

# Heparanase-1 facilitates bone remodeling on bone defect animal model with optimal dosage and treatment duration

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Bone is a well model to investigate regeneration or tissue engineering. Bone processes regeneration to remodel, while bone defect occurs, such as trauma, bone resection due to tumor surgery, pathological bone loss, or osteoporosis.<sup>1</sup> Under control by numerous and critical factors, bone remodeling procedure is affected by disease risks to nonunion, such as diabetes, obesity, or inflammatory arthritis. Bone defect is a challenge for orthopedic surgeons due to the limitation of bone grafting treatments, such as inadequate amount of bone materials or lacking of donor.<sup>2</sup> Tissue engineering with the development of various types of biomaterial scaffolds is a potential way for assist bone regeneration.

The bone defect animal model is well established for pre-clinical testing of various biomaterials, different compounds, or methods that improve bone remodeling<sup>1,3</sup> before using on human beings. The suitable animal model should be established according to the study design and the bearing capacity of the treatment bone during the experiments.<sup>4</sup> Different from tumor model that should be select suitable species for tumor cell types and inject into individual site for each tumor types,<sup>5</sup> the selection criteria of bone defect model depend on animal availability, acceptability to society, tolerance to captivity, and the physiological and pathophysiological analogies in comparison to humans.<sup>6</sup>

The most commonly used animal models for bone defect are rabbit, rodent, or pigs according to the availability. The rodent model is the most commonly used model, and it is easy to handle. However, the limitation is the small size and thin long bones that hard to create bone defect on long bone with fixation compare to other large animals. Most bone defect models on rodent create the defect location on skull instead of long bones.<sup>7,8</sup> Chiu et al<sup>9</sup> created bone defect on mouse distal femur with carefully take over the risk of leg fixation and broken from the defect site was a well-done mouse bone defect model for further experiments. With the assistance of image evidence, the remodeling on bone regeneration can be detected and evaluated under different treatments.

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Conflicts of interest: The authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

Journal of Chinese Medical Association. (2020) 83: 799-800.

Received June 8, 2020; accepted June 9, 2020.

doi: 10.1097/JCMA.0000000000000391.

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Heparanase is an endo- $\beta$ -D-glucuronidase that first isolated from human placenta and also from platelet. This enzyme is specifically cleave heparan sulfate proteoglycans that remodel extracellular matrix.<sup>10-12</sup> Being noticed to increase in various types of cancers, the expression of heparanase-1 may relate to the malignancy and poor prognosis of tumor and plays important role on tumor angiogenesis and metastasis.<sup>13</sup>

In osteogenesis, the overexpression of heparanase-1 was reported to benefit for bone healing by increasing bone mass and enhancing blood flow or angiogenesis in bone defect site.<sup>12</sup> However, the opposite reports were announced that heparanase showed suppression effect of osteogenesis.<sup>14</sup>

In the March issue of the Journal, Chiu et al<sup>9</sup> established a well bone defect model on mice for bone healing investigation and tried different doses of heparanase recombinant protein for osteogenesis evaluation. The result showed that low dose enhanced while high dose suppressed the remodeling of bone defect. The results indicated that the optimal dosage, route, and application period were required to prevent the occurrence of potential adverse effects in the event of overdose.<sup>9</sup> The findings of this study gave a new insight that though heparanase has the effect to improve bone regeneration, however, the critical dosage is important to be considered for optimal treatment. The further mechanism and potential signaling pathway needs more investigations about the effect of heparanase on osteogenesis.

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