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REVIEW

Cytotherapy of osteonecrosis of the femoral head: a mini review

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Abstract The pathogenesis and aetiology of nontraumatic osteonecrosis of the femoral head has not been revealed completely. However, with advances in stem cell research and regenerative medicine, it is believed that the onset of osteonecrosis of the femoral head probably has a cellular origin, and the possible therapy of osteonecrosis of the femoral head based on cytotherapy has great potential. In this review, the aetiology of osteonecrosis of the femoral head, animal experiments and clinical applications of cytotherapy are summarized and analysed. Current problems and future challenges are discussed.

Introduction

Since the pathogenesis and aetiology of nontraumatic osteonecrosis of the femoral head (ONFH) has not been revealed completely, current treatment of ONFH simply focuses on preventing irreversible complications, namely, biomechanical collapse of the femoral head and osteoarthritis of the hip joint [1], although tremendous progress has been achieved in all aspects [2–6]. In Free vascularised fibular grafting, for example, the aim of the operation is to gain complete decompression of the medullary cavity, remove necrotic bone, provide mechanical support and vital cellular replacement [7–9].

With the development of stem cell research and regenerative medicine, it is believed that the onset of ONFH originates at a cellular level [10, 11], and that therapy based on cytotherapy has great potential [12–14]. In this review, the aetiology of ONFH, animal experiments and clinical applications of cytotherapy are summarised and analysed. Current problems and future challenges are discussed.

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Cell research on the aetiology of ONFH: the foundation of cytotherapy

Although the aetiology of ONFH has not been revealed, the hypothesis that the disease has a cellular origin has been formed gradually [15, 16]. As is known, stem cells and progenitors hold the ability of inducible and multiple differentiation. Any issues that decrease the number or alter the function of differentiation and multiplication of progenitor cells can lead to imbalance between osteocyte formation and apoptosis or necrosis, and as a result ONFH will develop if the imbalance cannot be restored [4, 11].

Lee et al. [17] collected the marrow of proximal femurs from two patients undergoing total hip arthroplasty (THA) surgery for ONFH and isolated and culture-expanded mesenchymal stem cells (MSCs). They found that these cells were homogeneously positive for β1-integrin and held the capacity of multipotential differentiation to chondrocytes or osteocytes. The authors concluded that these findings implied that direct replacement therapy using MSCs from in situ marrow might be possible in the future. Hernigou et al. [18] evaluated bone-marrow activity in the proximal femur of patients with corticosteroid-induced ONFH and compared it with that of patients with ONFH related to sickle-cell disease and with a control group without ONFH. They found a decrease in the number of fibroblast colony-forming units (FCFUs) outside the area of ONFH of patients with a corticosteroid induction in

comparison with the other two groups and suggested that glucocorticosteroids might have an adverse effect on the progenitors of bone. Similarly, Lee et al. [19] investigated the osteogenic and adipogenic differentiation ability of MSCs in patients with nontraumatic ONFH according to the risk factors. They found that the osteogenic differentiation ability of MSCs in patients with alcohol-induced and idiopathic ONFH was significantly reduced in comparison with that of hip osteoarthritis (OA) patients, while the osteogenic differentiation ability in patients with steroid-induced ONFH was increased. The adipogenic differentiation ability of MSCs was not changed in ONFH in comparison with osteoarthritis patients. The authors concluded that altered osteogenic differentiation ability of MSCs was related to ONFH. In another similar study, Suh et al. [20] analysed the differentiation ability of MSCs from proximal femur in 33 patients with alcohol-related ONFH, and they suggested that the down-regulation osteogenic ability could result in the onset of ONFH. Upstream cells from proximal femur have biological alterations which are due to the adverse effects of variant factors, and although different methods were used, suggest that ONFH might result from changes in peogenitor cells.

Interestingly, Feng et al. [21] compared the number of endothelial progenitor cells (EPCs) in the peripheral circulation in 54 patients with nontraumatic ONFH and healthy people. It was shown that EPCs in patients with ONFH were obviously reduced, which might lead to a malfunction of angiogenesis, and ultimately induce the start of ONFH. Although angiogenic and osteogenic functions of progenitors in ONFH are not well elucidated, several factors have been found to interact in the angiogenesis–osteogenesis coupling, and further exploration should be centred on the exact pathogenesis of the linked complex [22–25].

In vivo findings in animal models: preclinical research

Encouraging results concerning the cellular origin of ONFH have triggered great interest into further research on the cytotherapy of disease. If nontraumatic ONFH is highly related to the alterations of MSCs or other progenitor cells osteogenic differentiation of progenitor cells could be induced in the femoral head, and stem cells therapy could prove to be effective in animal models with ONFH.

Asada et al. [26] have evaluated injection of bone marrow cells (BMCs) for the prevention of corticosteroid-induced ONFH. The incidence of ONFH in rabbits treated in control groups [methylpredisolone (MPSL) alone, 20mg/kg; MPSL + needling; MPSL + saline] was around 70%, while the incidence was 0% in MPSL and BMC injection group. There were fewer BMCs in the G_1 phase in the MPSL+BMC injection group in comparison with the control groups. The authors concluded that direct injection of autologous BMCs into femurs could prevent corticosteroid-induced ONFH following treatment with high-dose, short-term steroids. Yan et al. [27] employed MSCs to treat ONFH and investigated the survival and differentiation status. Their research demonstrated that the transplanted MSCs could survive, proliferate and differentiate into osteoblasts directly, which could accelerate the repair process. Although the animal model was induced traumatically in the experiment, the fate of MSCs transplanted to the femoral head should be similar to that in nontraumatic ONFH.

Treatment of ONFH based on cytotherapy: clinical reports

Hernigou et al. have published clinical data on their experience. They treated 189 hips in 116 patients with autologous BMCs and had a follow-up of five to ten years. Satisfactory results could be achieved in the majority according to the improvement of Harris hip score, radiographic assessment and refusal of THA. The prognosis was not only highly related to the stage of disease, but also to the progenitor cells transplanted. When patients were operated on before collapse and received a greater number of BMC injections, a better outcome could be expected [28]. In 2008, Hernigou et al. [29] retrospectively analysed 534 hips in 342 patients with ONFH treated with autologous BMC transplantation. The results were really encouraging. They showed that the volume of necrosis would decrease from 26 cm^3 to 12 cm^3 in 371 patients with an average follow-up of 12 years. There were only 94 patients who progressed to THA. The author concluded that the best indication for cytotherapy of ONFH was in the pre-collapse stage when the hip was symptomatic; and in some patients with Steinberg stage III, ONFH successful outcome could be obtained in five to ten years. Hernigou et al. also published details of clinical cytotherapy of ONFH with autologous BMC injection [30]. In another report from Gangji et al. [31], two patients with ONFH were treated by injection of bone marrow stromal cells (BMSCs). Osteoprogenitors and osteoblasts from bone marrow were separated and expanded in vitro, and injected into the necrotic zone after differentiation under autologous conditions. Pain reduction, necrotic lesion decrease and functional improvement was recorded in the early period, and only minor side-effects were found. Although these preliminary reports are poorly controlled and need further confirmation, the early signs are encouraging. Combined with previous animal-model research, it seems that the treatment by cell transplantation and replacement could improve the armamentarium for ONFH.

Hybrid of cytotherapy and conventional/novel therapeutics on ONFH

Cytotherapy of ONFH could be also combined with conventional therapy, including core decompression and autologous bone grafting. Wang et al. [32] treated ONFH by core decompression and implantation of concentrated autologous bone marrow containing mononuclear cells. The marrow aspirated from the iliac crest underwent concentration and the product of concentrated mononuclear cells were implanted in 59 hips in 45 patients with ONFH of ARCO stages I–IIIA. Harris hip score was improved from 71 to 83, and only 11.9% of the treated patients progressed to need THA in an average follow-up of 27.6 months. The treatment result was enhanced by cell concentration resulting in decreased volume of injected cells which would not increase intramedullary pressure. Kang et al. [33] reported the results of autoiliac cancellous bone combined with implantation of autologous bone marrow cells for ONFH, and showed good clinical results in a short-term follow-up of 32 months average. More recently, encouraging results came from the clinical use of growth and differentiation factors [34–36]. Xiao et al. [37] evaluated the effect of autologous BMSC seeded bio-derived bone materials combined with recombinant human bone morphologic protein-2 (rhBMP-2) in repairing defect of ONFH in the rabbit. They found that collapse could be prevented and new bone formation could be generated. These novel treatment protocols conform well to the concept of in vivo tissue engineering, which is also based on three essential factors: seed cells, various scaffolds and cytokines in an intracorporal environment.

Cytotherapy of ONFH: challenges and prospects

Although great advances have been achieved in the basic and clinical research of nontraumatic ONFH from cellular origin, it is premature to conclude which one is the primary trigger: whether the alteration of progenitors in number and nature leads to the initiation of ONFH, or the idiopathic ONFH induces the biological changes of progenitors. If the first hypothesis is true, the treatment of ONFH based on cytotherapy will be all in vain; however, if the second applies, cytotherapy will bring a fundamental revolution in the treatment of ONFH. To our knowledge from the review of the latest literature, it seems that stem cells inducing ONFH is most likely. Although we can not regard nontraumatic ONFH as a stem-cell disease, the detailed relationship between stem cells and ONFH has attracted more attention than ever. However, it should be noted that the biological relationship between BMSCs and MSCs is indistinct [38, 39], and these progenitors might be adversely affected by the systemic medications and individual pathological states; distinctions between different risk factors, type of cells used and design of clinical methodologies can not be simply mixed for comparison. Furthermore, it is proven that glucocorticoid has a negative effect on progenitor cells in vitro and in vivo [40]. The patient with ONFH induced by corticoid has poorer quality of transplanted cells *via* autograft; therefore, allogenic cells might be used as in marrow transplantation in leukemia. Meanwhile, the majority of preclinical and clinical reports are from direct injection of cells to the necrotic zone. There is a lack of direct support for a systemic therapy that can reverse the primary pathogenesis of ONFH.

Because the cases of ONFH selected for cytotherapy are mostly in pre-collapse stage, and ethical limitation creates a shortage of high-quality controlled trials for comparison, further exploration is required to differentiate the satisfactory outcome of cytotherapy from the natural history of nontraumatic ONFH. For some untreated nontraumatic ONFH in the early stages can recover and regain a normal hip joint naturally. Currently, a bipedal animal model is difficult to construct to mimic ONFH in humans. Moreover, great bias in collapse and repair process could not be neglected, and the method used to induce ONFH in animal models is far from the pathogenesis in humans, thus the unknown field is wider than ever [41, 42]. If one day we could construct the animal model of ONFH through the pathway of progenitors, it could also provide principal value in the research of pathogenesis and therapeutics of nontraumatic ONFH.

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