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CELLULAR SENESCENCE AND THEIR ROLE IN AGE RELATED DISEASES

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ABSTRACT

Cellular senescence is a process that affects most of all the cells an organism during aging. Numerous mechanisms have been identified in soft tissues which contribute to cell senescence. Due to the lack of understanding the processes governing ageing and disease occurrence have been studied differently. But in recent years due to advancement in understanding more about disease through careful studies there has been an increasing overlap in understanding the biology of ageing and disease processes. Cell-type specific changes were observed during cellular senescence. For example, nitric oxide synthase (eNOS) activity has been found to be decreased in senescent vascular endothelial cells. A gradual accumulation of senescent cells can lead to the progression of some age related diseases but in case of non-age related diseases a faster progression can be seen due to the presence and formation of certain factors that contribute to the formation of cellular senescence. Thus senescence is not solely responsible for the progression of diseases which are age related. Although it is now clear that some of these mechanisms may be targeted with a greater impact on bone formation and skeletal integrity based on our current knowledge. Several issues remain unaddressed although many important advancements are made regarding the underlying mechanisms of bone cell senescence. By understanding the mechanisms of ageing that causes alterations to tissues and its consequences brings us one

step closer for developing new therapeutic ways of treatment and more promptly preventing the appearance of age related impairments and diseases.

KEYWORDS: Cell Senescence, Apoptosis, Telomere.

INTRODUCTION

During ageing,most of the cells in an organism are affected by cell senescence. Majority of the disease are manifested due to tissue dysfunction resulting from an ageing mechanism. Both of which results in the impairment of normal biological function. Therefore if the processes that modulate the development is properly assessed it will lead to progression are understood it gates the way for the development of new therapeutic methods for disease treatment and prevention.[1]

Due to the lack of understanding the processes governing ageing and disease occurrence have been studied differently. But in recent years due to advancement in understanding more about disease through careful studies there has been an increasing overlap in understanding the biology of ageing and disease processes.[1]

Understanding replicative senescence: Those tissues that have the ability to divide when stimulated are called mitotic cells e.g. fibroblast, endothelial cells, smooth muscle cells etc. andthey are found within tissues as reversible growth arrested state know as quiescence and for the purpose of cellular replacement and these cells remain in quiescent state until stimulated to proliferate. Their proliferation depends upon the frequency of damage which in turn is linked with 'wear and tear' of the tissues in which they residue.[2] When fibroblast get exposed to uv radiation they are more likely to proliferate and should be replaced than less damage-prone tissues. Other factors like presence of disease may damage the cells.[1]

The gradual accumulation of senescent cells is considered as the cause of ageing mechanism of mitotic tissues. Behaviourally, morphologically, genetically senescent cells have an altered phenotype, they are distinct from its growth-competent counterparts and these changes affects the neighbouring cells and other structural components leading to tissue ageing, disease, and increased risk of cancer.[1]

Very short telomere is also considered as a cause of cellular senescence. Telomeres are highly repetitive DNA found at the end of linear chromosome which are bound by a number of proteins that protect the telomere from DNA double strand breaks. During each cell

division due to the inability of DNA to replicate at the end of chromosome telomeres get shortened, and this results in formation of short telomeres and telomere proteins cannot protect them and results in DNA damage and cellular senescence. This process is known as replicative senescence which are triggered by oxidative stress and oncogenes.[1]

General mechanisms of cell senescence: impact on bone cells

Bone cell differentiation is affected by telomere shortening. Telomere shortening characterised by irreversible cycle arrest is an important mechanism that influences cellular senescence. Telomerase and protein complexes composed of shelterin and other proteins maintains the length of telomere. It also helps the cells to increase the telomere in length and to maintain the stem cell population.[1] Many age-related diseases has been related with the decrease in length of the telomere. It leads to reduced cell replication which contributes to impaired DNA repair. Limited stem cell pools and their impaired differentiation are caused due to the same factor in osteoblast progenitor cells. Experiments on mice has revealed the findings which is supported with invalidated telomerase reverse transcriptase shows decreased bone mass and thus enhanced osteoclastogenesis.[2]

Mechanistically, cell cycle arrest and apoptosis induced by the activation of reduced osteoblast differentiation in mice which showed increased p53 expression. Thus osteoblast differentiation is reduced by dysfunction of telomere and contributes to age-related bone diseases. Therefore telomere shortening could be prevented by increasing telomere expression and replicative senescence in precursor cells of osteoblasts. A new area on focus on telomerase reactivation to limit cell senescence of bone is seen in the recent advancement of telomerase gene therapy in mice delays aging without increasing the number and spread of cancer. Bone cell damage is caused by increased oxidative stress. Damage caused by reactive species of free radicals to components of cell. Other adverse effects caused by reactive oxygen species also contributes to ageing.[1]

Increase in the number of reactive oxygen species (ROS) with age and associated cell damage and cell death has supported the concept that an increased oxidative stress plays a greater role in bone fragility with advancement in age. Cell senescence and cell ageing regulated by p53 and p66 are associated with increased ROS and increased glutathione reductase activity leading to the activation of apoptosis of osteocytes and a decrease mass in bone in mice. In mice deficient in the cytoplasmic copper/zinc superoxide dismutase(Sod1)gene is provided to reproduce the above mechanism. The Sod1 gene is involved in increased intracellular ROS,

fragility of skeleton and osteoblastic cell proliferation associated with reduced turnover osteopenia and impaired osteoblast viability, a mechanism which is accelerated by mechanical unloading. The shift toward adipocytes instead of osteoblasts, in age-related shift in bone marrow also contribute to ROS accumulation which occurs with the increase in age and this results in increased bone marrow adipogenesis, along with a decrease in osteoblastogenesis. The activation of PPARg signalling also results from the same in osteoblastic cells through the oxidation of lipids. In addition, increase in ROS production and FOXO activity is related to increased endogenous glucocorticoid expression which in return affects the activity of Wnt signalling. The age-related decrease in Wnt signalling is accounted by the ROS activation of FOXOs and that of fb-catenin by PPARg. This pathway also plays an important role in controlling differentiation of osteoblast and adipocyte. Finding that mice lacking FOXOs was a major task to identify the role of FOXOs as inhibitors of Wnt/b-catenin signalling. In addition to reduced osteoblastogenesis, ROS also contributes to age-related increased stimulation of resorption of osteoblasticbone. Low bone mass in women and increased bone resorption is found relative to oxidative stress. The mechanism through which bone damage caused due to accelerated damage in DNA is not fully understood though it is known that accumulation of DNA damage through oxidative stress plays an important role in dysfunction of osteoblast which is an age-related increase.[1]

Another pathway which is an important modulator of osteoblasts along with osteoclasts has been identified is the role of NF-kB pathway in age-related bone loss. Chen and colleagues showed that ERCC1-XPF deficient mice exhibited severe bone loss. The severe loss of bone was caused by NF-kB transcription in cells of osteoclasts and osteoblasts and the above study by Chen and colleagues were found to be in relation with NF-kb associated with DNA damage. RECC1-XPF is an endonuclease which is required for DNA repair. The results revealed that those mice which were deficient in the particular endonuclease showed reduced bone formation, increase in the number of senescent cells and increased expression of osteoclastogenesis.[2]

Recent studies indicate the part played by NF-kB dependant mechanism on bone cell dysfunction. Also it was found that DNA damages induce dysfunctions in bone cell. Age-related fragility in bone cells mainly occurs due to oxidative stress and this finding has been able to raise the hypothesis that oxidative stress can be antagonized by antioxidants. Animal models treated consistently with antioxidants prevented bone loss in them. A rise in

intracellular ROS, p66shc phosphorylation and FOXO transcriptional activity was seen with the administration of intermittent parathyroid hormone (iPTH) along with the administration of vitamin C. Antioxidant vitamin C was administered in mice which were SOD1deficient.[1] The adverse effects on Wnt signalling indicate that this agent can antagonize the activity of age-related increase in oxidative stress as seen in aging mice. Bone protective effects in mice were also contributed by the adequate administration of estrogens, androgens along with intermittent parathyroid hormone which had antioxidant properties. Bone loss can alsobe reduced by minimising oxidative stress. Reduced osteoclast number and high bone density were seen in mice deficient NOX4.NOX4 also called NADPH oxidase 4 is an enzyme involved in ROS production and reduced bone resorption is seen through its inhibition. Hence adverse effects of ageing on bone can be reduced by combating oxidative stress which is age associated.[1]

Apoptosis and stem cells: Removal and replacement of senescent cells also depends on apoptosis and availability of stem cells reserve. If senescent cells were removed by apoptosis it would be difficult to identify their relation with damage and if these cells are replaced with stem cell reserve and not from somatic tissue it would be difficult to understand how cell lose leads to reduction in replicative capacity of neighbouring somatic tissues and which in turn increases appearance of senescent cells.[1]

The number of in vivo studies conducted that have looked the survival time of senescent cells are very few. But the number of in vivo studies have suggested that senescent cells may be resistant to apoptosis particularly in fibroblasts were most of the studies have been performed. The apoptotic potential of senescent human vascular endothelial cells with other counterparts have been identified with no difference.[1]

The extent of role of stem cells and somatic cells in tissue regeneration is not clear, but the functional ability of stem cells are found to decline with age. Stem cells are unlikely to become senescent in response to telomere shortening. However in response to DNA damage it is possible for these cells to enter senescence. And if these senescent cells are present in tissues their altered secretome may have detrimental effects on local tissue. The ability of self-renewal when removed from stem niche of the stem cells reveals that the local environment plays a crucial role. The functional decline occurs due to altered stem cell behaviour which has occurred due to change in the environment of stem cell niches by senescent cells.[1]

Biological impact of senescent phenotype: The upregulation of growth factors, pro-inflammatory cytokines and extracellular matrix –degrading proteins are the common features of the senescent phenotype which can be detrimental to the tissues in which they reside.[1] The reason for senescent cells to adopt such phenotype is currently unknown. One possible way is that these cells secretes cytokines to attract immune cells to its location, secretes matrix degrading proteins to allow the immune cells access and secrete growth factors to stimulate surrounding cells to proliferate once the cell has been removed. Although they decrease with increase in age, this process may be effective.[2]

Following are the functions of ECM: providing support and anchorage for cells, separating different tissues and regulating intercellular communication. another action of senescent cells include the up-regulation of matrix metalloproteinases (MMPs) which are enzymes that are capable of degrading proteins such as collagen and elastin that forms the extracellular matrix. The activity of MMP is normally inhibited by TIMPs, but research suggests that these inhibitors themselves are down-regulated by senescence and they also thus contribute to cellular senescence. They have also shown effects in the pathogenesis of diseases such as coronary heart disease and implicated in the progression of osteoporosis. When senescent chondrocytes release MMPs they may contribute to the development of osteoarthritis.[1]

Many cytokines are secreted by senescent cells which due to their diverse function could have multiple consequences on the ageing of tissues and the progression of disease. These proteins not only affects the local tissues but also tissues found throughout the organism. Only a small fraction of senescent cells may need to be present for their significant impact on tissue impairment and cytokines are also involved here. Cytokines also causes the up-regulating and down-regulating several genes which results in the production of other cytokines. Vascular smooth muscle cells that have become senescent due to the activation of Ras have been shown to drastically increase the expression of proinflammatory cytokines (Minamino et al. 2003). IL1α was shown to be up-regulated 11-fold, IL1β 50-fold, IL-6 12-fold and IL-8 77-fold. It was then found that this proinflammatory phenotype will contribute to the progression of atherosclerosis. High levels of two cytokines, IL6 and TNFα were found to be produced by senescent cells in vivo. Upregulation of TNFα by T-cells in the bone marrow has been found to be a casual mechanism for bone loss.[1]

The culture report shows a higher expression of inflammatory genes in the replicative senescence of humans hepatic stellate cells. Interleukin-8 is up-regulated in senescent stellate

cells (SC), which correlates with increase expression observed with disease activity in human alcoholic liver fibrosis, similarly is the up regulation of fibrogenic cytokine Interleukin- 6. Normally, chronic tissue damage is characterised by proliferation, motility, contractility and synthesis of ECM and this results in reduced replicativecapacityofthesecellsand the accumulation of senescent cells will be accelerated. This activation ofSC is regulated by cytokines and growth factors. Therefore, within the liver unregulated secretion of pro-inflammatory cytokines and growth factors from senescent SC may cause further damage.

By SA-β-Gal staining the presence of senescent hepatocytes in liver grafts was assessed, with a total of 34 of the 103 biopsies analysed within the first year. This pro-inflammatory phenotype may partly be due totheup-regulationofintercellularadhesionmolecule-1 (ICAM-1), a molecule known to be involved in inflammatory response and is over-expressed in senescent cells and aged tissues.[2]

Abnormal secretion of some growth factors also contributes to senescent phenotype. for example, human senescent fibroblast cultures revealed increased secretion of vascular endothelial growth factor (VEGF). It has been found that cellular senescence may be a mechanism tosuppresstumourigenesisearly in life can contribute cancer in aged organisms and it may also stimulate premalignant and malignant, but not normal epithelial cells to proliferate in culture and form tumours in mice. Elevation of Fibroblast growth factor 7 (FGF7), hepatocyte growth factor and amphiregulin (AREG) were found in the extracellular environment of senescent prostate fibroblasts. Senescent prostate fibroblasts stimulated epithelial cell proliferation threefold and twofold throughdirect co-culture and conditioned medium. These results suggest that senescent cells may contribute to the progression of prostate neoplasia by altering the prostate microenvironment.[2]

Cell-type specific changes were observed during cellular senescence. For example, nitric oxide synthase (eNOS) activity has been found to be decreased in senescent vascular endothelial cells.As nitric oxide (NO) is an important component in regulating vascular function, a decline in its production may lead to detrimental consequences. A reduction in NO production by eNOS, has been suggests an increased risk for cardiovascular diseases.[1]
Cell-type specific alterations were demonstrated through a currently unpublished work on the transcriptional analysis of human vascular smooth muscle cells. The two major observations made from senescent vascular smooth muscle cells were a 24-fold decrease in the expression of matrix Gla protein (an inhibitor of calcification) and over a fourfold increase in bone

morphogenic protein2 (a promoter of calcification). A comparison of these changes with the other transcriptional profiles show that these changes appear to be specific to senescent vascular smooth muscle cells. A leading risk factor for stroke, coronary artery disease, heart attack, and heart failure is the stiffening of arteries which raises the blood pressure in older people. Therefore this shows us that age-related hardening and stiffening of the arteries is greatly influenced by senescent vascular smooth muscle cells. A reduced ability to migrate is another consequence in regard with cellular senescence. This impaired ability to migrate can be associated with the changes that occur to the cytoskeleton during cellular senescence. An important component required for cellular migration is actin of the cytoskeleton. However, for senescent fibroblasts, for example, down-regulation of vimentin has been found in place of actin. This migration deficit has important role during wound healing as the cells are stimulated to migrate into the wound, proliferate and construct a new ECM. Since proteins are secreted by senescent cells which degrade the matrix, wound repair would be further impaired. An alternative reasoning for the decline in the ability of senescent cells to migrate is the loss or impairment of the migratory response to stimuli such as growth factors. A majority of the research carried out to study about senescent cells on fibroblasts has been carried out with little or no understanding of the senescent phenotype of other cell types. New approaches in treatment and prevention can be developed through a detailed understanding of the age related pathology linked with senescent phenotype of cells as an alternative perceptive.[2]

Age-related changes in bone mass in the senescence-accelerated mouse (SAM): Several strains of the senescence-accelerated mouse (SAM) were investigated by Am J Pathol in 1986 to study the age-related changes of the femoral bone mass, and they found thatall strains same patterns of age changes, that is, the peak value of bone mass corrected by the diameter of the shaft where obtained when the mice were 4 or 5 months of age and a linear fall was found with age up to over 20 months of age. Two strains named, SAM-R/3 and SAM-P/6, of same ancestry on pedigree, found a significantly lower peak bone mass compared to other strains (SAM-R/1, SAMR/2, SAM-P/1, and SAM-P/2). On the other hand it was found that all these strains had the same rate of decrease, and a little difference in mineral and collagen contents per dry weight of bone s were found among the strains. During the histological studies of tibia, femur, and lumbar spine revealed that osteomalacia was not the reason for osteopenia but it is due to osteoporosis. The elderly mice among the strains under study were prone to fracture, thus found clinically more relevant to study about senile osteoporosis.[2]

One of the main physiologic changes associated with aging is loss of bone mass. Changes in normal pattern and a close negative correlation with the incidence of fracture due to aging were revealed by epidemiological studies on bone mass. Studies conducted on the bone mass of hetero- and homozygotic twins suggested that both genetic and environmental factors are linked to bone mass and it also shows the degree of susceptibility to osteoporosis and in addition to this some racial difference in bone mass or the incidence of fracture added value to this result.[2] In many studies of osteoporosis, by doing ovariectomy in relatively young animals, theosteopenic condition had been induced, but such experimental models were found inappropriate to study senile osteoporosis because in this induced situation there will be rapid decrease in bone mass that compared with the natural age associated loss.[2]

At early 1970s, a murine model was developed for of accelerated senescence (senescence accelerated mouse, SAM), which comprises of two series. In general, acceleration of aging is in the SAM-P series, and these can be determined by the shortened life span and various early signs and symptoms of senescence, including changes in physical activity, skin, eyes, and spinal curvature, as compared with the control of SAM-R series. Diseases closely associated with senescence observed in SAM are senile Amyloidosis and cataracts are thediseases which are closely associated with senescence observed in SAM series.[2]

Link between cellular senescence and disease: A gradual accumulation of senescent cells can lead to the progression of some age related diseases but in case of non-age related diseases a faster progression can be seen due to the presence and formation of certain factors that contribute to the formation of cellular senescence. Thus senescence is not solely responsible for the progression of diseases which are age related.[3]

Although the rates at which they progress differ, the mechanisms through which both of them develop are the same. Senescent cells are generated within mitotic tissues but their impact is not bound within the tissue itself. A mixture of mitotic cells, post-mitotic cells along with long-lived proteins make up tissues. Since all these components interact with each other, a change in either one of them will definitely have an impact on the other even though the ageing mechanisms for each of them are different.[3]

A major cause of low-back pain is mainly due to the degeneration of the intervertebral disc which occurs as a part of accelerated cellular senescence. Following were tested on cells isolated from normal and degenerate human tissue: mean telomere length, senescence-

associated β-galactosidase (SA-β-Gal) staining, and replicative potential. And a decrease in the mean telomere length were found in cells from non-degenerative tissue. The result for SA-β-Gal in non-degenerative patients were negative when compared to cells from degenerative discs, which exhibited 10–12% SA-βGal staining along with a decrease in replicative potential.[3]

In this conditions the three possible reasons why cellular senescence was accelerated

(1) Cell turnover for replacement accelerated by certain unknown factors that led to the damage and removal of cells

(2) Oxidativestress, resulting in stress induced premature senescence (SIPS), or

(3) Telomeres (started off shorter than normal).[3]

A correlation between some disease states and the presence of senescent cells in vivo was found. Detectionof senescent hepatocytes in normal liverwas done by suing SA-β-Gal staining method. Senescent hepatocytes in normal liver, liver with diseases such as chronic hepatitis C and hepatocellular carcinoma (HCC) were also detected. Out of three of 15 (20%) normal livers tested, 16 of 32 (50%) in livers with chronic hepatitis C and in six of ten (60%) livers with HCC the presence of senescent cells were found. A proportional increase in senescent cells in normal livers was found to be associated withage. And the increase in the amount of senescent fraction in chronic hepatitis is probably due to accelerated senescence. Senescent cells were also found in nontumoural tissues which was clearly linked with the presence of HCC. Premalignant and malignant cells were stimulated to proliferate in non-tumoural tissues by senescent cells, demonstrating that the ageing of one tissue has an impact on the other along with a contribution of senescent cells to carcinogenesis.[3]

Analysing cellular senescence in human benign prostatic hyperplasia (BPH) specimens reveal that BPH is a disease that occurs due to abnormal growth of the prostate. 40% of the analysed samples showed staining which was positive for SAβ-Gal. The expression of SA-β-Gal was correlated with a high prostate weight of more than 55g. But those weighing less than 55 g tended to lack senescent epithelial cells. A conclusion was then arrived that the accumulation of senescent epithelial cells may play a role that progress prostatic enlargement associated with BPH. Further progression may be led by the accumulation of senescent cells as a consequence of this disease. Unregulated stimulated proliferation, increasing cell turnover followed by the appearance of senescent cells were the results of the enlargement. This gives

the answer for which why a stronger expression of SA-β-Gal is detected in prostates (>55g) even though they have undergone more cellular divisions.[3]

Insulin resistance causes compensatory proliferation of pancreatic beta cells in the pathogenesis of type-2 diabetes. This compensatory proliferation might accelerate cellular senescence, contributing further to the progression of diabetes. To investigate this, Sone and Kagawa (2005) used nutrient-induced diabetic mice to analyse beta cells for SA-β-Gal and the proliferation marker Ki67. At 4 months, the proliferation of beta cells was 2.2-fold higher than in the control group. At 12 months, the frequency of Ki67 decreased to one-third that of the control and SA-β-Gal-positive cells increased to 4.7-fold that of the control group. This increase in the senescent betacell fraction correlated with insufficient insulin release, suggesting cellular senescence may contribute to diet-induced diabetes. In this instance, it is difficult to determine whether cellular senescence is the cause or the consequence of insulin resistance. It later appears to be a contributor, but whether it is also the initiating factor is unknown.[3]

Muller et al. (2006) found that in patients with emphysema there is an increase in the number of senescent primary lung fibroblasts compared with normal controls (an average of 4% of cells from control patients were stained positive for SA-β-Gal and it is compared with an average of 16% in emphysema patients). Long-term exposure of tobacco smoking accelerates senescent cells formation, which gradually leads to loss of elasticity of the lung tissue, and leads to destruction of structures supporting the alveoli, and there will be destruction of capillaries feeding the alveoli observed with emphysema.[3]

Instead of SA-β-Gal, Sis et al. (2007) used senescent-associated p16 increases to detect senescent cells in kidneys with glomerular disease (GD). The conditions of GDs, falls into two major categories: The inflammation of the membrane tissue in the kidney that serves as a filter, separating extra fluid and wastes from the blood is called glomerulonephritis; is the scarring or hardening of the tiny blood vessels within the kidney is called glomerulosclerosis.Studies found that when compared with normal there is an increased expression of the nuclear p16 in samples with GD. Independently increased expression of nuclear p16 is also associated witholder age and interstitial inflammation. In glomerulonephritis senescent cells have a greater contribution since they adopt a pro-inflammatory phenotype.[3]

All these examples demonstrate the presence of senescent cells in both tissues and disease states. Through general cell loss there will be appearance of senescent cells and replacement by mechanisms which accelerates cellular senescence, such as in disease condition. This suggests that ageing of mitotic tissues and the appearance of disease would be greatly reduced if there were no injuries occurred as a consequence of disease, environmental factors or by normal biological and mechanical wear and tear. In review, the ageing process and disease development/progression may be enhanced by senescent cells due to following factors.

1. Cellular dysfunction: inability to function properly.
2. Behavioural alteration of neighbouring cells.
3. Degradation of the structural components such as extracellular matrix.
4. Reducing the pool of growth-competent mitotic cells.
5. Stimulating cancer formation.[3]

Future considerations

By understanding the mechanisms of ageing that causes alterations to tissues and its consequences brings us one step closer for developing new therapeutic ways of treatment and more promptly preventing the appearance of age related impairments and diseases. In regard to cellular senescence, through an in-depth understanding of the senescent phenotype of all mitotic cell-types it is possible to assess the potential consequences of their appearance.[1]

To overcome the problem of senescent cells in tissues, our future research should be aimed on the following three strategies

(1) Prevention.
(2) Removal.
(3) Replacement.

The main aim of telomerase therapy is to elongate the telomeres of somatic cells so that appearance of senescent cells can be prevented, and this can be made possible by transiently turning on telomerase in cells which results in longer telomeres which increases the replicative capacity and there will be reduced chances for formation of senescent cells through replication.But, not all telomere shortening results in senescent cell formation. Apart of telomere shortening, senescent cell formation were found and this would be unaffected by telomere elongation by telomerase. Senescence can also occur due to DNA damage i.e,

elongated telomeres can also give rise to senescent cells but the ratio of DNA damage and senescent cell formation is not known.[1]

Even if telomerase therapy is made practical, senescent cells formation in tissues cannot be completely avoided. In such cases direct removal of senescent cells from tissues should be done. Two potential approaches include the development of drugs which have high specificity for target site, and the use of the body's self-immune system to remove senescent cells are the two potential approaches included.[1]

At present, a drug specifically for the targeted senescent cells is unavailable. However, drugs which are targeted to specific cancer cells could be adapted to target senescent cells because they would identify senescent specific cell-surface markers get bind to them and induce apoptosis, so that senescent cells will be removed.[1]

If senescent cells formation is due to failure of an aged immune system, then rejuvenation of the aged immune system can be done which would be greatly beneficial, and in such cases it is necessary to know the biology which leads to the dysfunction of immune system for designing the medications needed. Age-related changes which are associated with tumour-antigen capture and presentation should be considered. In brief, dendritic cells capture and they process tumour-specific antigens which begins to mature and migrate to the lymph nodes and their will be interaction with cytotoxic T-lymphocytes (CTLs), presents the tumour information and causing theiractivation and proliferation, targeting tumour cell removal. The removal of senescent cells will have the same mechanism as that of tumour cell removal. There are a number of stages during antigen capture and presentation that could be altered with age and thus they need further investigation.

1. Dendritic cells did not recognise the target cell.
2. The target cell specific marker was not displayed by dendritic cells.
3. In response to dendritic cells lymphocytes were not activated.[1]

Finally, the third way is the replacement of cells. If telomerase therapy is not possible, there will be only stimulation for the proliferation of surrounding cells for its replacement due to removal of senescent cells from tissues that reduces the replicative capacity of that tissue and there will be increased appearance of more senescent cells. However, stem cells present in tissues were also involved in cell replacement but up to what extent these stem cells or the

surrounding somatic cell plays in tissue regeneration is not known. The ageing mechanisms may also affects stem cells and that result in their dysfunction. So the addition of stem cells into tissues after the removal of senescent cells should be considered and necessary research should be done.[1]

Strategies for the prevention, removal and replacement of senescent cells are at its infancy. Inevitable benefits in regenerative medicines can be achieved only by knowing the biology of ageing and the ability to translate such knowledge practically into therapeutic applications.[4]

DISCUSSION

There will be an increase in the bone mass of humans up to the third decade of life and then it gradually decline. In case of women, this rate of decline is more rapid, and at the time of menopause there will be a temporary acceleration of bone loss. In these human studies, all indexes of bone mass used are of a relative value which is corrected based on the size of the bone, for example, divided by the width of the bone. In case of certain bones the absolute bone mass and their strength may well decline more slowly than the relative bone mass, it is because of the periosteal bone formation which occurs throughout life and due to continues expansion of bone width. But in small animals the formation of periosteal bone after the termination of the longitudinal growth is more prominent.[3]

Results obtained after 5 months of age revealed decelerated longitudinal growth in the femurs of SAM. And the same ceased up to 10months of age. The difference in the kind of index used differentiates the extent of bone loss. Tylan on his experiments related to the effects of bone loss related to spleen cell transplantation reported changes in femoral bone mass which were age related effects and the same was used as control. The absolute bone mass were represented as ash weight and no significant loss were seen before 20 months of age, then a decrease was seen.[2]

CONCLUSION

Our present understanding on cellular senescence is a collective phenotype composed of complex networks of effector programs. Intrinsic senescence mechanisms along with alterations in local factors and signalling pathways, are several interacting processes that arises from bone ageing.[1] Although it is now clear that some of these mechanisms may be targeted with a greater impact on bone formation and skeletal integrity based on our current knowledge. Several issues remain unaddressed although many important advancements are

made regarding the underlying mechanisms of bone cell senescence. First is the unavailability of good candidate markers in vivo for senescent cells as in other tissues. Reliable senescent markers are required to predict the effect of senescent cells on bone cells which can be later used to prevent the damaging processes in bone cells. Second, studies shows that cellular senescence leads to the secretion of proinflammatory proteins that contributes to chronic inflammation associated with ageing. Finally, our aim is to determine various senescence processes in bone cells which can be used for preserving the number and function of bone-forming cells. In the future, the answers to these questions may provide new insights into potential therapies for attenuating bone cell senescence and age-related bone loss.[3]

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