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Sexual Dimorphism in Stem Cell–Based Therapies for the Musculoskeletal System

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Musculoskeletal health is one of the areas of medicine in which the differences between males and females are most striking. Differences in disease prevalence, pain sensation, drug handling, and healing responses between individuals have known biologic bases; however, the impact of sex on these biologic processes is unclear. In skeletal muscle tissues, stem cells and progenitor cells are known to persist throughout life and contribute to the ongoing process of repair and regeneration. However, currently, there is a paucity of literature that describes the sex-related differences in satellite cells and other muscle stem cell populations that may have an influence on future stem cell applications. Therefore, an in-depth understanding of the sex-related differences in the biology of skeletal muscle and its resident stem cell populations would greatly enhance our ability to devise new individualized treatment strategies for tissue regeneration in many pathologic and non-pathologic conditions involving the musculoskeletal system.

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Introduction

In humans, sexual dimorphism refers to the inherent phenotypical differences that exist between males and females, with the most visually evident features being differences in body size and composition. In addition, dramatic differences in epidemiologic disease patterns also exist between sexes. For example, women are more prone to develop autoimmune disorders (such as systemic lupus erythematosus and thyroid disorders)[1,2] whereas men are more likely to develop metabolic syndromes and Parkinson's disease.[3-5] Furthermore, the lifetime of women has always been longer than men and the reasons for this difference in life expectancy between sexes are still unclear. Unfortunately, despite the obvious differences in disease patterns between males and females, very few studies have been done to elucidate the cellular and molecular differences between sexes that influence disease—the results of which could be used in the future to develop individualized therapeutic modalities using stem cells.

According to clinical trials.gov, there are currently 4592 federally-approved clinical trials using stem cells, and many studies have been published that identify, characterize, and explore the possible therapeutic applications of stem cells. However, despite the large volume of published research in this area, sex differences in stem cells for regenerative medical applications in the field of orthopaedics have seldom been addressed.

Interestingly, previous studies from our laboratory have found that muscle progenitor/stem cells obtained from female donors have greater capacities for muscle regeneration when compared to the same cell types obtained from male donors.[6] However, male muscle/progenitor cells have been shown to be capable of undergoing osteogenic and chondrogenic differentiation more effectively than the female muscle/progenitor cells.[7-9]

More recently, Nakada et al[10] reported that mouse haematopoietic stem cells (HSCs) also exhibit differences in cell cycle regulation in response to the presence of estrogen, suggesting

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that other stem cell types may also be affected by the differing ratios of sex hormones present in male and female specimens. These results indicate that sex-based differences stem cell biology may be an important, yet overlooked factor that may need to be controlled in future studies to avoid the possibility of confounding biases and to aid in the future development of individualized therapies.

The purpose of this article is to review the current knowledge and research applications pertaining to the sex-related differences in skeletal muscle morphology and muscle stem cell biology with the ultimate goal of providing safe, individualized stem cell treatments for future patients with a variety of musculoskeletal conditions.

Sexual Dimorphism in Skeletal Muscle

Skeletal Muscle Mass and Development

In animals, sex-related differences in muscle mass tend to be more pronounced as the overall size of the animal increases. In most mammals and birds, males are generally larger because of increased muscle mass,[11,12] which is likely attributable to sexual selection via male-male competition for suitable mating partners.[13] In contrast, although humans also exhibit significant sex-related differences in average body size, humans also feature substantial differences in the composition and distribution of lean muscle mass, fat mass, and bone mineral density between sexes.

Although the molecular basis for these differences is unclear, several studies have explored sex-related differences in gene expression in skeletal muscle. For example, Pas et al[14] reported that expression of muscle regulatory factor mRNAs, including myogenin, myf-5, and myf-6, were significantly increased in the anterior tibialis muscles of female rats when compared to those of male rats. Another study reported that the level of myostatin, which is a negative regulator of muscle growth, was 40%-60% lower in the skeletal muscles of male mice when compared to those of female mice.[15] A more recent study performed by Welle et al[16] found that expression of growth factor receptor-bound 10 (GRB10; encodes a protein that inhibits insulin-like growth factor-1 [IGF-1] signaling) and activin A receptor IIB (ACV2B; encodes a myostatin receptor), were increased 2-fold in human female skeletal muscles relative to those of males. These results suggest that several genetic factors, such as variations in the expression of GRB10 and ACV2B, may have contributing roles in the sexual dimorphism of skeletal muscle biology.

Sexual dimorphism in body composition is evident throughout each stage of human development. Although male children are generally larger in size when compared to female children, their rates of growth and soft tissue distributions remain relatively parallel until the onset of puberty.[17] At this point, the introduction of sex hormones induces the further development of reproductive structures and secondary sexual characteristics that ultimately leads to male and female gender identities, both physically and psychosocially. With particular consideration of the differences in skeletal muscle composition, further development of the female beyond the onset of puberty tends to result in a greater proportion of body fat relative to muscle mass. Males, in contrast tend to develop a greater proportion of lean muscle mass relative to body fat.[18] With regard to muscle size and strength, muscle hypertrophy occurs much more rapidly and produces a greater maximum power output in males when compared to females. However, female muscles are able to recover more quickly after injury and are more resistant to fatigue.[19] These observations may be related to the preferential development of anaerobic muscle types in males and aerobic muscle types in females at the genetic and molecular levels, perhaps as a result of sexual selection and social factors that ultimately serve to maintain survivability throughout the ongoing process of human evolution.

Beyond puberty, the levels of sex hormones in males decline very gradually over time through the remainder of life, which allows for an increased production of centripetal fat during the aging process. In females, involution and atrophy of the ovaries near 50 years of age results in an acute, dramatic decrease in estrogen production which, from the standpoint of body composition, tends to result in the gradual redistribution of fat from the periphery to more central areas.[18] These sex-related differences in the response to aging reflects the underlying ratio of sex hormones and their significant biochemical influences on dividing cells throughout the body—a phenomenon that which has particular importance in the realm of stem cell research and regenerative medicine.

Effects of Sex Hormones on Skeletal Muscle Biology

There have been many reports of sex-related differences in post exercise-induced muscle injury in humans and animal models.[20,21] Creatine kinase (CK) activity, inflammation response, and leukocyte infiltration are systemic molecular and cellular markers that imply the presence of recent or ongoing muscle damage. These markers are generally reported to be lower in females than in males.[20,22] Following the completion of endurance or resistance eccentric exercises, females exhibit decreased CK efflux in skeletal muscles when compared to that of males. This large difference in CK activity has been attributed to the effects of circulating estrogen on skeletal muscle. For example, Amelink et al found lower levels of circulating CK in male animals when estrogen was administered following exercise. Furthermore, the investigators also found that pre-exercise estrogen therapy may help prevent the accumulation of excessive muscle damage in ovariectomized female rats.[23] Current studies are being conducted that explore the potential protective role of estrogen and its ability to minimize inflammation and leukocyte infiltration at the site of muscle injury.

Estrogen, Progesterone, and Pregnancy

Estrogens, including estrone (E1), 17β-estradiol (E2), and estriol (E3) are known antioxidants, gene regulators, and membrane stabilizers that confer many protective effects on post-exercise muscle damage.[24-27]