Citation: BoneKEy Reports **2**, Article number: 330 (2013) | doi:10.1038/bonekey.2013.64

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REVIEW

Cadherins and Wnt signalling: a functional link controlling bone formation

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Cadherins are calcium-dependent cell adhesion molecules that have a major role in morphogenesis and tissue formation. In bone, cadherins control osteoblast differentiation by mediating cell–cell adhesion and signals that promote phenotypic osteoblast gene expression. Furthermore, cadherins can interact with Wnt signalling to modulate osteoblastogenesis. One mechanism involves the interaction of N-cadherin with β-catenin at the cell membrane, resulting in β-catenin sequestration, reduction of the cytosolic β-catenin pool and inhibition of Wnt signalling. In addition to modulating the β-catenin pool, N-cadherin can regulate osteoblasts by interacting with the Wnt coreceptors LRP5 or LRP6. We showed that the functional interaction between N-cadherin and LRP5/6 in osteoblasts promotes β-catenin degradation and reduces canonical Wnt signalling. This crosstalk between N-cadherin and Wnt signalling has a negative impact on osteoblast proliferation, differentiation and survival, independently of cell–cell adhesion, which results in decreased bone formation and delayed bone accrual in mice. The identification of this crosstalk between N-cadherin and Wnt signalling may have therapeutic implications, as a disruption of the N-cadherin–LRP5/6 interaction using a competitor peptide can increase Wnt/β-catenin signalling without affecting cell–cell adhesion, and this effect results in increased osteoblastogenesis and bone tissue formation *in vivo*. In this review, we summarize our current knowledge of the key crosstalks between cadherins and Wnt signalling that impact osteoblast function, bone formation and bone mass, and the possible therapeutic implications of such interactions for promoting osteoblastogenesis, bone formation and bone mass.

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Introduction

Osteoblasts derive from mesenchymal stromal cells in the bone marrow stroma, which can also differentiate into chondrogenic or adipocytic lineages. Bone-marrow stroma mesenchymal stromal cells can differentiate progressively into putative committed osteoprogenitor cells, pre-osteoblasts and mature osteoblasts by the induction of Runx2 and other transcription factors, when cultured in the appropriate microenvironment.[1] The phenotype of mature osteoblasts is characterized by the expression of alkaline phosphatase, the synthesis and deposition of type I collagen and non-collagenous bone matrix proteins.[2] Once the bone matrix has been deposited, most osteoblasts become flattened lining cells. However, a fraction of cells lose cell–cell junctions and become embedded within the matrix to become osteocytes. The remaining osteoblasts also lose both their adherence to the matrix and cell–cell junctions, and undergo apoptosis.[3] Cell proliferation, differentiation and apoptosis in osteoblasts are regulated by a variety of signalling pathways induced by diffusible factors and cell–matrix interactions.[4,5] In addition, there is growing evidence that cell–cell contacts mediated by cadherins can modulate osteoblastogenesis and bone formation.[6,7] The mechanisms underlying the regulatory effect of cadherins in cells of the osteoblast lineage are now better understood. Notably, molecular interactions between cadherins and the Wnt signalling pathway were recently shown to modulate osteoblastogenesis and bone formation. In this review, we examine the current knowledge on the interactions between cadherins and Wnt signalling, which significantly impact osteoblastogenesis, which could serve as a basis for promoting bone formation and bone mass.

Cadherins and Bone Formation: Not Simply a Sticky Link

Cadherins are cell adhesion molecules that have a major role in tissue development.[8] Specifically, cell–cell adhesion mediated

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Received 18 January 2013; revised 27 February 2013; accepted 4 March 2013; published online 17 April 2013

by cadherins controls cell proliferation, differentiation and survival of mesenchymal cells.[9,10] In bone, cells of the osteoblast lineage express mostly E-cadherin, N-cadherin and cadherin-11.[11–14] Several *in vitro* studies have shown that the expression of these cadherins changes during osteoblast differentiation.[11–14] Notably, the expression of N-cadherin increases in the early stages of osteoblast differentiation and this is associated with increased cell–cell interactions. In contrast, N-cadherin expression decreases in more mature osteoblasts, osteocytes or apoptotic osteoblasts, which exhibit reduced cell–cell adhesion.[11,12,15,16] N-cadherin expression also declines during mesenchymal stromal cell differentiation into adipocytes,[13] suggesting that N-cadherin is essential for early, but not late, osteoblast differentiation. Consistent with this concept, it was found that cell–cell adhesion mediated by cadherins has a role in osteoblast gene expression during the early stages of cell differentiation.[6,7] Most notably, specific inhibition of N-cadherin-mediated cell–cell adhesion can prevent osteoblast differentiation in basal conditions and under BMP-2 stimulation *in vitro*.[11,12,15] Consistently, N-cadherin-mediated junctions between osteoblasts are needed for phenotypic gene transcription.[17] The importance of N-cadherin in osteoblastogenesis is also supported by the finding that several hormonal or local factors act on N-cadherin expression or N-cadherin-mediated cell–cell adhesion to regulate osteoblast differentiation and survival *in vitro*.[6] *In vivo* studies also support a role of N-cadherin in early stages of osteoblastogenesis and bone formation. Conditional N-cadherin knockout in mice results in decreased N-cadherin-mediated cell–cell adhesion and decreased bone mass.[18,19] Targeted expression of a dominant-negative N-cadherin expressed in osteoblasts leads to decreased bone formation and delayed bone acquisition in mice.[20] Overexpression of N-cadherin in osteoblasts also decreases osteoblast differentiation and causes delayed peak bone mass in transgenic mice.[21] Overall, these studies highlight the potential role of cadherin-mediated cell–cell adhesion in pre-osteoblasts and osteoblasts in the regulation of osteoblastogenesis and bone formation. In addition, there is evidence that cadherins can regulate osteoblastogenesis and bone formation by mechanisms independent of cell–cell adhesion. Specifically, cadherins in osteoblasts can interact with Wnt signalling and thereby control bone formation, as detailed below.

Cadherins–Wnt Crosstalk: a Complex Interaction

As depicted above, cadherin-mediated cell–cell contacts participate in intracellular signalling events leading to gene expression. In addition, cadherins may also control cell behaviour and function through the modulation of signalling pathways, which are both cadherin-specific and cell-context-specific.[22,23] One pathway that is linked to cadherins and is highly relevant to bone remodelling is Wnt signalling.[24] The current model of the Wnt canonical pathway involves multiple interacting signalling proteins.[25] In the absence of a Wnt ligand, β-catenin is sequentially phosphorylated by the kinases CK1 and glycogen synthase kinase 3β (GSK3-β) in the destruction complex composed of axin and adenomatous polyposis coli protein, resulting in β-catenin ubiquitination and proteasomal degradation. In the presence of Wnt proteins, Wnt binding to the Wnt coreceptors LRP5 or LRP6, and Frizzled, leads to the binding of Dishevelled, phosphorylation of LRP5/6 by GSK3β and CK1, and recruitment of Axin/Frat1/GSK3-β/β-catenin complex to the cytoplasmic tail of LRP5/6. This results in the displacement of GSK3β from the axin and β-catenin complex, inhibition of GSK3β and decreased phosphorylation of β-catenin, causing β-catenin stabilization, accumulation of free β-catenin in the cytosol, its subsequent translocation into the nucleus and activation of T-cell factor/lymphoid enhancer factor-dependent β-catenin target genes (**Figure 1**). Cadherins were shown to interact with this canonical Wnt/β-catenin signal transduction pathway in multiple ways.[26–28] Cadherins are linked to the actin cytoskeleton through their binding to α-, β- and γ-catenins, which participate to the adherens junction[29] (**Figure 1**). Thus, one mechanism by which cadherins can interact and limit Wnt signalling may be by promoting the

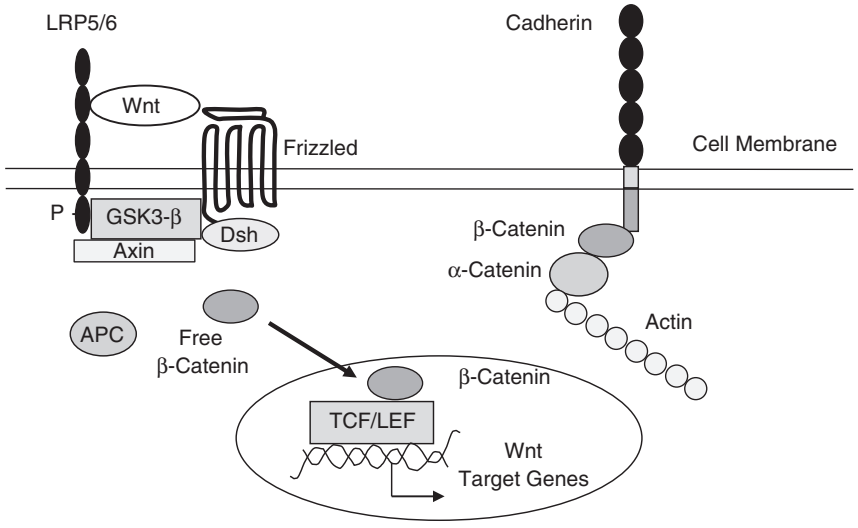

Figure 1 Cadherin–Wnt interactions. Wnt binding to the Wnt coreceptors LRP5 or LRP6, and Frizzled, leads to phosphorylation of LRP5/6, the recruitment of the axin/adenomatous polyposis coli protein/GSK3-β/β-catenin complex, resulting in the inhibition of GSK3-β, β-catenin stabilization, T-cell factor/lymphoid enhancer factor (TCF/LEF) transactivation and osteoblast gene expression. Cadherins are linked to the actin cytoskeleton via binding to catenins, notably β-catenin, in adherens junctions.

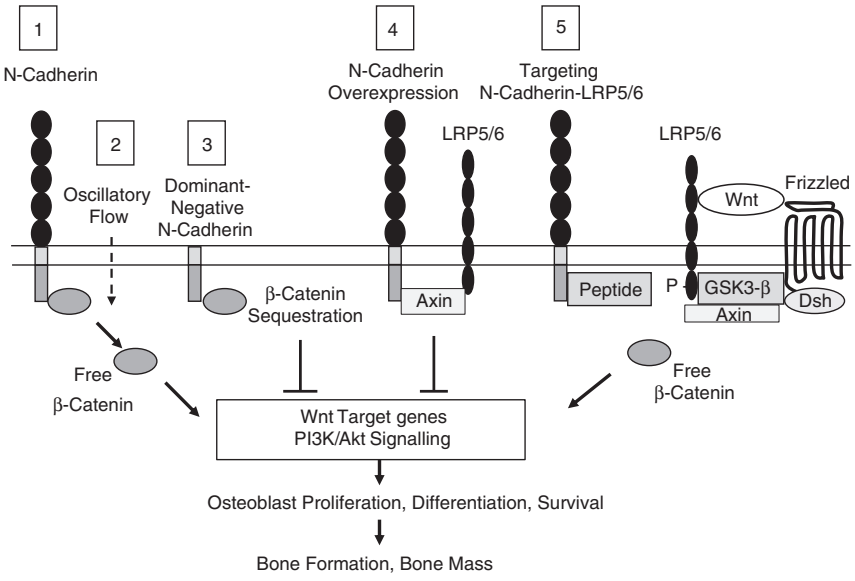

Figure 2 Cadherin–Wnt interactions in osteoblasts: a potential therapeutic target. Cadherin interactions with Wnt/β-catenin signalling molecules control osteoblastogenesis, bone formation and bone mass. Increased cadherin expression can lead to β-catenin sequestration at the cell surface, resulting in decreased osteoblast function (1). Conversely, the release of β-catenin from adherens junctions induced by oscillatory fluid flow leads to β-catenin nuclear translocation and osteogenic differentiation (2). Osteoblast-targeted overexpression of a truncated N-cadherin results in β-catenin sequestration and reduced osteoblast function (3). N-cadherin can functionally interact with LRP5/6, resulting in increased β-catenin degradation and decreased osteoblastogenesis (4). Disruption of this N-cadherin–LRP5/6 interaction with a competitor peptide increases Wnt/β-catenin signalling, osteoblastogenesis and bone formation (5).

activity of β-catenin phospho-destruction complex at the adherent junction site.[30] This mechanism is relevant to cell function, as, for example, the loss of E-cadherin engagement in dendritic cells results in β-catenin signalling and the activation of gene targets that promote immunotolerance.[31] Another mechanism by which cells can modulate Wnt signalling is through the cleavage of E- and N-cadherins by proteases.[32] Cadherins can be cleaved by proteases like ADAM10, presenilin-1 or calpain, resulting in the release of β-catenin into the cytosol, its translocation into the nucleus and activation of Wnt/ β-catenin target genes.[33] A third mechanism may involve the action of tyrosine kinases and phosphatases that control the carboxy-terminal phosphorylation of cadherins and, thereby, regulate β-catenin signalling, depending on the sites of phosphorylation.[34] The mechanism that is recognized as the most important, by which cadherins limit Wnt signalling, involves a direct interaction between the cadherin cytoplasmic tail and β-catenin.[24] This interaction, induced by increased cadherin abundance on the cell surface, may result in β-catenin sequestration at the cell membrane, reduction of the free cytosolic β-catenin pool, decreased β-catenin nuclear translocation and reduced T-cell factor/lymphoid enhancer factor-dependent transcriptional activity[35] (**Figure 2**). Consequently, β-catenin sequestration by cadherins at the plasma membrane leads to decreased Wnt/β-catenin signalling in several cell types.[36] Overall, the available data indicate that cadherins may have a dual functional role in the control of cell signalling, through a cell–cell adhesion-dependent mechanism and/or by modulating canonical Wnt/β-catenin signalling.

Control of Bone Formation by Cadherins–Wnt Interactions

In the skeleton, Wnt signalling has emerged as an important regulator of bone formation.[37,38] Notably, Wnt signalling via LRP5/6 coreceptors was found to promote osteoblast lineage commitment and function *in vitro*, and constitutive activation of this pathway leads to high bone mass *in vivo*.[39,40] As depicted above, cadherins are abundantly expressed by young osteoblasts. It can thus be surmised that cadherins could interact at different levels with Wnt signalling molecules, thus regulating the fate of cells of the osteoblast lineage. Consistent with this concept, recent studies have identified the importance of concerted crosstalks between cadherins and Wnt signalling molecules in osteoblasts, with a significant impact on Wnt/β-catenin signalling and bone formation. As discussed above, N-cadherin can interact with β-catenin at the plasma membrane, leading to β-catenin sequestration at the cell surface. In osteoblasts, this may have functional implications, as deletion of N-cadherin reduces β-catenin at the adherent junction site, resulting in decreased osteoblastogenesis.[18] Conversely, the release of β-catenin from adherens junctions induced by oscillatory fluid flow leads to β-catenin nuclear translocation and transcriptional activation, resulting in osteogenic differentiation *in vitro*.[41] Consistent with a role of such cadherin–β-catenin link in the control of bone formation, osteoblast-targeted overexpression of a truncated N-cadherin lacking the extracellular domain, but retaining its cytoplasmic β-catenin binding site, delays the acquisition of peak bone mass due to inhibition of Wnt signalling.[20] These studies revealed the importance of the balance between the free and N-cadherin-linked β-catenin in the control of osteoblasts (**Figure 2**).

In addition to the direct cadherin–β-catenin interaction, another mechanism linking cadherins and Wnt signalling was shown to control osteoblastogenesis. We found that N-cadherin overexpression in osteoblasts downregulates cell proliferation and differentiation, and increases cell apoptosis *in vitro* and *in vivo*, independently of β-catenin sequestration at the cell membrane. This suggests that another mechanism may

be primarily responsible for the defective osteoblastogenesis in these cells.[42] Indeed, we showed that N-cadherin can interact with the Wnt coreceptors LRP5/6 in osteoblasts in basal conditions, a mechanism that is amplified in case of N-cadherin overexpression. This interaction between N-cadherin and LRP5/6 results in increased β-catenin degradation and decreased Wnt signalling, causing decreased osteoblastic cell growth, differentiation and survival *in vitro*.[21] Young transgenic mice expressing N-cadherin in osteoblasts display attenuation of Wnt signalling, defective osteoblastogenesis and bone formation, and delayed bone mass accrual, supporting the concept of a negative impact of N-cadherin–LRP5/6 interaction on osteoblastogenesis *in vivo*.[21]

The molecular mechanisms by which N-cadherin can functionally interact with LRP5/6 involve the intracellular recruitment of axin, a key regulator of Wnt signalling, leading to the formation of an axin–LRP5 complex involving axin-binding sites in the cytoplasmic tail of LRP5.[21] In this context, N-cadherin overexpression may modulate osteoblast gene expression by regulating β-catenin expression and availability. Other mechanisms by which the increased N-cadherin interaction with LRP5/6 may affect osteoblast growth and survival include alteration of Wnt3a expression and attenuation of ERK and phosphoinositide 3-kinase/Akt signalling.[42] Consistent with this finding, it was reported that N-cadherin-mediated cell–cell adhesion is linked to activation of phosphoinositide 3-kinase signalling in osteoblastic cells.[17] Whether N-cadherin may also regulate non-canonical (β-catenin-independent) Wnt signalling in osteoblasts remains to be determined. Overall, the available data indicate that N-cadherin may control canonical Wnt signalling, osteoblastogenesis, bone formation and bone mass, not only through β-catenin sequestration but also by its interaction with the Wnt-receptor complex (**Figure 2**). As LRP5/6 is believed to have a role in controlling bone mass,[40,43] the interactions between N-cadherin and LRP5/6, which are abundantly expressed by osteoblasts, are likely to control osteoblastogenesis under physiological conditions. LRP5 is expressed by both developing and mature osteoblasts *in vivo*, but its expression level may change as cells differentiate along the osteoblastic lineage.[44] Thus, N-cadherin–LRP5/6 interactions may have distinct regulatory roles during early and late osteoblast differentiation, depending on the expression level of these two partners.

Cadherin–Wnt Interaction: a Target for Promoting Bone Formation

The identification of novel crosstalks between cadherins and Wnt signalling may have implications in bone therapeutics. A number of extracellular and intracellular proteins are known to antagonize Wnt signalling by acting on Wnt proteins or Wnt signalling partners.[25] For example, sclerostin, the product of the *SOST* gene, was shown to interact with LRP5/6, and thereby antagonizes Wnt signalling.[45] Our finding that N-cadherin acts as a LRP5/6 antagonist and negatively regulates Wnt/β-catenin signalling suggests that targeting N-cadherin may be of potential interest for modulating Wnt signalling and osteoblastogenesis. This concept was recently tested in a series of experiments. After having identified the specific intracellular domains of N-cadherin that interact with LRP5/6, we showed that disruption of the N-cadherin–LRP5/6 interaction using a truncated N-cadherin construct that impairs N-cadherin–LRP5/6 interaction, or a competitor peptide that functionally abrogates the interaction between N-cadherin and LRP5/6, increased both the β-catenin translocation and transcriptional activity in osteoblasts without affecting cell–cell adhesion.[46] Interestingly, this effect resulted in increased osteoblast function and survival *in vitro*. Furthermore, we showed that a disruption of the N-cadherin–LRP5/6 interaction using a competitor peptide resulted in increased osteoblast function and survival, and bone tissue formation *in vivo*.[46] These studies indicate that N-cadherin–LRP5/6 interactions can be targeted to increase Wnt signalling, osteoblastogenesis and bone formation *in vivo*.[47] If confirmed in osteopenic animals, this or other approaches targeting the N-cadherin–LRP5/6 interaction in osteoblasts could be a promising strategy for promoting osteoblast differentiation and bone formation in conditions where intrinsic osteoblast functions are compromised, such as aging.[48]

Conclusion

Both cadherins and Wnt signalling molecules are expressed by osteoblasts and are believed to have an important role in the control of osteogenesis. Previous studies have identified some links between cadherins and β-catenin that may modulate cell behaviour in osteoblasts. Our recent studies have revealed the importance of crosstalks between cadherins and the Wnt receptors LRP5/6 in the control of osteoblastogenesis. These emerging interactions were found to control osteogenesis through the modulation of signalling pathways controlling osteogenic cell proliferation, differentiation and survival, independently of cell–cell adhesion, with a functional impact on bone formation and bone mass. These findings led to the development of a concept proposing that targeting the cadherin–Wnt receptor interaction may be a potential strategy for promoting osteoblast differentiation and bone formation. This may provide potential tools for indirectly targeting Wnt signalling, to promote osteoblastogenesis in conditions where bone formation is compromised.

Conflict of Interest

The authors declare no conflict of interest.

Acknowledgements

This study was supported in part by grants from the European Commission FP7 research funding programme Talos (HEALTH-F2-2008-201099) and the Société Française de Rhumatologie (Paris, France). We thank all collaborators who contributed to our studies and Dr Zuzana Saidak for English corrections.

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