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LETTER TO THE EDITOR

Osteonecrosis of the jaw from bone anti-resorptives: impact of skeletal site-dependent mesenchymal stem cells

Dear Editor,

Recently, two Letters to the Editor addressed the use of bone mesenchymal (Gonzalvez-Garcia *et al*, 2012) and hematopoietic (Elad *et al*, 2012) stem cells in the management of osteonecrosis of the jaw (ONJ), a common complication of bone anti-resorptive therapies. Clearly, bisphosphonates and denosumab are highly efficacious in controlling dysregulated bone remodeling in osteoporosis, Paget's disease, multiple myeloma, and skeletal events of cancer metastasis; however, ONJ is still an unpredictable recalcitrant oral complication (Stopeck *et al*, 2010; Fusco *et al*, 2011). The underlying pathophysiological mechanism of ONJ is still unclear, so prevention of ONJ is challenging. Also, there is a paucity of randomized controlled clinical trials on ONJ therapies, so management algorithms are still empirical (Montebugnoli *et al*, 2007; Stockmann *et al*, 2010; Moretti *et al*, 2011). Both bisphosphonates and denosumab directly inhibit osteoclasts, but bisphosphonates inhibit osteoclastic activity also indirectly through osteoblasts and bone mesenchymal stem cells (BMSCs) both of which express the cell surface 'receptor activator of NFκB ligand' (RANKL) known to interact with RANK on osteoclast precursors (Nishida *et al*, 2005; Roelofs *et al*, 2006). As BMSCs can differentiate into multiple cell types including pre-osteoblasts and osteoblasts, some investigators have successfully transplanted BMSCs to treat ONJ both clinically and in animal studies (Kikuiri *et al*, 2010; Cella *et al*, 2011; Li *et al*, 2013). The function of BMSCs in these studies, although attributed to immune modulation, does not explain the jaw-specific character of ONJ.

Osteonecrosis of the jaw, induced by bone anti-resorptives, specifically targets the jaw unlike other forms of osteonecrosis in response to irradiation (osteoradionecrosis), infection (osteomyelitis), corticosteroid therapy (steroid-induced osteonecrosis), and alcoholism (alcohol-induced osteonecrosis) which can develop in non-oral skeletal sites (Akintoye and Hersh, 2012). It is still unclear why ONJ targets orofacial bones, so the successful use of BMSC transplants to treat ONJ draws attention to possible roles of jaw-specific characteristics of orofacial BMSCs (OFMSCs) in ONJ pathogenesis and its preference for oral bone. It has been shown that BMSCs are phenotypically and functionally site specific in terms of their survival, differentiation, and response to growth factors when compared with MSCs from axial/appendicular bones (Akintoye *et al*, 2006; Aghaloo *et al*, 2010). Moreover, OFMSCs are more responsive to bisphosphonate and irradiation relative to non-oral BMSCs (Stefanik *et al*, 2008; Damek-Poprawa *et al*, 2010). These jaw-specific characteristics of OFMSCs could shed some light on the preferential jaw localization of ONJ as well as high incidence of jaw osteoradionecrosis following head and neck cancer radiotherapy (Stefanik *et al*, 2008; Damek-Poprawa *et al*, 2010). Osteogenic differentiation and osteoclast recruiting abilities of BMSCs are necessary for bone homeostasis and repair; therefore, it is possible that anti-resorptives such as bisphosphonate and denosumab apparently uncouple osteoblast–osteoclast balance in a skeletal site-specific pattern to favor the onset of ONJ. The elusiveness of mechanisms that underlie the jaw-specific nature of ONJ has made prevention and complete cure of ONJ challenging without invasive surgery. Further understanding of OFMSC functions and cellular interactions in ONJ could shed more light on its pathogenesis and promote the development of potential preventive therapies.

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