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Marrow Stromal Cells as Stem Cells for Continual Renewal of Nonhematopoietic Tissues and as Potential Vectors for Gene Therapy

Darwin J. Prockop*

Center for Gene Therapy, Allegheny University of the Health Sciences, Hahnemann School of Medicine, Philadelphia, Pennsylvania 19102

As has been known for some time, bone marrow contains hematopoietic stem cells (HSCs) that provide a source of progenitors for circulating blood cells [Weatherall, 1997]. It is less well known that bone marrow also contains cells that have many of the necessary properties to be defined as stem cells for nonhematopoietic tissues [Prockop, 1997]. The precursor cells for nonhematopoietic tissues were initially referred to as plastic-adherent cells or colony-forming units-fibroblasts, because they readily adhered to tissue culture plastic and formed fibroblast-like colonies. Somewhat later, they were referred to as mesenchymal stem cells or mesenchymal progenitor cells because they readily differentiated into a variety of mesenchymal-like cells. They have also been referred to as marrow stromal cells (MSCs) because they arise from a complex of supporting structures found in marrow, and because they provide effective feeder layers for the growth of HSCs. MSCs are now the focus of a great deal of attention because of their biological role in providing circulating progenitor cells that can repopulate a number of nonhematopoietic tissues, and because of their obvious potential to serve as safe and effective vehicles for both cell and gene therapy.

The German pathologist Cohnheim [1867] was apparently the first to suggest the possibility that circulating blood cells, and by implication bone marrow, might be a source of progenitors for nonhematopoietic tissues. During the 1970s, Friedenstein and colleagues [Friedenstein and Kuralesova, 1971; Friedenstein et al., 1976] demonstrated that the small fraction of cells easily isolated from bone marrow by their adherence to plastic could differentiate into osteoblasts, chondrocytes, and adipocytes. These observations were subsequently confirmed and extended by a number of investigators [Piersma et al., 1985; Owen et al., 1988; Caplan, 1991; Rickard et al., 1996; Krebsbach et al., 1997; Bruder et al., 1997; Joyner et al., 1997]. More recently, the same cells have been shown to be able to differentiate into myoblasts and myotubes [Wakitani et al., 1995; Prockop, 1997]. Differentiation of MSCs into multiple lineages has now been demonstrated *in vivo* both by implantation into tissues [Owen and Friedenstein, 1988; Krebsbach et al., 1997] and by infusion into the general circulation [Pereira et al., 1995, 1998; Guinn et al., 1996; Hou et al., 1997; Onyia et al., 1998]. For example, we and others demonstrated that systemically infused MSCs become incorporated into bone and take on some of the phenotypic tissues of osteoblasts and osteocytes [Pereira et al., 1995, 1998; Hou et al., 1997; Azizi et al., 1998]. They also appear in cartilage and apparently become chondroblasts [Pereira et al., 1995, 1998]. Surprisingly, a few of the cells also appear in the central nervous system [Pereira et al., 1998] and in muscle [Ferrari et al., 1998]. Eglitis and Mezey [1997] have found that a few of the cells from infusions of whole bone marrow appear in the brain as early astrocytes. More recently, we found that direct infusion of human MSCs into the corpus striatum of albino rats is followed by engraftment of the cells and migration of the cells along known pathways for the migration of neural stem cells [Azizi et al., 1998].

*Correspondence to: Darwin J. Prockop, Center for Gene Therapy, Allegheny University of the Health Sciences, MCP-Hahnemann School of Medicine, 245 North 15 Street, Mail Stop 421, Philadelphia, PA 19102.

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Taken as a whole, these observations demonstrate a previously unsuspected role of marrow stromal cells in normal biology both in embryonic development and in adult mammals. The MSCs are apparently a part of a vestigial pathway whereby cells from marrow can slowly contribute to the renewal of a large number of different tissues. Because the cells are relatively easy to isolate from patients and relatively easy to gene-engineer, they also offer extremely attractive vehicles for both cell therapy and gene therapy [Caplan, 1991; Horwitz et al., 1996; Guinn et al., 1996; Hurwitz et al., 1997; Onyia et al., 1998; Azizi et al., 1998].

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