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Emerging regulators of BMP bioavailability

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Citation

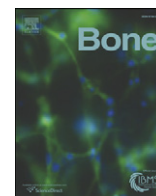
Sanchez Duffhues, G., Hiepen, C., Knaus, P., & Dijke, P. ten. (2016). Emerging regulators of BMP bioavailability. *Bone*, 93, 220-221. doi:10.1016/j.bone.2016.01.022

Version: Publisher's Version

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Note: To cite this publication please use the final published version (if applicable).



Correspondence

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Dear Editor,

We thank you for providing us with the opportunity to respond to the *Letter to the editor* by Sun et al., entitled “A crucial role for upstream regulators of the Bone morphogenetic protein (BMP) signaling in osteoblast differentiation”, recently published in *Bone* [1]. We appreciate the interest in our recent publication “Bone morphogenetic protein signaling in bone homeostasis” [2], and we agree with these authors that certain fibulins and in particular CCN family members play an emerging role in modulating the bioavailability of Bone morphogenetic proteins (BMPs).

As we discussed in our comprehensive review, the activity of the BMPs, which form part of the transforming growth factor- β (TGF- β) family, can be modulated at different levels, from the extracellular space to the cell nucleus. As such, once secreted, the availability of BMPs is modulated by ligand binding proteins at the extracellular space. In our publication (Fig. 3), we have cited several manuscripts where a number of such extracellular BMP antagonists (e.g., Noggin, Chordin and Follistatin) were described in detail [3–5]. Furthermore, other extracellular molecules do not inhibit, but enhance BMP signaling (e.g., KCP/Kielin, Cross-veinless 2) [6,7]. Fibulins, a family of extracellular matrix proteins that share a Fibulin domain at the carboxy terminal end, is yet another set of regulators of TGF- β family bioavailability. In contrast to BMPs, the regulation of TGF- β activity by fibulins has been extensively studied [8–12]. As mentioned by Sun et al., among all fibulins, thus far exclusively Fibulin-1 has been suggested to regulate BMP activity in bone, although whether its activity is mediated by a direct interaction with BMP-2 has not been demonstrated in vivo [13]. Indeed, calvariae from Fibulin-1 knock-out mice exhibited downregulated *Osterix* mRNA expression, whereas upstream and BMP-inducible *Runx2* expression was not affected. It would be of particular interest to follow up this research and determine the underlying mechanisms, as well as investigating the (possible) role of other fibulins in BMP signaling.

Cysteine rich 61 (CYR-61), connective tissue growth factor (CTGF) and nephroblastoma over expressed (Nov) comprise the CCN family of matricellular proteins, which can modulate BMP-induced signal transduction, as well as signaling initiated by other TGF- β family members. In contrast to fibulins, more is known about the role of such factors in bone homeostasis. As such, mice over-expressing CCN3 (also named Nov) under the control of an osteoblast specific promoter (*Osteocalcin*) exhibited decreased trabecular bone volume and eventual osteopenia in abnormally high over expressed CCN3 [14]. This was confirmed by a study from Matsushita et al., which showed that mice expressing CCN3 under the control of *Col1a1* promoter developed osteopenia, while KO mice exhibited no skeletal malformations [15]. CCN3 is upregulated in early bone regeneration and acts as a negative regulator.

CYR61, a ligand for integrin receptors, induces BMP-2 expression and subsequent osteoblast differentiation via the ERK pathway [16]. The molecular interaction of BMPs and CYR61 is however still unclear. *CTGF* is an early response gene after stimulation with TGF- β or BMP-2 in chondrocytes. The function of CTGF has been associated with endochondral bone formation, affecting not only osteoblasts and chondrocytes differentiation, but also endothelial cell functions [17]. CTGF contains a Cystein Rich (CR) domain that has been shown to directly interact with both TGF- β_1 and BMP-4 [18]. Interestingly, in over-expression studies CTGF inhibited BMP-4-induced SMAD1 phosphorylation at low, but not high concentrations of BMP-4. On the contrary, CTGF over-expression potentiated the phosphorylation of SMAD2 in response to low doses of TGF- β_1 . In a later publication by Nguyen et al., CTGF was shown to physically interact and block BMP-7 activity in diabetic mice and renal cells [19]. Nevertheless, these authors did not describe any bone phenotype in the CTGF^{+/−} mice.

Importantly, the activity of CCNs has not always been associated to bone-related pathologies. For example, CCN6 expression has been inversely correlated with breast cancer progression. CCN6 was found to interfere with the activation of a BMP4-TAK1-p38 signaling pathway, thereby resulting in decreased cell invasion and metastasis [20]. Noteworthy, bone metastases are commonly associated to breast cancer. Another CCN member, CCN3, was found to be highly expressed in bone metastatic lesions of breast cancer patients. Furthermore, overexpression of CCN3 potentiates the ability of weakly metastatic breast cancer cell lines to colonize bone tissues [21]. Also in the context of malignancies, CCN3 expression is increased in osteosarcoma cell lines, including Saos-7 and OS7 [14]. All together, these publications exemplify how CCNs proteins interact, not only with BMPs, but with other TGF- β family members in different cellular contexts. Often, such crosstalk occurs out of the scope of bone homeostasis. We appreciate the comments from Sun. et al., and consider that a dedicated review on CCNs proteins in bone homeostasis would be a valuable contribution to the field.

Disclosure

The authors declare no conflict of interest.

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21 January 2016