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Do adipogenic stromal cells undergo lineage plasticity in response to bone injury?

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Bone maintenance and repair are achieved through the maintenance and differentiation of rare skeletal stem cells (SSCs). Despite the development of numerous lineage tracing models and/or cell surface markers to label and track the *in vivo* SSCs, the *in vivo* identity and function of skeletal stem/progenitor cells remains largely elusive because these labeled populations are highly heterogeneous. In fact, endogenous SSCs are heterogeneous, and distinct SSC populations maintain different bone compartments.[1] Therefore, which and how different SSCs functionally orchestrate and form fracture-repairing osteoblasts are largely open questions.

In the hypothesis paper in this issue, Matsushita et al.[2] proposed the theory that mature skeletal cells (i.e., osteoblasts, adipocytes, and chondrocytes) can transform their identities into skeletal stem-cell-like cells in response to specific stimuli. Recently, Matsushita et al. developed an inducible Cxcl12-CreER model and found that Cxcl12-creER preferentially marks a quiescent $CXCL12^{+}LepR^{+}$ bone marrow stromal cells (BMSCs) known to encompass a subset of bone marrow SSCs. Interestingly, the majority of Cxcl12-$CreER^{+}$ BMSCs express adipocyte specific genes–specifically adiponectin (AdipoQ)–but they do not readily contribute to osteogenic differentiation. Thus, the authors termed these cells Cxcl12-$CreER^{+}$ adipogenic precursors. Upon injury however, Cxcl12-$CreER^{+}$ cells localize to injury sights, proliferate, and undergo osteogenic differentiation, suggesting that adipogenic Cxcl12-$CreER^{+}$ cells de-differentiate into SSC-like cells and re-differentiate (cell plasticity) into osteoblasts. This cellular plasticity in bone regeneration appears to be unique to Cxcl12-$CreER^{+}$ adipocyte precursors as opposed to Osterix-$CreER^{+}$ osteogenic cells in response to injury.[3] From these data, the authors hypothesize that Cxcl12-$CreER^{+}$ adipogenic precursors transform their identities into skeletal stem-cell-like cells and then become a source of new osteoblasts in response to injury. Although cell plasticity may occur in response to injury, multiple questions remain surrounding the identity and plasticity of Cxcl12-$CreER^{+}$ adipocyte precursors.

First, it is known that $CXCL12^{+}LepR^{+}$ BMSCs can be heterogeneous and contain multiple lineage progenitors. It is possible that Cxcl12-$CreER^{+}$ cells include quiescent osteogenic

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CONFLICT OF INTEREST

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progenitors that are inactive under physiological conditions but that become active after injury. It is also possible that a subset of Cxcl12-CreER$^+$ cells can be bipotential–adipogenic and osteogenic–progenitors, and preferentially respond to injury and differentiate into osteoblasts. Since Cxcl12-CreER can label both adipogenic and osteogenic progenitor cells, endogenous identification and tracking of these separate Cxcl12-CreER$^+$ populations is not possible using only the Cxcl12-CreER mouse model.

Second, it remains unclear whether Cxcl12-CreER$^+$ adipocyte precursors are the major source of new osteoblast/osteocytes during injury repair. Previous studies have revealed that the ablation of skeletal stem/progenitor cells with osteogenic lineage potential results in a significant hinderance in bone formation and repair.[4] On the other hand, ablation of bone marrow adipogenic lineage-restricted stromal cells using adiponectin (AdipoQ)-Cre with diphtheria toxin (DTR or DTA model systems) substantially increases bone formation and volume under homeostatic conditions.[5,6] Although under homeostatic conditions AdipoQ-Cre and AdipoQ-CreER lineage cells do not significantly contribute to osteogenic cells, it is currently unknown whether this remains true in response to injury. To truly determine whether adipogenic precursors can transdifferentiate and contribute to osteogenic cells during fracture healing, one would want to test this proposal using an inducible trigenic lineage reporter mouse model to label adipogenic progenitors (i.e., AdipoQ-CreER) in combination with an osteoblast-specific reporter such as osteocalcin (Ocn-GFP) or Col1a1 2.3 kb (Col2.3-GFP).

The hypothesis presented by Matsushita et al. explores a compelling new concept that mature skeletal cells can transform their identities into skeletal stem-cell-like cells in response to injury. However, more studies are required to test direct conversion of “mature” skeletal cells into stem-cell-like cells at single cell level. Additional lineage tracing models specific to adipogenic cells will need to be used and/or developed to answer these fundamental cell plasticity questions.

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