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Stem cell therapy: is there a future for reconstruction of large bone defects?

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ABSTRACT

Large bone defects caused by fracture, non-union and bone tumor excision has been a major clinical problem. Autogenous bone grafting and Ilizarov method are commonly performed to treat them. However, bone grafting has limitation in volume of available bone, and Ilizarov method requires long periods of time to treat. Accordingly, there is need for stem cell therapy for bone repair and/or regeneration. Mesenchymal stem cells (MSCs) hold the ability to differentiate into osteoblasts and are available from a wide variety of sources. The route of "intramembranous ossification (direct bone formation)" by transplantation of undifferentiated MSCs has been tested but it did not demonstrate the success initially envisaged. Recently another approach has been examined being the transplantation of "MSCs pre-differentiated in vitro into cartilage-forming chondrocytes" into bone defect, in brief, representing the route of "endochondral ossification (indirect bone formation)". It's a paradigm shift of Stem Cell Therapy for bone regeneration. We have already reported on the healing of large femur defects in rats by transplantation of "MSCs pre-differentiated in vitro into cartilage-forming chondrocytes". We named the cells as Mesenchymal Stem Cell-Derived Chondrocytes (MSC-DCs). The success of reconstruction of a massive 15-mm femur defect (approximately 50% of the rat femur shaft length) provides a sound foundation for potential clinical application of this technique. We believe our results may offer a new avenue of reconstruction of large bone defect, especially in view of the their high reproducibility and the excellent biomechanical strength of repaired femora.

Why bone tissue engineering with stem cells?

Bone tissue engineering with mesenchymal stem cells (MSC) has been one of the most important research areas showing a potential for the treatment of the large bone defects [1–3].

Current surgical strategies for large bone defects

The reconstruction or regeneration of large critical size bone defects, resulting from bone tumor excision, fractures with critical sized defect, and nonunion, is still a major clinical problems. A critical-sized bone defect (CSBD) is a defect that will not heal spontaneously despite surgical stabilization and will require further intervention to achieve union [4]. The CSBD varies according to both anatomical location and degree of soft tissue injury, but as a general rule, defects that involve a length superior than 2 cm and over half of the circumference of the affected bone are defined as CSBD [4].

Surgical treatment options available for reconstruction of CSBD include vascularized or non-vascularized autogenous bone graft (Fig. 1) and the Ilizarov distraction osteogenesis technique (Fig. 2) [5]. These two current strategies show relatively satisfactory results. However, they include unavoidable problems and as such bone tissue engineering technology offers other alternative treatment options.

Unavoidable problems of current strategy

Present surgical procedures, such as the Masquelet technique and Ilizarov technique, can reconstruct large bone defects, but the volume of harvested bone required to fill the defect and the long periods of time that the patient has to undergo treatment are two of the limitations of the techniques. Another option that would provide "incredible volume" of the newly formed bone, and "incredible speed" of the ossification and consolidation processes would be desirable. A possible option providing such an outcome would be 'Bone tissue engineering with stem cells'.

Two ossification pathways

There are two ossification pathways: intramembranous ossification and endochondral ossification. Both types of

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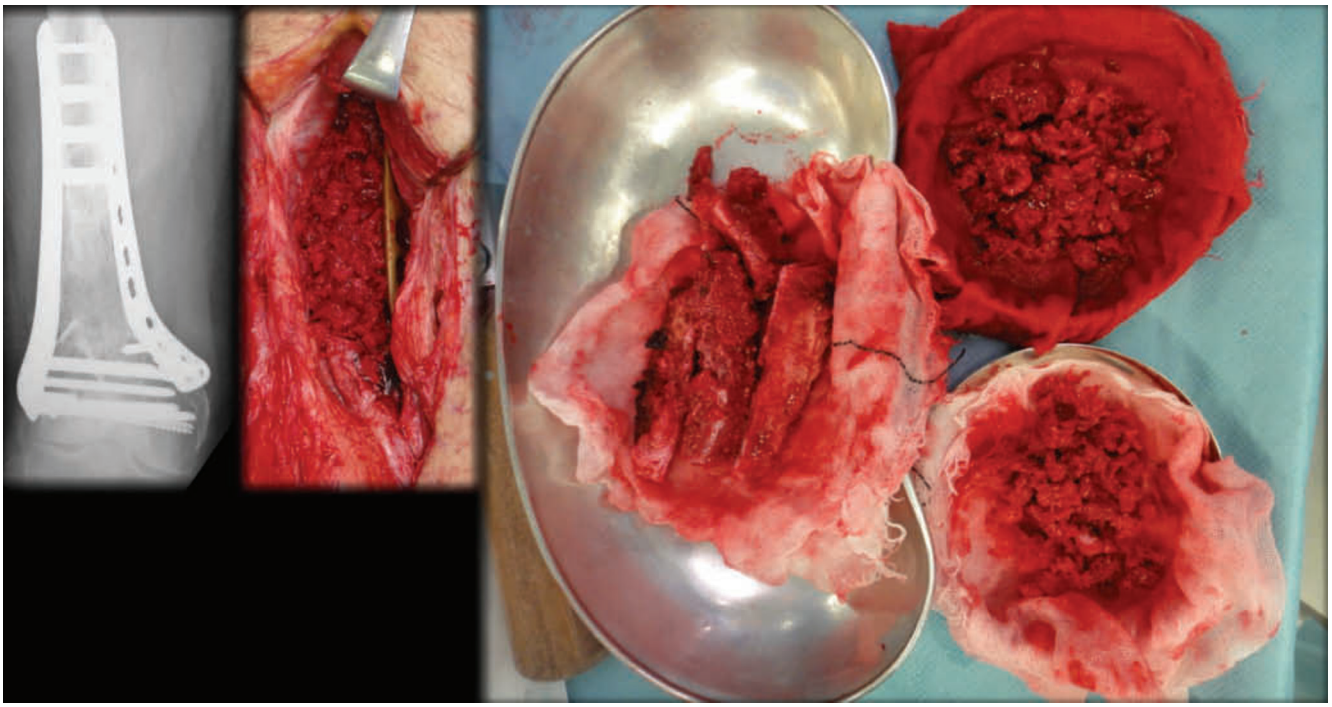

Fig. 1.Masquelet's induced membrane reconstructive technique. A lot of cancellous bone needed for reconstruction.

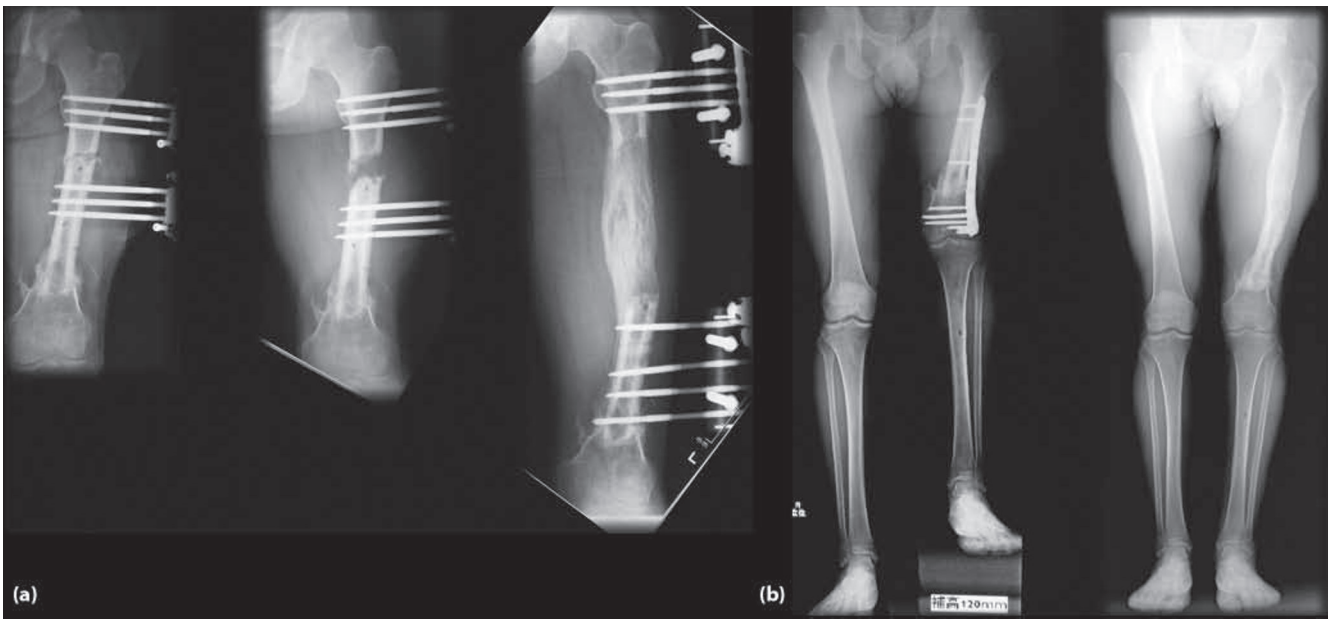

Fig. 2. Distraction osteogenesis (Ilizarov technique) for reconstruction of limb length discrepancy.

ossification involve an initial condensation of mesenchymal stem cells and the eventual formation of calcified bone [6]. However, intramembranous bone formation accomplishes this directly, whereas endochondral ossification incorporates an intermediate step in which a cartilaginous template regulates the growth and patterning of the developing skeletal element [6].

Intramembranous ossification

Intramembranous ossification gives rise to the flat bones that comprise the cranium. Intramembranous ossification follows four steps. (1) Undifferentiated MSCs differentiated into osteoprogenitor cells to group clusters, and ossification centers form. (2) Secreted osteoid traps osteoblasts, which then become osteocytes. (3) Trabecular matrix and periosteum form. (4) Compact bone develops superficial to the trabecular bone, and crowded blood vessels condense into red marrow.

Endochondral ossification

Endochondral ossification gives rise to long bones that comprise the appendicular skeleton, facial bones, vertebrae amongst others Endochondral ossification follows five steps. (1) Undifferentiated MSCs differentiate into chondroblast. (2) Chondroblast secretes matrix to form the cartilage template of the future bony skeleton and the perichondrium forms around the cartilage template. (3) Capillaries penetrate cartilage and perichondrium transforms into periosteal bone