mutations, the primary effect appears to be either on osteoblast differentiation and/or on the osteoclast axis leading to altered bone resorption. Presumably the osteoclast effects are mediated by osteoblasts and/or osteocytes through the expression of OPG and RANKL by one of both cells. These subtle differences are perhaps not surprising as regulation of β-catenin can occur through several other interacting pathways that intersect with the degradation complex and specifically glycogen synthase kinase-3. Therefore, the β-catenin mutants have a perhaps broader implication for bone cells because of the potential for more than just one pathway to be affected.

A Different Twist

The LRP5 and bone mass regulation story took an unexpected turn in 2008, when Yadav *et al.* [22] published a very provocative paper in which they proposed that Lrp5 expression in the gut enterochromafin cells regulated bone mass through an endocrine mechanism involving serotonin. They presented data that Lrp5 controlled the expression of *Tph1*, a key regulator of serotonin synthesis. In their model, Lrp5 normally inhibits Tph1 and gut enterochromafin cell-derived serotonin synthesis. In the case of the *Lrp5* knockout, this releases the inhibition of *Tph1* expression, serotonin synthesis increases and following binding to the Htr1b serotonin transporter in osteoblasts inhibits *Creb* expression, which results in a decrease in osteoblast proliferation. Their model is based on considerable *in vivo* and *in vitro* evidence, in which they manipulated serotonin levels and assessed a series of genetic manipulations in mice that targeted critical genes in their proposed pathway in osteoblasts or in the gut and determined the consequences on cancellous bone and osteoblasts. These later studies were achieved by crossing α_1*(I)Col-Cre* and *Villin-Cre* mice with mice carrying floxed alleles of *Lrp5*, *β-catenin* or *Tph1* to delete genes in osteoblasts or the gut, respectively. In addition, they analyzed the bone consequences of various serotonin receptor-deficient mice and the heterozygous loss of various transcription factors along with Lrp5 plus transcription factor heterozygous double mutant knockout mice. They also created a conditionally activatable Lrp5^{G171V} allele to produce a HBM mouse model recapitulating the human phenotype. Two key results from all of their reported studies were that deletion of *Lrp5* or knock-in of the *Lrp5 G171V* mutation in osteoblasts had no effect on cancellous bone parameters, whereas in the gut *Lrp5* deletion reduced and *Lrp5 G171V* knock-in increased cancellous bone parameters. The net result of all of their studies was to propose a mechanism whereby Lrp5 controls bone formation through a serotonin-dependent pathway based on Lrp5 expression in the gut and not in bone.

Very recently, however, Cui *et al.*[51] conducted a similar set of experiments in which they too created mice with either *Lrp5 HBM* knock-in alleles or conditional *Lrp5* knockout alleles. This group introduced one of two different HBM point mutations that had been previously identified in human subjects (G171V and A214V) into exon 3 of the mouse *Lrp5* gene along with a *Neo*^{R} resistance gene (as part of their targeting vector). Mice heterozygous for the G_N or A_N alleles (exon 3 G or A containing along with the flanking *Neo*^{R} gene) had bone mass similar to WT mice. The *Neo*^{R} gene is driven by a strong promoter, which they

demonstrated interfered with the expression (reduced) of the A and G *HBM* alleles. However, when the *Neo*^{R} gene was deleted by crossing to a Cre mouse line, expression of the A or G *HBM* allele was similar to the WT *Lrp5* allele. Crossing to the Dmp1-Cre mouse line in which the Cre will be mainly expressed in late osteoblasts and osteocytes, the A and G HBM mice developed HBM. The original description of the Dmp1-Cre mouse[52] indicated expression of the Cre mainly in late osteoblasts and osteocytes, but as this mouse line has been distributed and bred in other labs, expression in other tissues has been noted.[53] Therefore, to rule out the possible expression of HBM alleles in intestine as causal for the HBM, a cross to the *Villin1-Cre* mouse that drives Cre expression in the intestine was performed. In contrast to the results of Yadav *et al.*,[22] activation (expression) of the *Lrp5 HBM* alleles in the gut had no effect on bone mass. Cui *et al.*[51] next deleted Lrp5 in osteocytes using the *Dmp1-Cre* cross to an *Lrp5*-floxed (exon 2) mouse and these mice had decreased bone mass. Deletion of *Lrp5* in the gut by crossing to the *Villin1-Cre* mouse had no effect on bone mass. Perhaps the most compelling evidence for Lrp5 acting locally in bone were the experiments using crosses to the *Prrx-1-Cre* mouse line in which the expression of the Lrp5 HBM alleles was restricted to the appendicular versus the axial skeleton. This resulted in increased bone mass only in the limbs (distal femur) and not the spine (fifth lumbar vertebrae). Additional studies examined the relationship between serum serotonin levels and *Lrp5* genotype. Unlike the results reported by Yadav *et al*,[22] Cui *et al.*[51] did not find an association. The end result of the studies by Cui *et al.*[51] was to conclude that Lrp5 functions locally in bone to regulate bone mass and they could not corroborate a mechanism involving Lrp5 regulation of intestinal serotonin synthesis.

Given these two disparate results, what might explain these reported opposite findings and what can we conclude at this point about the role of Lrp5 and bone mass regulation? At this point possible explanations are merely speculative. Other recent commentaries/reviews have weighed in the Lrp5/serotonin stories.[54–57] Careful examination of the Yadav *et al.*[22] and Cui *et al.*[51] papers reveals several technical differences, such as the choice/source of the Cre lines that were used and the manner in which the floxed alleles were constructed. The fact that Cui *et al.*[51] had to remove the *Neo*^{R} gene from their construct in order for the variant HBM alleles to be fully expressed and the increased bone mass phenotype to be observed serves as an important lesson about the design and use of different floxed alleles. In light of the Neo^R effects, one has to wonder if the Flag-epitope tag present on the C-terminal end of the Lrp5-G171V construct used by Yadav *et al.*[22] somehow altered the function of that allele in bone and/or other tissues? Another issue that needs to be considered is whether the use of different Cre mice (or even the same Cre line) in different labs might contribute to the different results. As noted for the Dmp1-Cre, the specificity of that mouse from its initial description[52] seems to have changed as it has been distributed and bred in other labs.[53] Given the genetic drift that seems to have occurred in the *Dmp1-Cre* mouse line, should this be interpreted as a cautionary note for potential changes in tissue/cell specificity of other Cre lines and what impact would this have on the resulting phenotypes under study?

Obviously, knowing whether Lrp5 functions through a direct or indirect mechanism to regulate bone mass is an important question to resolve because this has important ramifications for the future design of clinical interventions based on targeting Lrp5 to treat diseases such as osteoporosis. However, equally important may be understanding the biological basis for the different results that were obtained from two highly respected labs because the answer to this question may reveal very important biology for the bone field.

LRP5 and Mechanical Loading

The final issue worth considering about Lrp5 is its hypothesized role in the response of bone to mechanical loading. Our group had speculated very early on after the discovery of the G171V mutation in LRP5 that this mutation altered the sensitivity of bone to mechanical loading.[58] Our logic for proposing this hypothesis was based upon the question; how could the affected members of the HBM kindred build a skeleton with this increased bone mass and retain what appeared to be essentially normally shaped bones without any obvious radiographic evidence of pathology, unlike so many other diseases of increased skeletal mass such as the known osteopetrotic conditions.

This concept was supported by our studies of the HBM transgenic mice[21] that demonstrated greater structural strength and material properties than WT mice[59] and ulna-loading response.[60,61] Sawakami *et al.*[62] performed ulna-loading studies on the Lrp5$^{-/-}$ mice and observed almost no new bone formation further implicating a role for Lrp5 in bone responsiveness to mechanical loading. Recently, Saxon *et al.*[51] examined bone formation responses to loading in the *LRP5*^{G171V} (HBM) transgenic and *Lrp5*$^{-/-}$ mice. They observed an increased osteogenic response in the HBM transgenic mice, but lack of Lrp5 only marginally reduced the loading response in males, whereas the data were inconclusive for the Lrp5$^{-/-}$ female mice. At present, all of the data suggest an increased sensitivity to mechanical loading in the case of the *Lrp5*^{G171V} mutation. The role, if any, of Lrp6 or Lrp4 is another unanswered question that needs to be determined.

As to the role of the Wnt/β-catenin signaling pathway there is considerable evidence supporting its role in the responsiveness of bone to mechanical loading. This has been reviewed previously[63,64] and will not be discussed in detail in this Review. What has emerged from all of these studies is that activation of the β-catenin signaling pathway occurs as a consequence of mechanical loading both *in vivo*[61,65–68] and *in vitro*.[67,69–71] At the 2011 ASBMR meeting, our group presented our findings that deletion of a single allele of β-catenin in osteocytes is sufficient to significantly reduce (nearly eliminate) new bone formation in response to loading.[72] Thus, there is compelling evidence from several groups defining a central role for β-catenin in the response to loading. However, these studies do not directly address the role of Lrp5 in the activation of β-catenin signaling and, in fact, evidence suggests that crosstalk with other signaling pathways such as Akt signaling[73] activated by PGE_2 is involved in an early Lrp5-independent activation of the pathway.[69,74,75] We have proposed a model that takes into account both early Lrp5-independent responses to loading in osteocytes, and a feedback loop that is Lrp5 dependent,[63] but there is still much to understand about the role of Lrp5 in bone response to mechanical loading.

Lrp5 and Bone: Where Are We Now?

Perhaps the safest answer to this question is that we know Lrp5 (along with Lrp4 and 6) has an important role, but the details

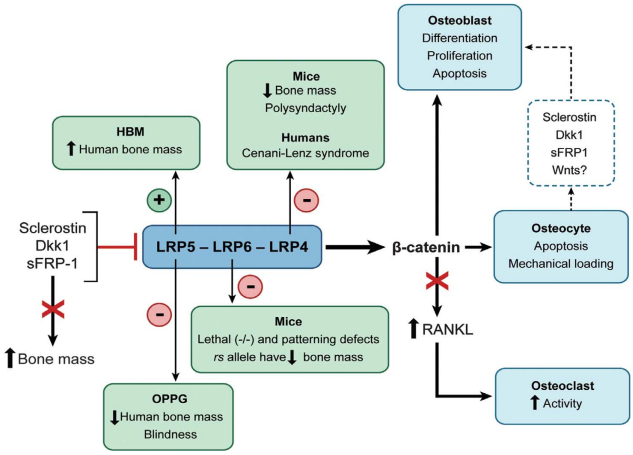

Figure 1 LRP5, LRP6 and LRP4 are important components of the Wnt/β-catenin signaling pathway. Under normal conditions, Sclerostin, Dkk1 and sFRP-1 inhibit β-catenin signaling through their interactions with the LRPs. Human mutations in the Sost (produces sclerostin) and Dkk1 genes give rise to increased bone mass. sFRP-1 loss in mice also results in increased bone mass. Human mutations in LRP5 that result in a gain-of-function give rise to conditions of high bone mass (HBM), whereas loss-of-function mutations give rise to osteoporosis pseudoglioma syndrome (OPPG) and its associated juvenile onset osteoporosis and progressive blindness, which is recapitulated in mice. Homozygous loss of LRP6 in mice results in a lethal phenotype and skeletal patterning defects. The *ringleschwanz (rs)* allele in mice results in multiple dysmorphologies and low bone mass. LRP4 deletion mutations result in polysyndactyly and low bone mass in mice and the Cenani-Lenz syndrome in humans. Downstream of the LRPs is the key signaling molecule β-catenin, which in various studies has been shown to be important in osteoblast differentiation, proliferation and apoptosis in osteoblasts. In osteocytes, β-catenin signaling is important in the regulation of apoptosis and in the response of bone to mechanical loading and can affect osteoblast function through its production of sclerostin, Dkk1, sFRP-1 and Wnt proteins. Targeted loss of β-catenin in osteoblasts and osteocytes results in a dramatic increase in osteoclast activity, perhaps through increased RANKL production, which ultimately produces a dramatically decreased bone mass. (See text for more details and references.)

remain to be fully understood. This is summarized in **Figure 1**. One key concept that emerges from the collective studies to date is the tight regulation of the β-catenin signaling pathway at multiple levels and that the relative ratios of these regulators must somehow be critical to the overall activity of the pathway as mutations in any one of these regulatory components can have a profound effect on the skeleton.

There are many unanswered questions regarding the role of Lrp5 in bone and in many instances the data seems to raise more questions than it answers, but the biology that is being revealed seems to be propelling the bone field forward and will hopefully lead to the development of new anabolic therapies to treat diseases such as osteoporosis. In the decade since the first description of Lrp5 mutations that gave rise to conditions of decreased and increased bone mass in humans, several reports of agents that target key components of the pathway have appeared and these hold great promise toward developing these new treatments. Although this has been extensively reviewed by others,[76–81] it appears that the emerging targets that hold the most promise at present are neutralizing antibodies to sclerostin[82,83] or Dkk1[84,85] and small molecule inhibitors of sFRP-1.[86,87] Whatever the ultimate understanding for the role of Lrp5 in bone, what is clear right now is that before those initial publications of the human mutations, no one suspected that the Lrp5 and the Wnt/β-catenin signaling pathway had a role in bone mass regulation and those reports gave birth to one of the most active areas of investigation in the bone field today.

Conflict of Interest

The author declares no conflict of interest.

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