Changes in Chondrogenic Progenitor Populations Associated with Aging and Osteoarthritis

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Abstract

Chondrogenic progenitor populations, including mesenchymal stem cells, represent promising cell-based transplantation or tissue engineering therapies for the regeneration of damaged cartilage. Osteoarthritis (OA) predominantly affects the elderly and is a leading cause of disability worldwide. Advancing age is a prominent risk factor that is closely associated with the onset and progression of the disease. Understanding the influence that aging and OA have on chondrogenic progenitor cells is important to determine how these processes affect the cellular mechanisms of the cells and their capacity to differentiate into functional chondrocytes for use in therapeutic applications. Here, we review the effect of age- and OA-related changes on the growth kinetics and differentiation potential of chondrogenic progenitor cell populations. Aging differentially influences the proliferative potential of progenitor cells showing reduced growth rates with increased senescence and apoptotic activity over time, while chondrogenesis appears to be independent of donor age. Cartilage tissue affected by OA shows evidence of progenitor populations with some potential for repair, however reports on the proliferative propensity of mesenchymal stem cells and their chondrogenic potential are contradictory. This is likely attributed to the narrow age ranges of samples assessed and deficits in definitively identifying donors with OA versus healthy patients across a wide scope of advancing ages. Further studies that investigate the mechanistic effects of chondrogenic progenitor populations associated with aging and the progression of OA using clearly defined criteria and age-matched control subject groups are crucial to our understanding of the clinical relevance of these cells for use in cartilage repair therapies.

Keywords

cartilage, aging, osteoarthritis, chondrogenesis, mesenchymal stem cells

Introduction

Articular cartilage is an avascular tissue with limited ability to self-repair. Because of its healing restrictions and the reduced capacity of tissues to regenerate with aging, cartilage injuries and advancing age are major risk factors for the development of osteoarthritis (OA). While cell-based transplantation and tissue engineering approaches hold great therapeutic potential for cartilage repair strategies, it is important to consider the biological implications of the aging process and the presence of OA on chondrogenic progenitor cell populations.

Mesenchymal stem cells (MSCs) are a population of progenitor cells that were first identified in the bone marrow as adherent colony forming unit–fibroblasts (CFU-Fs).¹ Under the appropriate stimuli, MSCs exhibit multilineage differentiation potential along musculoskeletal lineages including the ability to produce chondrocytes.² The differentiation and proliferation capacity of MSCs suggests that these cells may have therapeutic value for use in cartilage

repair applications. MSCs derived from human fetal bone marrow during gestation as well as adult bone marrow throughout postnatal life demonstrate chondrogenic potential.^{3–6} Similarly, normal articular cartilage contains a subpopulation of progenitor cells capable of undergoing chondrogenesis.^{7,8} However, the effect that advancing age and/or the development of OA have on the progenitor population pool and its influence on functional capacity and regenerative potential is not clearly understood.

Deficiencies in MSC frequency and functional capacity may have a direct effect on tissue biology that contributes to the aging process and the onset of OA. Aging and OA are often inextricably linked,^{9,10} and it is important to understand

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how age-related changes affect MSC potency in the context of OA development and progression to determine their potential for cartilage repair applications. This review highlights the changes in chondroprogenitors related to advancing age and OA progression and how this affects their proliferative propensity and chondrogenic capacity.

Age-Related Changes

The Effect of Age on Growth Kinetics

The yield of CFU-Fs isolated from the mononuclear fraction of bone marrow and the subsequent proliferative propensity of MSCs seem to be differentially influenced by donor age. The CFU-F frequency has been shown to decrease with advancing age in older (59-75 years old) compared with younger donors (0-18 years old)¹¹ and in a range of patients aged between 7 and 55 years old.¹² Similarly, a significant age-related decline in the prevalence of alkaline phosphatase positive CFU-Fs was observed for younger donors (3-36 years old) however there was no further reduction in patients older than 40 years (41-70 years old).¹³ This suggests a negative correlation between CFU-F number and aging, which appears to occur more rapidly in younger donors while there is a reduced rate of decline in older donors.

STRO-1 is a proposed marker of a subset of MSC progenitors within the stromal cell population.^{14,15} Isolation of the STRO-1 expressing cells from the mononuclear cell fraction of bone marrow from young (22-44 years old) and older (66-74 years old) patients revealed no correlation between CFU-F number and age.¹⁶ This could in part explain the age-related reduction in total CFU-F frequency, whereas specific progenitor populations are renewed and remain active throughout the aging process.

The yield of CFU-Fs was also shown to be independent of aging in the number of MSCs isolated from donors ranging from 5 to 80 years of age.¹⁷ The bone marrow aspirates for the donors older than 20 years were obtained during total hip replacement surgery, which is suggestive of joint disease such as OA although there is no indication of pathology detailed in this study. Differences in the precise age of the donors within the ranges presented and counting techniques may also account for the discrepancies between aging and CFU-F frequencies in these studies.

The effect of age on the proliferation rate of MSCs has also revealed conflicting results. Some studies report that MSC growth rate is independent of donor age.^{18,19} However, MSCs from older donors (>60 years old) were shown to have a slower initial proliferation phase compared with younger donors (<20 years old).¹⁷ The delayed activation from dormancy of older MSCs may imply an age-related decline in proliferation potential or proportion of MSCs. The articular cartilage of second trimester fetuses is predominantly comprised (95%) of a

mesenchymal progenitor population that express the MSC surface markers CD166 and CD105 and have a greater proliferation rate compared to the equivalent population, which constitutes approximately 5% of the cartilage of adult (28-46 years old) and elderly (60-75 years old) donors.²⁰ Similarly, MSCs isolated from the bone marrow of first trimester fetuses and pediatric donors (2-13 years old) have enhanced proliferative propensity and a shorter population doubling time compared with adult bone marrow-derived MSCs.^{3,21} The increased growth rate of fetal MSCs is likely to be attributed to their higher telomerase function and longer telomere length compared with adult MSCs.³ Adult bone marrow-derived MSCs do not exhibit telomerase activity and undergo progressive telomere shortening during *in vitro* expansion.^{22,23} A study by Baxter *et al.*¹¹ showed that MSCs isolated from adult donors (59-75 years old) have significantly shorter telomeres compared with MSCs from younger donors (0-18 years old). This indicates that telomere erosion occurs *in vivo* as a consequence of aging.¹¹ Interestingly, ectopic expression of telomerase reverse transcriptase on human MSCs enables maintenance of the osteogenic progenitor population and enhances osteogenesis and bone forming potential without senescence.^{24,25} This approach may be beneficial for the production of immortalized MSCs without having to consider the functional implication of replicative senescence during *in vitro* expansion.

Mesenchymal stem cells derived from older donors (66-81 years old) undergo accelerated senescence and have half of the maximum lifespan of MSCs from younger patients (18-29 years old).²⁶ Replicative senescence in MSCs is associated with an altered gene expression profile including upregulation of transcripts associated with apoptosis and cell death and downregulation of genes that control cell division and mitosis.²⁷ The gene expression changes induced by replicative senescence during long term *in vitro* culture have been shown to correlate with the differential expression between MSCs isolated from donors ranging from 21 to 92 years old.²⁸ There is a significant age-related increase in the number of cells that are positive for markers of senescence, including the tumor-suppressor protein p53 and the cell-cycle regulation protein p21 as well as the rate of apoptosis in culture in MSCs derived from young (7-18 years old) and aged (>40 years old) donors.¹² These findings are confirmed by another report that shows a 4-fold increase in senescence activity with upregulation of apoptosis marker expression in MSCs isolated from older donors (>55 years old).²⁹ Together these studies show a positive correlation between telomere erosion, apoptotic activity and senescence with advancing age. Further investigations on how these processes affect the functional capacity of MSCs will enhance our understanding of the aging process and its biological implications for progenitor cells.

The Effect of Age on Immunophenotype

The aging process induces changes in the expression of specific surface markers on MSC populations. There is a progressive decline in the proportion of cells that express the MSC-specific markers CD90, CD105, and STRO-1 with advancing age in young (7-18 years old), adult (19-40 years old) and aged (>40 years old) donors.¹² In contrast, we have shown that MSCs derived from first trimester fetal and adult bone marrow share a similar immunophenotype.³⁰ Comparable expression of cell surface markers was also reported for MSCs isolated from pediatric (2-13 years old) and adult (20-50 years old) donors.²¹ Maijenburg *et al.*³¹ highlighted changes in the stromal compartment of the bone marrow with age showing that elderly patients (>55 years old) have significantly reduced expression of CD146 on CD271 positive MSCs compared with younger donors (19-55 years old). Furthermore, MSCs isolated from fetal bone marrow have a unique subpopulation of CD271-/CD146+ MSCs that possess trilineage differentiation potential.³¹ This suggests changes in the composition of bone marrow-derived MSC subsets with aging and differences in immunophenotype may indicate altered functional abilities of these cells during development and postnatal life.

The Effect of Age on Chondrogenic Potential

There are very few studies that directly compare the chondrogenic differentiation potential of progenitor cells in relation to advancing age. Age-related changes and osteogenesis have been more widely studied and could provide some insight into cartilage progenitor populations and aging.

There is an age-related decline in the proportion of osteogenic progenitors in MSCs derived from mouse and rat bone marrow.^{32,33} Although differentiation induced similar upregulation of osteogenic marker genes *in vitro*, MSCs derived from the bone marrow of adult rats (6-12 months old) showed significantly greater bone formation *in vivo* compared with aged rats (24 months old).³³ These studies cannot be directly compared with human MSCs due to differences in the rate of development and progression of aging between the two species.

The osteogenic potential of MSCs is independent of advancing age in adult donors.^{16,34} However, the accelerated senescence and lower rate of population doublings in MSCs isolated from older (61-80 years old) compared with younger (18-29 years old) donors suggests a decline in the osteogenic precursor population, which may undergo reduced osteoblast formation and contribute to the age-related reduction in bone formation in the elderly.²⁶

A relationship between aging and chondrogenesis has been shown in animal studies. MSCs derived from the bone marrow of adult rats (15 months old) have a reduced capacity for chondrogenesis compared with MSCs from younger

animals (4 months old).³⁵ Similarly, murine MSCs isolated from animals at 6 days, 6 weeks, and 1 year show a progressive decline in chondrogenic differentiation potential and proteoglycan accumulation.³⁶ Chondrogenesis of fetal and juvenile bovine MSCs produces tissue with greater matrix formation and improved mechanical properties compared with adult MSCs.³⁷ These studies show a reduced capacity for cartilage extracellular matrix formation with aging and suggest a negative correlation between advancing age and chondrogenic potency of MSCs.

The mesenchymal progenitor population in the articular cartilage from second trimester fetuses had the greatest upregulation of type II collagen and aggrecan mRNA following chondrogenic differentiation compared to the adult and elderly samples.²⁰ This indicates an age-related decline in chondroprogenitors in fetal articular cartilage during development compared with postnatal adult donors.

The potential of MSCs to differentiate along specific lineages is altered with aging. MSC clonal populations from younger donors (0-11 years old) contained a greater proportion of bipotent clones with chondrogenic and osteogenic potential. In contrast, MSCs from older donors (22-30 years old) predominantly showed trilineage differentiation potential.³⁸ Advancing age appears to modulate MSC potency and the associated changes may reflect differences in functional capacities of MSCs during aging. Similar chondrogenic potencies have been reported for MSCs isolated from human fetal and adult bone marrow.^{3,4} However, we have shown that fetal and adult MSCs are differentially regulated by unique transforming growth factor- β (TGF- β) superfamily stimuli to activate the onset of chondrogenesis.³⁰ This suggests that the distinct mechanisms that govern chondrogenic regulation of MSCs may be a consequence of age-related changes following development and postnatal maturation.

The chondrogenic differentiation potential of adult MSCs is reported to be independent of donor age.^{17,18,39} It is important to note that the study by Im *et al.*³⁹ represents an aged population, with a patient range between 51 and 78 years of age and does not consider the potential of fetal or pediatric MSC populations. In addition, Dexheimer *et al.*¹⁷ included 75% of patients that suffered from OA in their older donor group and therefore the effects of age cannot be distinguished from the effects of disease in the aged population. Another study has shown a negative correlation between chondrogenesis and advancing age in male donors (16-82 years old) with no association evident in female donors (20-77 years old).¹⁸ The donor MSCs used in this study were isolated from bone marrow reamings harvested during fracture stabilization or joint replacement surgery. There is no detail regarding the age of the donor and the associated procedure so the influence of OA or other joint diseases, which are primary causes for joint replacement surgery, on MSC function during aging cannot be excluded.

From the available literature, it is unclear whether aging directly affects the chondrogenic differentiation potential of MSCs. While the changes in frequency and proliferative propensity of MSCs could modulate their chondrogenic potency, additional studies that directly compare chondrogenesis in MSCs with advancing age in donors without joint disease is crucial to furthering our understanding of MSC functional capacity.

Osteoarthritis-Related Changes

The Effect of Osteoarthritis on Growth Kinetics

The presence of OA appears to influence the growth capacity of adult MSCs. Murphy *et al.*⁴⁰ have shown that MSCs isolated from the bone marrow of donors with OA have a reduced rate of proliferation compared with MSCs from healthy subjects. The donor groups in this study however include a healthy subset from a younger age range (23-61 years old) and the patients with OA represent an older population (59-82 years old); therefore, any level of decline in proliferative potential due to aging cannot be completely excluded in this study. In patients with OA, the mononuclear cell yield and subsequent MSC proliferation is independent of OA etiology (whether the disease was age-related or caused by joint trauma or joint dysplasia).⁴¹ This shows that the presence of OA does not inhibit the proliferative ability of MSCs completely. In order to determine the precise influence of OA on MSC growth rates, MSCs from individuals with and without OA should be directly compared.

The Effect of Osteoarthritis on Chondrogenic Potential

The articular cartilage of healthy donors and patients with OA contains a mesenchymal progenitor population that expresses CD105 and CD166 and is preferentially localized within the superficial and middle zones of the tissue.⁴² Selection of the CD166 positive cells enhances chondrogenic potential and the CD105+/CD166+ subset shows similar chondrogenesis of progenitor cells harvested from both normal and OA cartilage.^{42,43} Another unique chondrogenic progenitor population that expresses CD9 and CD90 in addition to CD166 has been shown to populate 32% of the articular cartilage of patients with severe end-stage OA.³⁴ Progenitor cells appear to migrate from the bone marrow through breaks in the tidemark and into the cartilage matrix where they are capable of repopulating diseased tissue *ex vivo*.⁴⁴ These studies show that cartilage tissue affected by OA appears to contain subsets of chondroprogenitor cells with some potential for repair but it remains to be established whether these cells are capable of generating repair tissue that recapitulates that of healthy native articular cartilage.

The effect of OA on the chondrogenic potential of MSCs has been scarcely studied. The limited literature that is available presents conflicting results. MSCs derived from patients with OA have been shown to undergo chondrogenesis irrespective of the etiology of the disease.⁴¹ Although, MSCs isolated from individuals with OA appear to have a poorer potential for chondrogenic differentiation with reduced proteoglycan deposition compared with MSCs from healthy donors.⁴⁰ It is noteworthy that the patients with OA (59-82 years old) represent an older population group than the healthy donors (43-61 years old) and it is unclear whether advancing age has contributed to the reduced chondrogenic potential of these cells. In addition, both of these studies have relied on gene expression studies and histological analyses of micromass pellet cultures to determine chondrogenesis. We have previously shown that these methods are unable to accurately quantify collagen and proteoglycan deposition and matrix formation.⁴⁵ Kafienah *et al.*⁴⁶ have demonstrated that MSCs isolated from a range of donors with OA (42-90 years old) are capable of undergoing chondrogenesis and produced 3-dimensional tissue engineered cartilage with an extracellular matrix composed of proteoglycan and type II collagen. It is apparent that MSCs isolated from individuals with OA possess some chondrogenic potential. Specific comparisons of MSCs derived from healthy and OA age-matched donors are important to ascertain the functional implications of OA for chondrogenesis of MSCs. It would also be of interest to study the correlation between the chondrogenic potential of MSCs with the severity of OA throughout disease progression.

Concluding Remarks

Aging and OA are both characterized by a decline in self-renewal and repair potential. It is likely that these processes are associated with alterations in chondrogenic progenitor populations that contribute to the progression of aging or OA; however, the effect of these changes on cell function is unclear. Age-related changes during development and post-natal adulthood appear to have a profound implication on the proliferation and differentiation potential of MSCs. Although, while many reports include MSCs derived from patients undergoing joint replacement surgery the influence of disease is often not detailed or accounted for. Similarly, considering OA predominantly affects the elderly it is difficult to isolate disease-induced effects from those of aging. In combination with the wide scope of age ranges between donors across different studies, these factors highlight the necessity for a standardized approach to enable accurate division of subjects into specific categories when comparing age- and OA-related changes in MSCs.

There is a clear need for researchers to study the molecular changes in progenitor cells associated with aging and OA progression to explore the mechanisms that underlie

modifications to MSC proliferation and differentiation potential. Additional studies that incorporate age- and disease-matched controls will be integral to identify how aging or the development of OA specifically impacts on cell function. Improved understanding of age- and OA-induced effects on MSCs and how this in turn affects their functionality and chondrogenic capacity will have important implications for the clinical relevance of these cells in cartilage repair therapies.

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