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Research lectures

Mesenchymal stem cells and rheumatoid arthritis

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1. Introduction

Mesenchymal stem cells are progenitors for several connective tissue cell lineages including bone, cartilage, muscle, fat, and bone marrow cells [1]. Stem cells are found in adulthood in many tissues and may be involved in the pathogenesis of some autoimmune diseases. As mesenchymal stem cells can target diseased organs, they may hold potential as vehicles capable of expressing and secreting proteins with therapeutic effects. In addition, stem cells exhibit immunologic properties that may have beneficial effects in autoimmune diseases. Improved knowledge of the pathophysiology of immunologic diseases such as rheumatoid arthritis (RA) or Crohn's disease has opened up new avenues for immunotherapy, the most striking example to date being the demonstration of a role for TNF [2]. Administration of agents that antagonize this cytokine receptor has proven therapeutic efficacy in RA. The rule of mesenchymal cells will be discussed.

2. Characteristics of mesenchymal stem cells

The mesenchymal stem cells found in bone marrow are identified by the expression of surface markers such as CD90, endoglin CD105, VCAM1, and hyaluronan receptors [3]. The generation of mesenchymal stem cells requires conditions based on adhesion properties, with culturing for 10–14 days in a medium supplemented with calf serum and a growth factor such as bFGF or PDGF [4]. Recent data, show that these mesenchymal cells originate from a common progenitor, the multipotent adult progenitor cell, which gives rise to an array of lineages including the endothelium, endoderm, and ectoderm. Mesenchymal stem cells should be distinguished from hematopoietic stem cells. They are not blood cell progenitors and do not express CD34, CD45 or CD14. However, mesenchymal stem cells promote the growth of hematopoietic progenitors by secreting numerous cytokines such as MCSF, IL-6, IL-11, IL-15, and LIF. Mesenchymal stem cells can also attract hematopoietic cells by expressing chemokine receptors and secreting SDF-1 [5].

3. Immunologic properties of mesenchymal stem cells

Mesenchymal stem cells are not rejected by the immune system, even after allogeneic transplantation, because they are not recognized by T cells. They express little or no class II MHC molecules or costimulation factors such as B7 1, B7 2, or CD 40. In addition, mesenchymal stem cells have been shown to suppress the T-cell response in mixed lymphocyte reactions [6] in a dose-dependent manner, the effect being greatest when the ratio of mesenchymal stem cells over T cells is equal to 1. Under these culture conditions, adding IL-2 abolishes the ability of mesenchymal stem cells to suppress the mixed lymphocyte reaction. It as been suggested that the immunosuppressive effects of mesenchymal stem cells may be mediated by cytokines such as tumor growth factor (TGF) or hepatocyte growth factor (HGF) but IL-10 and IL-11 do not seem involved [7]. In vivo, mesenchymal stem cells have proved to be able of inducing immune tolerance. Thus, xenogeneic mesenchymal cells colonized and divided in rat myocardium after experimental coronary artery ligation [8]. Intravenous injection of mesenchymal cells prolonged the survival of an allogeneic skin implant to the same extent as done in cyclosporine therapy.

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4. Migration of mesenchymal stem cells

Mesenchymal stem cells adhere to the extracellular matrix and migrate preferentially to the bone and lungs, as well as to the cartilage. One month after intravenous injection of mesenchymal cells carrying a marker gene, 8% of bone cells and 5% of lung cells expressed the label [3]. In baboons, labeled mesenchymal cells were found in the bone marrow more than 500 days after the injection [9]. In a clinical study of osteogenesis imperfecta, injection of mesenchymal cells was followed by growth of osteoblasts, which accounted for 1–2% of bone marrow cells [10]. After 3 months, an increase in bone mineral density was noted. No adverse effects were seen after in vivo injection of mesenchymal stem cells in this study. Taken in concert, these experimental and clinical data strongly support a major therapeutic role for mesenchymal stem cells.

5. Presence of mesenchymal cells within the synovial tissue

Mesenchymal cells are present within joints affected with arthritis and may contribute to the disease process. Early migration of mesenchymal stem cells from the bone marrow to the synovial membrane occurs in animals with collagen-induced arthritis [11] and is abolished by pretreatment with an anti-TNF antibody. Within the rheumatoid synovial membrane, mesenchymal cells expressing receptors for BMP and CD44 (the hyaluronan receptor) represent up to 25% of synovial cells [12]. In addition, the chondrogenic potential of synovial mesenchymal cells has been abundantly documented in various models.

Precursor cells found within synovial tissue have been shown to express morphogenesis genes such as *wnt*. Overexpression of *wnt* 5a genes may result in secretion of proinflammatory cytokines, which may result in chronic inflammation [13]. The persistence of immature progenitors within the synovial tissue may impair the regulation of cytokine secretion. The exact role for these cells in the genesis of arthritis has not been clearly determined. The *wnt* genes are also protooncogenes that promote cell division and phenotype transformation, resulting in functional impairment of the p53 protein [14]. Thus, overexpression of these morphogenes within the synovial tissue may explain the proliferation, transformation to an invasive phenotype, and inflammation that characterize the rheumatoid synovium.

6. Mesenchymal cells in the treatment of autoimmune disease

Mesenchymal cells can be used in a variety of treatment strategies. Thus, the goal may be alleviation of the arthritis by immunosuppressive factors secreted by mesenchymal cells or expression of therapeutic agents by mesenchymal cells that target inflammatory tissues [15]. Furthermore, mesenchymal stem cells have reparative properties. For instance, mesenchymal stem cells in the presence of BMP-2 may differentiate into bone or cartilage after implantation within muscle or inside a joint cavity [16]. Thus, therapy mediated by mesenchymal cells may allow both expression of a therapeutic agent and repair of tissue damage caused by chronic inflammation. In one study, mesenchymal stem cells expressing a cytokine, such as IL-3, were seeded into ceramic cubes and implanted in vivo in mice with severe combined immunodeficiency [17]. The cells underwent differentiation within the cubes, inducing bone formation and systemic IL-3 secretion that stimulated hematopoiesis for 12 weeks. Mesenchymal cells have been successfully used to express therapeutic genes such as erythropoietin and anti-hemophilia factors, with effects that lasted more than 3 months [18]. Preliminary results show that mesenchymal cells genetically engineered to express a soluble TNF receptor can be used to express this receptor in the serum and to inhibit the production of TNFα [19]. In MLR lpr mice, characterized by spontaneous development of lupus, immunosuppressive effects of mesenchymal stem cells have been documented. In these animals, bone marrow transplantation ensured survival for longer than 12 months and was followed by a decrease in anti-DNA titers. However, when bone marrow previously subjected to mesenchymal cell depletion was used, 75% of the animals died within 90 days of transplantation [20]. Reinjecting mesenchymal cells associated with hematopoietic cells ensured effective treatment of the autoimmune disease, confirming the key therapeutic role for mesenchymal stem cells.

In conclusion, mesenchymal cells hold promise for the treatment of autoimmune diseases. Their therapeutic effects are mediated by immunosuppressive properties, which have been abundantly documented in xeno-allogeneic graft experiments. In addition, these cells can be used to achieve targeted expression of anti-inflammatory molecules such as cytokines or TNF receptor within diseased tissues. Finally, the ability of mesenchymal cells to regenerate bone or cartilage tissue opens up exciting prospects for treatment, although much work will have to be done before use in clinical practice can be considered.

References

[1] Pittenger MF, Mackay AM, Beck SC, Jaiswal RK, Douglas R, Mosca JD, et al. Multilineage potential of adult human mesenchymal stem cells. Science 1999;284:143–7.
[2] Illei GG, Lipsky PE. Novel, non-antigen-specific therapeutic approaches to autoimmune/inflammatory diseases. Curr Opin Immunol 2000;12:712–8.
[3] Prockop DJ. Marrow stromal cells as stem cells for nonhematopoietic tissues. Science 1997;276:71–4.
[4] Gronthos S, Simmons PJ. The growth factor requirements of STRO-1-positive human bone marrow stromal precursors under serum-deprived conditions in vitro. Blood 1995;85:929–40.
[5] Deans RJ. Mesenchymal stem cells: cell and gene therapy applications. Eur Cytokine Netw 2000;11:323–4.

[6] Deans RJ, Moseley AB. Mesenchymal stem cells: biology and potential clinical uses. Exp Hematol 2000;28:875–84.
[7] Di Nicola M, Carlo-Stella C, Magni M, Milanesi M, Longoni PD, Matteucci P, et al. Human bone marrow stromal cells suppress T-lymphocyte proliferation induced by cellular or nonspecific mitogenic stimuli. Blood 2002;99:3838–43.
[8] Saito T, Kuang JQ, Bittira B, Al-Khaldi A, Chiu RC. Xenotransplant cardiac chimera: immune tolerance of adult stem cells. Ann Thorac Surg 2002;74:19–24 [Discussion 24].
[9] Devine SM, Mierisch CM, Jang E, Anderson PC, Balian G. Mesenchymal stem cells are capable of homing to the bone marrow of non-human primates following systemic infusion. Exp Hematol 2001; 29:244–55.
[10] Horwitz EM, Prockop DJ, Fitzpatrick LA, Koo WW, Gordon PL, Neel M, et al. Transplantability and therapeutic effects of bone marrow-derived mesenchymal cells in children with osteogenesis imperfecta. Nat Med 1999;5:309–13.
[11] Marinova-Mutafchieva L, Taylor P, Funa K, Maini RN, Zvaifler NJ. Mesenchymal cells expressing bone morphogenetic protein receptors are present in the rheumatoid arthritis joint. Arthritis Rheum 2000;43: 2046–55.
[12] Marinova-Mutafchieva L, Willimas RO, Funa K, Maini RN, Zwaifler NJ. Inflammation is preceded by tumor necrosis factor-dependent infiltration of mesenchymal cells in experimental arthritis. Arthritis Rheum 2002;46:507–13.
[13] Sen M, Lauterbach K, El-Gabalawy H, Firestein G, Corr M, Carson DA. Expression and function of wingless and frizzled homologs in rheumatoid arthritis. PNAS 2000;10:1073–86.
[14] Hardiman G, Albright S, Tsunoda J, Mcclanahan T, Lee F. The mouse Wnt10b gene isolated from helper T cells is widely expressed and a possible oncogene in BR6 mouse mammary tumorigenesis. Gene 1996;172:199–205.
[15] Harrington K, Sturgeon C, Siatskas M, Ferrer K, McIntosh K, Patil S, et al. Cells as vehicles for cancer gene therapy: the missing link between targeted vectors and systemic delivery? Hum Gene Ther 2002;13:1263–80.
[16] Gazit D, Turgeman G, Kelley P. Engineered pluripotent mesenchymal cells integrate and differentiate in regenerating bone: a novel cell-mediated gene therapy. J Gene Med 1999;1:121–33.
[17] Allay JA, Dennis JE, Haynesworth SE, Majumdar MK, Clapp DW, Shultz LD, et al. LacZ and interleukin-3 expression in vivo after retroviral transduction of marrow-derived human osteogenic mesenchymal progenitors. Hum Gene Ther 1997;8:1417–27.
[18] Bartholomew A, Sturgeon C, Siatskas M, Ferrer K, McIntosh K, Patil S, et al. Baboon mesenchymal stem cells can be genetically modified to secrete human erythropoietin in vivo. Hum Gene Ther 2001;12:1527–41.
[19] Liu L, Fujiki K, Dixon B. Expression of soluble TNF-RII from transduced human mesenchymal stem cells: in vitro and in vivo efficacy (abstract). Blood 1999;94.
[20] Ishida T, Inaba M, Hisha H, Sugiura K, Adachi Y, Nagata N, et al. Requirement of donor-derived stromal cells in the bone marrow for successful allogeneic bone marrow transplantation. Complete prevention of recurrence of autoimmune diseases in MRL/MP-Ipr/Ipr mice by transplantation of bone marrow plus bones (stromal cells) from the same donor. J Immunol 1994;152:3119–27.