Clin Orthop Relat Res (2015) 473:1812–1814 / DOI 10.1007/s11999-015-4237-6

Clinical Orthopaedics and Related Research®
A Publication of The Association of Bone and Joint Surgeons®

Published online: 7 March 2015

CORR Insights

CORR Insights®: Development of a Mouse Model of Ischemic Osteonecrosis

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Where Are We Now?

Osteonecrosis is a persistent and confounding orthopaedic pathology that can arise in any bone; common causes include compromised vasculature, exposure to radiation therapy, treatment with corticosteroids, or bisphosphonates treatment [2, 5, 6]. In the appendicular skeleton, osteonecrosis is managed surgically using total joint implants (among other approaches) while osteonecrosis of the jaw is treated with prophylactic antibiotic rinses followed by surgical resection when disease progression leads to substantial pain [1, 3]. Researchers have developed animal models that correspond to the different clinical presentations of osteonecrosis [2]. These models include trauma-induced osteonecrosis, which was modeled through surgical ligation of local blood vessels or femoral dislocation, while corticosteroid-induced osteonecrosis has been modeled through the administration of high doses of methylprednisone or dexamethasone.

Other models have tried to replicate the condition by treating animals with ethanol directly injected into the bone marrow, intravenous injections of lipopolysaccharides, or through the injection of horse serum to stimulate a severe immune reaction. Physical methods have also been employed to induce osteonecrosis, including cryogenic or thermal insult. Most of these experimental models result in a high rate of animal mortality, which limits their utility [2]. Additionally, the variability in cell death and the time course of recovery vary across these animal models [1], further complicating our ability to interpret them in the context of the human disease they seek to replicate. In the current study, Kamiya and colleagues cauterized four blood vessels (the popliteal and three genicular vessels) around the distal femur, creating a model of avascular osteonecrosis, and, importantly, doing so without resulting in the premature death of the animals.

Where Do We Need To Go?

Motivated by the need for better prophylactic therapies prior to total joint surgery or resection of the necrotic bone, researchers are now in the process of developing new osteonecrosis models. It is in this context that the work presented by Kamiya and colleagues represents an important advancement in the development of a mouse model of trauma-induced osteonecrosis. However, these

This CORR Insights® *is a commentary on the article* "Development of a Mouse Model of Ischemic Osteonecrosis" *by Kamiya and colleagues available at:* DOI: 10.1007/s11999-015-4172-6.

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This *CORR* Insights® comment refers to the article available at DOI: 10.1007/s11999-015-4172-6.

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experiments need to be repeated in an adult mouse model in order to confirm that the proposed surgical approach creates an ischemic event that results in pathology that is independent of the process of active longitudinal bone growth. It is impossible to predict whether the proposed ischemic injury in adult mice would result in an osteonecrotic phenotype similar to that observed in growing mice. Nevertheless, an appropriately designed aging study should be able to determine if the surgically induced ischemia results in a more or less severe osteonecrotic pathology in adult mice. Additional late time points beyond 6 weeks need to be investigated along with an examination of the mechanical properties of the bone following the induction of the ischemic injury. Kamiya and colleagues show that increased cell death (terminal deoxynucleotidyl transferase dUTP nick end labeling staining and the numbers of empty lacunae) coupled with suppressed measures of bone formation and bone reabsorption (the numbers of osteoblasts and osteoclasts) at 6 weeks are similar to control values for these parameters, suggesting that the osteonecrosis is transient. Extending these observations to include later time points and mechanical outcomes in both growing and adult mice will be critical to developing novel prophylactic therapies for osteonecrosis.

How Do We Get There?

Engineering pharmaceutical interventions or cell-based therapies for the treatment of osteonecrosis will require the development of detailed genetic and functional analysis of the mesenchymal and myeloid cell lineages contained within the bone marrow niche. In particular, researchers should identify the ischemic effects in mesenchymal lineage cells, which include mesenchymal stem cells, osteoblasts, osteocytes, and adipocytes. Researchers must also investigate the effects of ischemia in monocytes and osteoclasts, which are part of the myeloid lineage, because Mesenchymal and myeloid differentiation are physiologically coupled with the process of bone formation and bone reabsorption. In this context, an ischemic injury would potentially disrupt the mesenchymal or myeloid differentiation resulting in an altered numbers of osteoprogenitors or monocyte progenitors. This can only be accomplished by using flow cytometry to assay cell death in parallel with a lineage analysis. Similarly, in vitro functional assays could be employed to assay whether ischemic mesenchymal stem cells retain the ability to commit to the osteoblast lineage and participate in bone formation or monocytes remain able to differentiate into osteoclasts that reabsorb bone. The process of mesenchymal stem cell differentiation into osteoblasts and monocytes differentiation to become osteoclasts is required for sustained bone formation, which is lost following an ischemic event [4] and is consistent with the measurements of decreased bone volume in the osteonecrotic mice made by Kamiya and colleagues. The postischemic process of bone formation, however, represents an appealing therapeutic target that should be further explored. The mouse model proposed by Kamiya and colleagues would be an ideal system to conduct the proposed experiments, potentially leading to the development of novel therapies.

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