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COMMENTARY

An intracrine mechanism regulates the relationship between fat and bone

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Increasing marrow fat infiltration is one of the hallmarks of age-related bone loss, which is also observed, although with a larger extension, in osteoporotic bones.[1] Mesenchymal stem cells (MSCs) obtained from osteoporotic bones have higher adipogenic capacity than MSCs obtained from normal donors,[2] thus suggesting that increased marrow adipogenesis is one of the pathophysiological mechanisms of osteoporosis.

Osteoporotic subjects have higher levels of marrow fat that are reduced after receiving osteoporosis treatment,[3] supporting the concept that 'fat loss is bone gain'[4] and vice versa. Recently, a new therapeutic approach to osteoporosis has been found to regulate marrow fat infiltration while inducing an increase in bone formation, an effect that corrected the osteoporotic phenotype observed in oophorectomized mice.[5]

Considering that the regulation of MSC differentiation is a new and effective therapeutic target in osteoporosis, an understanding of the molecular mechanisms that regulate MSC differentiation in bone is pivotal. Among these mechanisms, the balance between the osteogenic factor runt-related transcription factor 2 (RUNX2) and the adipogenic factor peroxisome proliferator-activated receptor gamma2 (PPARγ2) has been proposed as a key determinant of MSC differentiation.[6] Following this principle, inhibition of PPARγ both by gene knockdown[7] and pharmacologically[5] has shown an increase in bone formation and a significant reduction in marrow fat. However, there is evidence suggesting that other factors could be involved in the regulation of MSC differentiation either by controlling the expression and activity of RUNX2 and/or PPARγ, or by physically interacting with them, thus facilitating/blocking their nuclear translocation and regulating their DNA-binding capacity. Among these factors, transcriptional coactivator with PDZ-binding motif (TAZ),[8] Maf[9] and lamin A/C[10] have been reported as very promissory targets that may facilitate the development of new therapeutic strategies against bone and metabolic diseases.

In this interesting study, Liu *et al.*[11] have identified vascular endothelial growth factor A (VEGF) as another important factor that controls MSC differentiation by regulating RUNX2 and PPARγ2. Using a very well-designed experimental approach, the authors tested the role of VEGF in MSC differentiation. Interestingly, studies looking at the role of VEGF in MSC differentiation are scarce. Whereas no studies have been performed looking at the role of VEGF in adipogenesis, a study by Furumatsu *et al.*[12] reported a role of VEGF as an angiogenic factor in early osteoblastogenesis *in vitro*. This limited evidence allowed the authors of the present study to assess the role of VEGF in MSC differentiation in an animal model of conditionally targeted VEGF using an osterix-cre (Osx-cre) promoter. Using Osx, the authors were able to target the early phases of osteoblast differentiation. Mice carrying floxed alleles of VEGF and expressing Cre recombinase under the control of Osx-cre exhibited an interesting osteoporosis-like bone phenotype characterized by reduced bone density and an increased amount of marrow fat. This effect was clearly correlated with *ex vivo* cultures of bone marrow stromal cells (BMSCs), which showed a predominant osteoblastic differentiation at the expense of adipogenesis.

Very intriguingly, the authors report an intracrine mechanism in which VEGF produced by osteoblastic precursor cells regulates the balance between osteoblast and adipocyte. To reach this conclusion, the authors exposed mutant cell cultures to either recombinant VEGF or neutralizing antibodies against VEGF without observing any effect on the treated cells. The authors conclude that MSC differentiation involves the activation of an intracrine signaling loop for VEGF. Indeed, the absence of activation of any specific signaling downstream of activated VEGF2 indicates that this intracrine activation of VEGF is followed by a previously unknown VEGF-regulated mechanism.

To assess this new mechanism, the authors looked at alternative ways of interaction between VEGF and the transcription factors RUNX2 and PPARγ. Low levels of VEGF were associated with reduced RUNX2 protein and activity. In addition, suppression of adipocyte differentiation was independent of VEGF-dependent signaling mechanisms. The investigators then faced the challenge of identifying a common link between VEGF, RUNX2 and PPARγ, which would be

activated/repressed under osteogenic and adipogenic conditions. They found a very novel and interesting link by looking at the role of lamin A/C in this process. Lamin A/C is a protein of the inner nuclear envelope that has become an important research target in bone biology after recent reports that lamin A/C deficiency is associated with osteoporosis playing an important role in MSC differentiation both *in vitro* and *in vivo*.[10] Since lamin A/C closely interacts with RUNX2 and PPARγ in differentiating MSC, the authors tested their hypothesis of a reciprocal functional interaction between VEGF and lamin A/C that regulates the levels of expression and activity of RUNX2 and PPARγ, thus determining the differentiation of MSC into bone and fat respectively. The authors conclude that 'most, if not all, effects of lamin A on osteoblast differentiation may be mediated by the effects of lamin A on the level of VEGF in the cells'. Considering that lamin A/C is one of the 'guardians of the soma'[13] and interacts with multiple factors within the nucleus, this conclusion could be an overstatement that should be given its correct dimension once further studies are performed. Nevertheless, the interaction between lamin A/C and VEGF is intriguing and worthy of further exploration.

In summary, the authors of this interesting study have strongly demonstrated a role of VEGF in MSC differentiation in an intracrine manner. They also demonstrated that VEGF secreted by BMSC has a paracrine effect on osteoclast differentiation, a finding that also deserves further exploration. By reporting an interaction between lamin A/C and VEGF in differentiating MSC, the authors have taken a further step in the understanding of the role of these two important factors in bone biology. Although in their analysis the authors excluded some other important mediators of MSC differentiation such as Wnts and β-catenin, the fact that lamin A/C directly regulates these factors[14] indicates that further studies looking at the role of these proteins in the intracrine effect of VEGF on MSC differentiation are still required.

Conflict of Interest

The author declares no conflict of interest.

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