Therapeutic Potency of Physioxia Cultured Cardiac Mesenchymal Cells for Myocardial Repair in Mice with a 30-day-old Myocardial Infarction

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Cardiac mesenchymal stem cells (CMCs) are novel and promising stem cells that have shown significant efficacy in improving heart function in rodents after myocardial infarction (MI) and may soon be used in clinical trials. Stem/progenitor cells are usually cultured at atmospheric oxygen tension (21%); however, physiologic O2 tension in the heart is only ~ 5%. This raises the concern that culturing cells at 21% O2 may cause toxicity due to oxidative stress. The hypothesis of this study is that, compared with 21% O2 tension, physiologic (5%) O2 tension enhances the therapeutic efficacy of CMCs. Murine CMCs were cultured at 21% or 5%O2. Compared with 21%O2, culture at 5%O2 significantly ($P<0.001$) increased cell proliferation, telomerase activity, telomere length, and resistance to severe hypoxic stress (1% O2 for 24 h). Then, mice with heart failure caused by an MI received (via echocardiography-guided intraventricular injection) CMCs cultured at 21%O2 or 5%O2, or vehicle (16 mice/group). Thirty-five days later, 5%O2-CMC treatment produced a much greater ($P<0.01$) increase in cardiac function (left ventricular ejection fraction, assessed by echocardiography) and viable myocardium compared with vehicle and 21% O2-CMC groups, indicating superior efficacy in promoting cardiac repair. In conclusion, use of physiologic (5%) oxygen tension to culture CMCs results in more rapid cell proliferation (saving time and money), less senescence, and greater ability to withstand severe hypoxia in vitro, and greater efficacy in repairing the failing heart in vivo. These results could potentially benefit millions of patients with heart failure and have important social and medical significance.

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