INTRODUCTION

Identifying strategies, such as stem cell transplantation, to prevent the progressive loss of tissue homeostasis and functional reserve associated with aging is essential for maintaining the health of our aging population. Direct experimental evidence supports the hypothesis that DNA damage promotes aging. For example, genetic deletions of either the excision repair cross-complementation group 1 (Ercc1) gene or the xeroderma pigmentosum, complementation group F (Xpf) gene in mice causes severe phenotypes including ataxia, kyphosis, weight loss, epidermal atrophy, sarcopenia, intervertebral disc degeneration, bone marrow degeneration, and liver and kidney dysfunction. ERCC1-XPF-deficient (Ercc1−/−) mice express a unique phenotype that mimics human progeria (or symptoms of accelerated aging). Study of which populations. Direct experimental evidence supports the hypothesis that DNA damage promotes aging. For example, genetic deletions of either the excision repair cross-complementation group 1 (Ercc1) gene or the xeroderma pigmentosum, complementation group F (Xpf) gene in mice causes severe phenotypes including ataxia, kyphosis, weight loss, epidermal atrophy, sarcopenia, intervertebral disc degeneration, bone marrow degeneration, and liver and kidney dysfunction. Here we report the ability of MDSCs to delay the onset of age-related pathologies of a unique progeroid mouse model. Our preliminary results demonstrate in a limited number of Ercc1−/−mice that MDSCs engraft in skeletal muscle after intramuscular injection and pervade the bone marrow and various other tissues after IP injection. We posit that the MDSCs can affect age-related pathologies both through their direct contributions to tissue regeneration, as observed by the presence of LacZ-positive cells in different tissues, and also by the secretion of factors that modulate the aging process. Our pilot studies revealed that the delivery of MDSCs, via IP injection, was associated with an overall improvement in the health of the mice including typical histopathologic symptoms of accelerating aging and premature lifespan. We believe this line of research is highly significant and it has the potential of developing stem cell therapy approaches which could delay or ameliorate the pathologies associated with premature aging while revealing the underlying contributions that stem cells have on the basic biological mechanisms of aging.

RESULTS

Injection of normal murine MDSCs into Ercc1−/−mice resulted in MDSC engraftment, reduction of the age-related pathologic symptoms, and extension of lifespan. We investigated the ability of MDSCs to improve muscle regeneration in these mice in order to potentially prevent sarcopenia and may act as a cellular reservoir for the secretion of molecules which could benefit the mice by delaying or preventing their accelerated aging. When MDSCs were injected into the GN muscles of Ercc1−/−mice, we observed the presence of LacZ+ centrally-nucleated myofibers (Fig. 1) which suggests that active myofiber regeneration was occurring by the donor MDSCs. As evidenced by the presence of LacZ+ cells, the IP injected donor cells were able to pervade into the marrow of the long bones; 14% of the cells isolated from the bone marrow of the Ercc1−/−mice tested positive for LacZ (Fig. 2). LacZ-expressing MDSCs were also detected in a variety of other abdominal organs including the liver, spleen, diaphragm, and pancreas (Fig. 3).

Of particular interest was the observation that MDSC IP injected mice displayed pronounced weight gain when compared to their PBS IP injected littermates (greater than 150% of initial weight). Furthermore, the MDSC IP injected animals outlived their PBS IP injected littermates and also greatly exceeded the normal 28 day life expectancy of Ercc1+/+ mice (Fig. 4). In addition, some of the typical symptoms of accelerating aging such as kyphosis, dystonia, muscle wasting, growth retardation, cachexia and loss of vision were not observed in the MDSC IP injected Ercc1−/−mice. They still exhibited trembling, ataxia, and lethargy, though onset of these symptoms was greatly delayed.

Acknowledgements

The authors are grateful for funding support from LJN: The Ellison Medical Foundation AG-NS-0303-05 and NIEHS ES016114, the Henry J. Mankin Endowed Chair for Orthopaedic Research at the University of Pittsburgh, the William F. and Jean W. Donaldson Chair at Children’s Hospital of Pittsburgh, and the Hirtzel Foundation.

References