Mesenchymal Stromal Cells: A Novel Treatment Option for Steroid-Induced Avascular Osteonecrosis

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Key words: mesenchymal stromal cells, avascular osteonecrosis, core compression

Abstract
Mesenchymal stromal cells are multipotent cells capable of tissue repair and immune modulation. They are primarily found in bone marrow, but are also present in other tissues of mesenchymal origin, such as fatty tissue, muscle, tendons, etc. MSC can easily be obtained by bone marrow aspiration, showing a rapid expansion in vitro. New protocols enable cell culture without the use of animal-derived sera and artificial growth factors. Avascular necroses of the bone may have different causes. AVN in autoimmune and hematological diseases show a strong association with corticosteroid treatment, which is often unavoidable in severe cases. Until recently, core decompression of the affected osseous area was the standard approach. Because of their differentiation properties, easy accessibility and proliferative capacity, autologous MSCs could potentially complement AVN treatment by adding fresh “osteogenic cells” to the healing process.

MSC are multipotent and have osteogenic potential

The homing mechanisms of MSC are poorly understood. Based on chemokine/chemokine-receptor interactions and adhesion molecules, MSC are potentially capable of finding the site of injury and, given intravenously, of restoring damaged tissue on site due to their plasticity and/or paracrine properties [10]. However, the efficiency of this process is very variable and depends on...
the diseased tissue. This problem in clinical application can be overcome by local use in certain settings, in particular for unifocal lesions, such as osteonecrosis. MSC are able to form new osseous tissue not only in vitro but also in vivo, thus giving hope for restoration of damaged bone [1-3,11,12].

Steroid-induced avascular necrosis

Most reports on AVN in the literature refer either to idiopathic conditions or chemotherapy regimens for hematological/oncological diseases. The most commonly affected sites are the femoral head and the knee. In those cases steroids seem to play a major role in disease onset and progression. The particular mechanism of bone necrosis induction is not known. Decrease in local blood flow and probably endothelial cell dysfunction, as well as deteriorated local blood coagulation and thrombus formation could play a role in bone destruction [13,14]. All the latter conditions frequently accompany systemic lupus erythematosus, the most common autoimmune disease associated with AVN when treated with steroids, and could also follow high dose steroid therapeutic regimens for hematological/oncological conditions [15-17].

MSCs and core decompression to treat AVN

The standard therapy for AVN is the core decompression technique [18]. The procedure shows a satisfactory effect in early-stage AVN. Unfortunately, in many cases the condition is recognized only at a more advanced stage, when little or no effect of core decompression on bone reconstitution can be expected, necessitating surgical intervention with total hip replacement [17].

The osteogenic potential of bone marrow-derived MSC was shown to be sufficient in bone repair in animal models and in humans [11,12,19]. Because of their comparatively small number in bone marrow aspirates [Figure 1], in vitro expansion before application during core decompression would have a favourable effect on the final outcome, facilitating reconstitution of bone integrity by providing more “new material” for bone formation. Novel protocols enable the process without usage of animal-derived sera and growth factors, thus making MSC application more secure [20].

**Figure 1.** Fluorescence-activated cell sorter analysis of bone marrow. Only a small percentage (typically 0.01-0.1%) conforms phenotypically to MSC. [A] Bone marrow cells double-stained for CD73 and CD105. [B] MSC after 3 weeks of culture in animal protein-free conditions. [C] Immune phenotype of culture-expanded MSC (circles in top panel = positive CD expression; circles in bottom panel = no CD expression).

**Combination therapy with core decompression and MSC may improve AVN outcome**

Conclusions

AVN could arise after treatment with steroids in autoimmune and hematological/oncological conditions. Core decompression is a promising procedure in recently acquired AVN, but has little or no effect on progressed stages. New therapeutic strategies are needed to treat more advanced cases.

References

9. Tse WT, Pendleton JD, Beyer WM, Egaikia MC, Guinan EC.


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**Capsule**

**Potent stem cells**

By introducing defined transcription factors into mouse and human fibroblasts, stem cell researchers have demonstrated that differentiated cells can be reprogrammed to a pluripotent state, in which the resultant iPS (induced pluripotent stem) cells display properties similar to those of embryonic stem cells. This work holds great promise for therapy; however, a number of serious obstacles remain. For example, some reprogramming protocols involve the introduction of the c-Myc transcription factor, which has been shown to increase tumorigenicity in mice. Nakagawa et al. describe a modified method for generating mouse and human iPS cells without using c-Myc. This altered protocol shows greater specific induction to iPS cells, albeit at lower efficiency and at a slower rate than when c-Myc is added.

*Nat Biotechnol* 2008;26:101

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**Capsule**

**Chromosome X Inactivation**

One of the two X chromosomes in mammalian females is randomly inactivated early in development to match the single active X chromosome of males. This process is regulated through the X-inactivation center (Xic). The two Xics interact in trans at the beginning of X-inactivation, presumably to allow reciprocal activation/inactivation. So far, single copies of elements from the Xic have not been able to recapitulate X inactivation, suggesting that additional elements are necessary. Augui et al. found that a region ~200 kilobases upstream of the Xic – the X-pairing-region (Xpr) – is sufficient in a single copy to allow a transient interaction between the two Xics at a time before the beginning of X inactivation. This pairing is cell cycle dependent, can occur from an ectopic location, and may activate the expression of Xist, a non-coding RNA that coats the inactive X chromosome.

*Science* 2007;318:1632

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