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Review Article

Cell therapy for avascular osteonecrosis of femoral head

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Abstract

Avascular osteonecrosis of femoral head causes severe musculoskeletal disability. There is not standard treatment to cure avascular osteonecrosis. Recently, cell therapy using bone marrow stromal cells has begun for this disease.

Key words; avaslucar osteonecrosis, cell transplantation, mesenchymal stem cells

Introduction

Avascular osteonecrosis of the femoral head occurs in patients in their 20s to 40s, causing severe musculoskeletal disability. This disease is idiopathic and is secondary to diseases and treatments, such as dislocation and fracture of the femoral head, sickle cell anemia, high-dose steroid therapy, and alcohol. High-dose steroid therapy particularly causes osteonecrosis in a dose dependent manner[1] which causes severe problems clinical. If insufficient treatment is administered, the hip joint, especially the femoral head, will collapse (Figure 1). Joint replacement surgery is rescue treatment for such collapse, however, younger patients will require multiple revision surgeries. For younger patients, joint salvage procedures seem to promise a better prognosis, but there are many difficult problems for treating this disease. Recently, cell therapy using bone marrow stromal cells has begun for this disease.

Number of bone marrow stromal cells decrease around osteonecrotic lesion

A necrotic lesion lacks viable cells, because of the interruption of blood flow. The number of bone marrow stromal cells is decreased in steroid-induced osteonecrosis, not only in the necrotic lesion, but also its surroundings [2, 3]. The osteogenic differentiation ability of mesenchymal stem cells is also altered in osteonecrosis patients[4]. The adipogenic ability of bone marrow cells is elevated in steroid-induced osteonecrosis patients2),[5]. These results suggest that supplying osteogenic cells to necrotic lesions is necessary to cure osteonecrosis.

Mesenchymal stem cells as cell therapy

Mesenchymal stem cells (MSCs) represent a stem cell population in adult tissues that can

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be isolated and expanded in extra vivo culture, and differentiate into mesenchymal and non-mesenchymal tissues[6]. It is reported that the transplantation of MSCs to an environment enabling them to differentiate into bone-lineage cells, is a promising procedure to treat several pathological osseous conditions, including avascular necrosis of bone[7, 8]. A simple procedure to supply such cells may be the core decompression technique[9] the main purpose of which is to reduce pressure on necrotic lesions. Some cells may be induced to necrotic lesions from a penetrating hole. This core decompression technique is useful for early stage osteonecrosis[9].

Concentrated bone marrow transplantation therapy for osteonecrosis

Although MSCs exist in adults and are rich in bone marrow, the fraction of MSC is too small[10]. Hernigue found that bone formation activity depended on the fraction of MSC in bone marrow [11]. He therefore considered that concentrated bone marrow is needed[11]. He concentrated MSC from 150ml bone marrow to 30ml by centrifugatiion[12]. Combined with core decompression surgery, he transplanted this concentrated bone marrow in to the necrotic lesion. As a result, 59% of cases became radiographically stable and 8% were completely cured[12]. Gangji investigated this procedure in a prospective controlled double-blind study, and concluded it to be useful[13,14]. Concentrated bone marrow transplantation can be combined with surgery, such as osteotomy and artificial bone graft[15]. The advantage of concentrated bone marrow transplantation therapy is its low cost, easy technique and low risk for infection or transformation (Table 1). This low-risk cell therapy may boost the effect of existing therapy.

Extra vivo cultured MSC transplantation

The fraction of MSCs in bone marrow differs among individuals and the technique of aspiration. Hernigou pointed out this issue to explain the different results between each case[12] (Table 1). To reduce the difference between individuals and techniques, extra vivo culture is useful. About 107 mononuclear cells can be prepared from 10ml bone marrow during two-week culture[15], suggesting that a huge number of MSCs can be prepared by extra vivo culture. Kawate cultured MSCs with beta-tricalcium phosphate (β-TCP) and transplanted with free vascularlized fibula for two cases of severe osteonecrosis[16]. Muller cultured MSCs under low oxygen tension[17]. Differentiation to bone and revascularization are expected under low oxygen conditiona[17]. Not only for increasing cell numbers, tissue engineering and manipulation may be a benefit of extra vivo culture, however, the cost of extra vivo culture is too high. In Japan, the construction of a cell processing center for extra vivo culture costs $ 30 billion, with $ 1 billion for maintenance per year. Huge expansion may have a risk of cell transformation[18] and genome instability[15]. Strict quality control is needed for extra vivo culture.

Figure 1

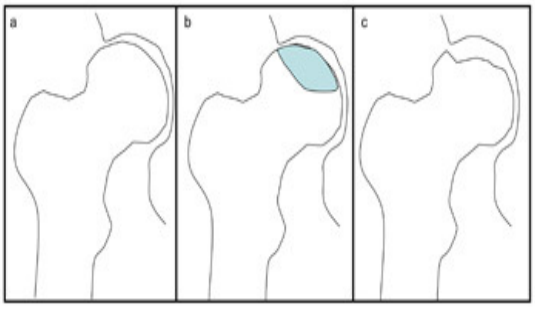

Figure 1. The femoral head collapses quickly in avascular osteonecrosis disease. a: Normal. b: Onset of osteoncerosis. Gray zone: necrotic area. c: 12 months later.

Table 1

Table 1. Comparison of concentrated technique and extra vivo culture

	Concentration technique	Extra vivo culture
Cell number	Limited	Infinity
Differences among individuals	Exist	Corrected
Differences among techniques	Exist	Corrected
Tissue engineering	Impossible	Possible
Cell manipulation	Impossible	Possible
Technique	Easy	Complicated
Cost	Inexpensive	Expensive
Risk of viral infection	Low	Exist (if not cultured in CPC)
Risk of transformation	Low	?

CPC: Cell Processing Center

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Conclusion

Bone marrow stromal cell transplantation is a promising therapy for osteonecrosis of the femoral head, but there remain several problems; for example, cost, technique, standardization of procedures, and indication. Further investigation and research are needed to cure this intractable disease.

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