

WJO 5<sup>th</sup> Anniversary Special Issues (6): Osteoporosis**Osteoporosis and obesity: Role of Wnt pathway in human and murine models**

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**Abstract**

Studies concerning the pathophysiological connection between obesity and osteoporosis are currently an intriguing area of research. Although the onset of these two diseases can occur in a different way, recent studies have shown that obesity and osteoporosis share common genetic and environmental factors. Despite being a risk factor for health, obesity has traditionally been considered positive to bone because of beneficial effect of mechanical loading, exerted by high body mass, on bone formation. However, contrasting studies have not achieved a clear consensus, suggesting instead that excessive fat mass derived from obesity condition may not protect against osteoporosis or, even worse, could be rather detrimental to bone. On the other hand, it is hitherto better established that, since adipocytes and osteoblasts are derived from a common mesenchymal stem cell precursor, molecules that lead to osteoblastogenesis inhibit adipogenesis and vice versa. Here we will discuss the role of the key molecules regulating adipocytes and osteoblasts differentiation, which are peroxisome proliferators activated receptor- $\gamma$  and Wnts, respectively. In particular, we

will focus on the role of both canonical and non-canonical Wnt signalling, involved in mesenchymal cell fate regulation. Moreover, at present there are no experimental data that relate any influence of the Wnt inhibitor Sclerostin to adipogenesis, although it is well known its role on bone metabolism. In addition, the most common pathological condition in which there is a simultaneous increase of adiposity and decrease of bone mass is menopause. Given that postmenopausal women have high Sclerostin level inversely associated with circulating estradiol level and since the sex hormone replacement therapy has proved to be effective in attenuating bone loss and reversing menopause-related obesity, we hypothesize that Sclerostin contribution in adipogenesis could be an active focus of research in the coming years.

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**Key words:** Osteoporosis; Obesity; Bone; Fat; Wnt; Peroxisome proliferators activated receptor- $\gamma$ ; Dickkopf; Sclerostin

**Core tip:** Here we will discuss the role of the key molecules influencing adipocytes and osteoblasts differentiation, which are peroxisome proliferators activated receptor- $\gamma$  and Wnts, respectively. Besides these proteins, the Wnt inhibitor molecules are also necessary to control the Wnt signalling balance from active to inactive state, in favour of osteogenesis or adipogenesis. It seems remarkably important a deepen analysis of these molecules, not only for their involvement in the regulation of the differentiation processes but also in coordinating the switch toward osteo- or adipo-genesis fate within bone marrow.

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## INTRODUCTION

### ***Bone and fat connection: The loss and gain of a relationship***

Several lines of evidence have largely supported the tight relationship between the adipose tissue and the skeleton. In particular, thorough molecular examination of the fat-bone connection, similarities between obesity and osteoporosis, the most important diseases affecting these two tissues, have been identified<sup>[1]</sup>. For instance, aging is associated with high incidence to develop both obesity and osteoporosis<sup>[1]</sup>, which are often simultaneous pathological conditions deriving from an altered balance between fat and bone cells in bone marrow. Moreover, the finding that pharmacologic strategies have opposite effects on fat versus bone mass further supports the inverse correlation between these two tissues. In particular, in aged women affected by menopause, the sex hormone replacement therapy has proved to be effective in attenuating bone loss<sup>[2,3]</sup> and reversing menopause-related obesity<sup>[4]</sup>. For example, in postmenopausal women, because ovaries no longer secrete estrogens, replacement therapy with estrogen and progestogen or estrogen alone or with selective estrogen receptor modulators (SERMS) has been, for long time, the treatment of choice for prevention and treatment of bone loss. Likewise, the effect of postmenopausal hormone replacement therapy has also been linked to the reversal of both obesity and loss of lean mass<sup>[3,4]</sup>.

Furthermore, the clinical use of glucocorticoids has been shown to affect bone remodelling<sup>[5-7]</sup> and increase obesity<sup>[8]</sup> or bone-marrow infiltration by adipocytes<sup>[1]</sup>. The ongoing researches, studying the balance of adipose and bone cells differentiation in bone marrow, have established a negative relationship between fat and bone mass. Thus, adipocytes and osteoblasts originate from a common mesenchymal precursor that can also differentiate into other cell types, but among the various fates, differentiate in adipocyte or osteoblast becomes of particular relevance because factors that enable osteoblastogenesis inhibit adipogenesis and vice versa. For example, activation of peroxisome proliferators activated receptor- $\gamma$  (PPAR- $\gamma$ ) promotes the differentiation of mesenchymal stem cells into adipocytes over osteoblasts<sup>[9]</sup>. In contrast, the wingless-type MMTV integration site (Wnt) signaling pathway inhibits adipogenesis<sup>[10]</sup> while supporting osteogenesis<sup>[11]</sup>. These two pathways can also influence each other. Indeed, it has been demonstrated that Wnt signaling negatively regulates adipogenesis through  $\beta$ -catenin, which inhibits PPAR- $\gamma$ -induced genes<sup>[12]</sup>. Moreover, Kang *et al.*<sup>[13]</sup> reported that induction of osteogenesis mediated by Wnt10b was also due to its ability in inhibiting PPAR- $\gamma$  expression.

### ***Fate of mesenchymal stem cells to become osteoblasts or adipocytes: Roles of the key regulators Wnt(s) and PPAR- $\gamma$***

The relevance of the canonical Wnt signaling in bone is

well acknowledged and several reports have unanimously established that Wnt/ $\beta$ -catenin activity is essential for bone development<sup>[14]</sup>. Wnts are a highly conserved family of proteins that can operate through two different signaling pathways. In the canonical pathway, when Wnt signalling is absent, a multiprotein complex, including adenomatous polyposis coli (APC), glycogen synthase kinase 3 (GSK3) and Axin, induces the degradation of  $\beta$ -catenin, thus reducing the free cytoplasmic pool of  $\beta$ -catenin. When Wnt signal is active through the Frizzled (FZD) receptor and low density lipoprotein receptor-related protein 5 and 6 (LRP5/6) receptor complex, it inactivates GSK3 and causes its dissociation from Axin preventing the phosphorylation of  $\beta$ -catenin. Hence, this pool of  $\beta$ -catenin in the cytoplasm increases and translocates to the nucleus where it binds members of the LEF/TCF family of transcription factors to provoke transcriptional induction of target genes<sup>[14]</sup>. In non-canonical pathway, Wnt signaling is induced through Frizzled independent of LRP5/6. This pathway causes cytoskeletal changes through activation of the small GTPases Rho and Rac<sup>[14]</sup>.

Wnt10b, one of Wnt family member, plays a key role in bone formation. It is expressed by osteoblast progenitors in bone marrow<sup>[15]</sup> and, hence, its transgenic overexpression in mesenchymal cells enhances osteoblastogenesis and leads to increased bone density. Accordingly, Wnt10b deficient mice display reduced trabecular bone<sup>[16]</sup> by  $\mu$ CT analysis. Thus, the distal metaphyses of these mice showed a 30% reduction in bone volume/total volume and bone mineral density. This loss was ascribed to a decrease in trabecular number with a associated increase in trabecular spacing. In addition to decreased bone mass in the femur, Wnt10b deficient mice also displayed reduction in bone volume fraction in proximal tibia<sup>[16]</sup>.

Furthermore, non-canonical Wnt members may also be involved in regulating osteogenesis. In particular, Wnt5a seems to be the most important Wnt member, acting through non canonical way, that is expressed during osteoblastic differentiation of mesenchymal stem cells<sup>[17]</sup>. Wnt-5a stimulates osteoblast differentiation through an autocrine loop<sup>[18]</sup> and haploinsufficient mice for Wnt-5a display a lower bone mass with decreased osteoblast number<sup>[19]</sup>. Another non-canonical Wnt member with a potential interest in bone accrual is Wnt4. Chang *et al.*<sup>[20]</sup> reported that human mesenchymal stem cells, genetically engineered to express Wnt-4, have enhanced commitment toward osteogenesis. Moreover, the ectopic Wnt-4 expression was able to ameliorate craniofacial defects in two different models of craniofacial bone injury<sup>[20]</sup>.

Regarding Wnts functions in adipogenesis, studies of Moldes *et al.*<sup>[21]</sup>, demonstrated that transgenic expression of Wnt1 in preadipocyte cell line strongly suppresses adipogenesis. This study also suggests a reciprocal relationship between PPAR $\gamma$  activity and  $\beta$ -catenin expression, since the concomitant over-expression of PPAR $\gamma$  and Wnt-1 in preadipocytes rescued the inhibition of adipogenesis by suppressing  $\beta$ -catenin expression, after the exposure to the PPAR $\gamma$  agonist, troglitazone. Based

on these observations, authors have proposed a model according to which, if Wnt signalling at the early stage of adipogenesis has been lowered to a level that permits induction of PPAR $\gamma$ , this latter, once activated, can further down-regulate  $\beta$ -catenin levels, leading differentiation of mature adipocytes. Likewise, pharmacological treatments that activate Wnt signaling and stabilize free cytosolic  $\beta$ -catenin are able to inhibit preadipocyte differentiation<sup>[22]</sup>. Conversely, by blocking Wnt signaling in preadipocytes, stimulates their differentiation<sup>[22]</sup>, suggesting that preadipocytes might synthesize endogenous Wnt molecules. Indeed, it has been showed that Wnt10b is highly expressed in confluent preadipocytes and it is immediately downregulated after exposure to elevated cAMP occurring during adipocyte differentiation<sup>[22]</sup>. Accordingly, if Wnt-10b is constitutively expressed, it stabilizes cytosolic  $\beta$ -catenin leading to suppression of adipogenesis<sup>[22]</sup>. On the contrary, Wnt-5b is transiently induced during adipogenesis and destabilizes  $\beta$ -catenin to enhance adipocyte differentiation<sup>[23]</sup>, indicating that preadipocytes could be targeted by opposite Wnt signals.

While mesenchymal stem cells activate their differentiation process toward adipo- or osteogenic cell fate, specific transcription factors become up-regulated. These include CCAAT/Enhancer binding protein (C/EBP) alpha and PPAR $\gamma$  for adipocytes<sup>[24]</sup> and core binding factor alpha 1 (Cbfa1/Runx2) for osteoblasts<sup>[25]</sup>. The reciprocal relationship between adipogenesis and osteoblastogenesis is also dependent on the ability of these lineage-specific transcription factors to inhibit differentiation of other lineages. For example, PPAR $\gamma$  also inhibits terminal osteoblast differentiation by suppressing Runx2 expression<sup>[26]</sup>.

### **Canonical vs non-canonical Wnt signalling: How this switch controls mesenchymal stem cell fate**

A reversal process, from non-canonical Wnt signaling to canonical Wnt signaling or vice versa, drives the progression into the differentiation stage. Indeed, during early adipogenesis, a prompt activation-inactivation of the Wnt pathway is crucial for the induction of PPAR $\gamma$ <sup>[27]</sup>. Specifically, the non-canonical Wnt5a pathway induces a signaling, through PPAR $\gamma$ , that regulates differentiation and insulin sensitivity of mature adipocytes<sup>[28]</sup>. On the other hand, canonical Wnt signaling is responsible for promoting cell proliferation *via* activation of cyclin D1 and c-myc while inhibiting PPAR $\gamma$ . This accounts for the mechanism involved in keeping pre-adipocytes in an undifferentiated state. Thus, cyclin D1 and c-myc directly bind and inhibit PPAR $\gamma$  and the C/EBP $\alpha$  transcription factor, respectively<sup>[29]</sup>. At the same time, the expression of C/EBP $\alpha$  leads per se to the phosphorylation of  $\beta$ -catenin and its subsequent degradation. Therefore, nuclear  $\beta$ -catenin activity is down-regulated and non-canonical signaling is switched on in order to promote adipocyte differentiation<sup>[21]</sup>. Notably, the concomitant induction of PPAR $\gamma$ , after  $\beta$ -catenin proteasomal degradation, further suggests that  $\beta$ -catenin could suppress PPAR $\gamma$  expression, as vice versa<sup>[12]</sup>.

Based on what has been described, it appears ques-

tionable how Wnts molecules are capable of exert different stimuli in mesenchymal stem cells. A reasonable explanation might be given considering other molecules involved in the Wnt signalling, that have inhibitory functions.

### **Wnt signaling inhibitors: Novel perspective in the control of adipogenesis**

Wnt signaling can be blocked by secreted antagonists including Dickkopf (DKK)<sup>[10]</sup> and Sclerostin<sup>[30]</sup>. DKK1 and Sclerostin inhibit WNT signaling by binding to the co-receptors LDL receptor-related proteins (LRPs) 5 and 6, preventing formation of the active LRP/Frizzled complex. The involvement of DKK1 in adipocyte differentiation has been demonstrated in several experiments. Transfection of human mesenchymal stem cells with DKK1 small interfering RNA reduced adipogenesis<sup>[31]</sup>. Furthermore, Dkk1 was found to be highly expressed in differentiated 3T3-L1 adipocytes and its expression was enhanced by PPAR- $\gamma$  agonists<sup>[32]</sup>. Therefore, secretion of DKK1 might be the mechanism whereby PPAR- $\gamma$  promote adipogenesis, while inhibiting Wnt signalling<sup>[31]</sup>.

Sclerostin is the other inhibitor of the powerful bone anabolic Wnt pathway<sup>[30]</sup>. Targeting deletion of Sclerostin in mice leads to high bone mass, due to a great increase in bone formation in both trabecular and cortical bone<sup>[33]</sup>. It has been demonstrated that antibody-based sclerostin inhibition increased bone mass and strength in healthy female rats and rescued ovariectomy-induced bone loss<sup>[34]</sup>. Furthermore, in a model of hindlimb disuse, antibody-based sclerostin inhibition was able to increase cortical and trabecular bone mass either in loaded upper limbs or in immobilized hind limb. This effect was characterized by coupling of high bone formation and decreased bone resorption, suggesting that inhibition of sclerostin might be useful for the treatment of immobilization-induced osteopenia<sup>[35]</sup>.

Conversely, an important clinical study in the field of rehabilitation, performed enrolling 39 subjects with chronic spinal cord injury and 10 without spinal cord injury, demonstrated that greater total limb bone mineral content was significantly associated with greater circulating levels of Sclerostin. Thus, Sclerostin levels were reduced in subjects with spinal cord injury who use a wheelchair compared to those with spinal cord injury who walk normally. Likewise, Sclerostin levels were lower in patients with spinal cord injury who use a wheelchair compared to persons without spinal cord injury. These results showed that circulating Sclerostin can be used as biomarker of severe osteoporosis, but not as biomarker of bone loss, in long-term absence of mechanical loading<sup>[36]</sup>.

However, to date it is well known about conditions where Sclerostin is genetically absent, such as in the disease known as Sclerostosis with bone mass markedly enhanced<sup>[37]</sup>. Conversely, there are currently few notions about the molecular mechanism involved in Sclerostin up-regulation, unless for the knowledge that postmeno-

pausal women have high serum Sclerostin level inversely associated with the circulating free estradiol (E2) index<sup>[38]</sup>. Furthermore, the reduction in Sclerostin circulating levels after E2 treatment<sup>[38]</sup> provides a meaning for addressing the key question about the involvement of sex steroid as regulators of Sclerostin expression.

The understanding of the molecular mechanism whereby Estrogen reduces the circulating Sclerostin levels might support the use of an anti-Sclerostin antibody in preventing bone loss, but also in avoiding fat mass augmentation, occurring at the decline of sex hormones. However, nowadays there are few data regarding the relationship between Sclerostin levels and obesity. Only one cross-sectional study, performed by Urano et colleagues<sup>[39]</sup> aimed to identify the relationship between serum sclerostin levels and markers of metabolic disease. Authors measured serum sclerostin levels in 352 Japanese postmenopausal women and analyzed the relationship of these levels with abdominal fat mass. Their result show that serum Sclerostin levels were positively correlated with percentages of abdominal and gynoid fat.

## CONCLUSION

Recently, it has become evident that Wnt family members are key molecules regulating differentiation of multipotent mesenchymal stem cells into osteoblasts and adipocytes, as showed both by animal models and by several clinical studies in humans. Besides Wnt proteins, the Wnt inhibitor molecules are also necessary to control the Wnt signalling balance from active to inactive state, in favour of osteogenesis or adipogenesis. This molecular control could be evidently crucial in the pathogenesis of obesity, as it is established to be fundamental in osteoporosis. Finally, it seems remarkably important a deepen analysis of these bioactive molecules, not only for their involvement in the regulation of the differentiation processes but also in coordinating the switch toward osteo- or adipogenesis fate within bone marrow.

Moreover, in the view of using the antibody-based sclerostin inhibition, as therapeutic approach to shift the balance in favor of osteogenesis at the expense of adipogenesis, further studies could be extremely relevant in the understanding the role of Sclerostin in regulating adipogenesis. These future studies could likely open an exciting avenue in osteoporosis and obesity research field, which may outcome in the development of novel therapeutic approaches to treat these burden diseases. Therefore, Sclerostin antibody will be extremely useful as skeletal anabolic agents to treat osteoporosis, but might also have potential utility in the therapy of obesity.

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