Mesenchymal stem cells and the stem cell niche: a new chapter

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Bone marrow-derived mesenchymal stem/stromal cells (MSCs) are self-renewing multipotent cells with therapeutic effects in diverse models of tissue injury (27). In the rodent lung, MSCs reduce collagen deposition in the bleomycin model of pulmonary fibrosis (26) and reduce lung injury and improve survival following intrapulmonary delivery of endotoxin or Escherichia coli (10, 11) and following severe gram-negative peritonitis (18). In the hyperoxia model of bronchopulmonary dysplasia, exposure to high concentrations of oxygen during early postnatal life in rats and mice causes simplification of alveolar and lung capillary structure and reduced pulmonary capillary surface area, leading to pulmonary hypertension. Two groups reported simultaneously in 2009 that MSCs given by airway to rats (12) or by blood to mice (2) during prolonged hyperoxia in early postnatal life prevented arrested alveolar growth. However, engraftment of MSCs during hyperoxia and in other models has not accounted for the therapeutic effects, thus prompting a search for other mechanisms.

MSCs are potent immunomodulators, suppressing several functions of lymphocytes, natural killer cells, and monocytes (1), and reduce inflammatory cell lung infiltrates and cytokines during sepsis and acute lung injury (11, 23, 25). In addition, MSCs have direct antibacterial effects (19), secrete epithelial growth factors (21), and can rescue epithelial cellular bioenergetics with mitochondrial transfer (14).

MSCs and the Stem Cell Niche

Recent evidence points to a novel therapeutic mechanism: regulation of endogenous tissue stem and progenitor cells. Within bone marrow, MSCs exist as elongated cells covering the abluminal surface of sinusoids. In the 1970s, Weiss (34) termed these cells adventitial reticular cells, theorizing that they played a critical role in the trapping and differentiation of hematopoietic stem cells (HSCs) based on their close proximity to cells of hematopoietic lineage. Indeed, MSCs have long been known to support the growth of HSCs in vitro (7). MSCs produce critical HSC regulatory factors, including CXCL12 (stromal cell-derived factor-1), stem cell factor, angiopoietin-1, N-cadherin, and Jagged-1 (3). Elegant in vivo work indicates that MSCs are capable of establishing a hematopoietic microenvironment following heterotopic transplantation, directing the formation of sinusoids through interactions with host endothelial cells (31).

Neurogenesis occurs in adult mammals within two brain regions, the subventricular zone and the hippocampal dentate gyrus, the latter playing an important role in memory formation (6). Human MSCs injected into the hippocampus of immunodeficient mice increased proliferation, survival, and migration of endogenous neural progenitor cells, mediated in part by enhanced local secretion of nerve growth factor and neurotrophin-4/5 (24). Similarly, rat MSCs supported the growth of neural stem cells in vitro (32). Furthermore, intraventricular administration of MSCs increased hippocampal neurogenesis in association with local increases in mRNA of the potent neurogenic factor FGF-2.

MSC therapy reduces infarct size and improves functional recovery in large animal models of myocardial infarction (35). Porcine MSCs injected through the endocardium after myocardial infarction resulted in reduced infarct size, accompanied by evidence of modest MSC engraftment and cardiac differentiation (13). Impressively, MSC injections also produced a 20-fold increase in recipient c-kit+ cardiac stem cells (CSCs) in and near the infarct. Donor MSCs appeared to form cellular connections with c-kit+ cells, many of which expressed markers of cardiac lineage commitment. MSCs were also found to promote the growth of CSCs in vitro. Taken together, the data from bone marrow, brain, and heart suggest MSCs are capable of modulating critical processes in stem cell niches throughout the body.

Lung Stem and Progenitor Cells

Although endogenous stem and progenitor cell populations are well described in many adult tissues including bone marrow, brain, and heart, considerable controversy persists as to the location, types, and differentiation potential of stem and progenitor populations within the adult lung. It remains unclear, for example, whether the lung contains a small population of c-kit+ cells capable of producing all of its components, as suggested by Kajstura et al. (15), or instead is limited to regional pools of fate-restricted progenitors (17). However, a substantial body of evidence indicates that discrete progenitor populations do exist within the lung and respond to various types of injury.

Alveoli. Classic work in rats by Evans and colleagues in the early 1970s (8) showed that type II alveolar epithelial cells (AECs) divide following injury with inhaled nitrogen dioxide and give rise to type II AECs as well as type I AECs. Until recently the consensus had been that only type II AECs could repopulate damaged alveoli following lung injury. However, Chapman et al. (5) reported last year that a previously unrecognized population of alveolar cells expressing integrin α6β4 but not the type II AEC marker surfactant protein C (SPC) can proliferate and differentiate into many epithelial cell types in vitro and in vivo, including type II AECs. Similarly, McQuater et al. (22) recently reported the isolation from whole lung cell suspensions of stemlike cells expressing integrin α6β4.

Airways. In the trachea and mainstem bronchi, basal cells self-renew and generate secretory and ciliated cells in adulthood and following several types of injury, prompting some to argue that basal cells are the dominant stem cell in the large airways (30). Within the smaller intralobular airways, Clara cells

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unanswered questions. Many important questions remain. What are the paracrine factors secreted by MSCs that increase BASC proliferation? The authors tested several likely candidates, including VEGF, keratinocyte growth factor, FGF-2, and HGF alone and in combination but could not replicate the effect of the MSC-conditioned media. Given their dramatic effect on c-kit+ cardiac stem cells, might MSCs be affecting c-kit+ lung stem cells or other progenitor populations in the hyperoxia model? Do effects on lung progenitor populations account for some of the therapeutic effects of MSCs in other models of lung injury in adult animals? Given that neonatal hyperoxia involves endothelial injury, might MSCs work in part through effects on endothelial cells, such as organizing and stabilizing nascent capillary networks as they do in vitro and in vivo (4)? Finally, do the lung’s own pericytes (with many similarities to MSCs) play a role in normal development or in response to injury? These and other questions should be more tractable with the continuing improvements in lineage tracing technology.

REFERENCES