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Mini Review

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Gender, age and differences in stem cell expression and efficacy

Abstract

Regenerative Medicine holds the promise of an endless supply of replacement cells, tissues and organs. To fully realize the potential of Regenerative Medicine, it is now time to gain a better understanding of the effect of cells in different patient cohorts. Two important differences in patient cohorts are their gender and age. This mini-review will briefly discuss the effects of age and gender on the expression patterns of cells and their relative ability to regenerating tissues. These two factors could play a critical role in the efficacy of cell therapy. Thus, approaches in these cohorts may need to be modified accordingly.

Keywords: estrogen, hormone replacement therapy, muscle stem cells, rodents, nonhuman primates, aging, genes

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Introduction

In large part, stem cell therapy is considered for both men and women with ageing associated diseases. There are extensive examples of age and gender differences in the risk of chronic conditions such as heart disease, osteoporosis and urogenital dysfunction. There are also differences in the ability of different genders and ages to respond to treatments. It stands to reason there may be age and gender differences in their ability to regenerate tissues in response to cell therapy. This review will address the evidence for and against these potential differences.

Discussion

What is the evidence that there are important differences in male and female cells that may influence regeneration?. In 2012, Anguera et al report that induced pluripotent cells from women may be epigenetically less stable in culture than cells from men and may result in qualitatively less desirable stem cell lines.[1] In 2014, Lindholm et al.[2] reported that there are over 500 different isoforms within muscle biopsies collected from men than in women.[2] They report that the transcriptome of the female cells is enriched with genes associated with oxidative metabolism and protein catabolic processes. Both of these processes could influence cell longevity and their ability to divide. There is also evidence that sex hormones, especially in females, may influence the ability of cells to regenerate tissues. Pregnancy and related changes in sex hormone concentrations have been shown to increase hematopoietic stem-cell self-renewal in female mice.[3] Specifically, these cells divide more frequently than in male mice and the difference depends on the ovaries, not the testes. It has also been reported that sex hormones affect muscle stem cell derived stem cell-mediated bone formation on bone formation with the male cells producing greater volumes of bone in this bone defect model.[4] In this study using unaltered male, castrated male, unaltered female, and ovariectomized female mice, muscle-derived progenitor cell-mediated ectopic bone formation and cranial defect healing were examined. Male hosts, whether unaltered or castrated, formed larger volumes of ectopic bone than female hosts (either unaltered or ovariectomized), and no differences were noted in ectopic bone volume between hosts of the same sex. Yuan et al.[5] report that bone marrow stem cells from female nonhuman primate produce more nestin$^+$ (neurogenic) cells, than from males, which may increase their ability to contribute to re-innervation of damaged tissues. However, these monkeys were very young and may not have been at sexual maturity at the time of this study.

Changes in estrogen concentrations during the pre-menopause (cyclicity, stress) may also influence the ability of stem cells to regenerate tissues. This is important to women with dysmenorrheal, amenorrhea or those at different stages in their menstrual cycle. Ronkainen et al.[6] published an interesting finding that female twins, discordant for hormone replacement therapy (HRT), have differences in muscle transcript profiles with the HRT user having improved regulatory actions on cytoskeleton, preservation of muscle quality via regulation of intramuscular extracellular matrix and a switch from glucose-oriented metabolism to utilization of fatty acids. This effect is not confined to menopausal women taking or not taking HRT. We recently published that socially subordinate premenopausal cynomolgus monkeys (which have a 28day menstrual cycle) have reduced ability of autologous muscle progenitor cells to restore urinary sphincter structure and function following creating of intrinsic sphincter deficiency.[7] In this paradigm, social subordination creates dysmenorrheal with the monkeys having more irregular cycles, reduction of estrogen production diminished sex hormone signals during the cycle. This is clinically relevant to women with dysmenorrheal because of disease, extensive physical training, or stress. This may implications for the response to cell therapy between premenopausal, perimenopausal and postmenopausal women.

Aging is also one of the most important risk factors for reduced tissue regeneration. We have shown modest differences in age between older and younger female nonhuman primates (the age equivalent of comparing 30 vs. 50year olds) have a significant effect on muscle progenitor cell therapy to restore structure and function of the urinary sphincter following creation of intrinsic sphincter deficiency.[7] Interestingly, there appears to be age-by-gender interactions in stem

cell expression patterns and the ability of stem cells to stimulate regeneration. Liu et al.[8] report extensive sex differences in the muscle transcriptome of older individuals and different patterns of transcriptional changes with aging in men and women. In older women-transcriptional up-regulation of immune activation, extracellular matrix remodeling, and lipids storage; and a down-regulation of mitochondrial biogenesis and function and muscle regeneration. Neal et al.[9] Investigated age and sex differences between mouse satellite cells in vitro and assessed the importance of these factors as mediators of donor cell engraftment in an in vivo model of satellite cell transplantation. Satellite cell numbers were increased in growing compared to adult and in male compared to female adult mice, but saw no difference in the expression of the myogenic regulatory factors between male and female mice. Despite observed changes in satellite cell populations, there was no difference in engraftment efficiency either between satellite cells derived from adult or pre-weaned donor mice, male or female donor cells, or between male and female host muscle environments. This study is important because it emphasizes that differences in cell expression profiles do not necessarily translate to differences in function. Similarly, a study by von Roth et al.[10] in rats reports no differences in muscle to regeneration following stem cell therapy. Therefore, not all studies report significant differences between ages and gender on the ability of stem cells to regenerate tissues.

Conclusion

Results of these studies indicate that men and women may respond to regenerative medicine therapies differently. Furthermore, the effects of aging on regenerative medicine therapies may be different in men and women. These differences underscore the need to identify and possibly adjust therapies based on these determinates of treatment efficacy.

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Conflicts of interest

The author declares no conflict of interest.

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