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Mini Review

Senescence and Diabetes

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Abstract

It has long been the dream of humanity to regain youth and defeat aging. Research tried for decades to explore the mechanisms of aging and possible ways to intervene therapeutically in order to delay/prevent aging. Senescence is one of the processes by which aging cells can invoke deleterious effects on other cells and remote organs. Cellular senescence could be the missing link between aging and related chronic diseases including diabetes and cardiovascular diseases. Senescent cells are in a state of cell cycle arrest but remain metabolically active by secreting inflammatory factors. In this mini-review, we summarize current knowledge on cellular senescence and its secretory phenotype and their mechanistic role, that may help identify potential drug targets for age-related diseases, and treating them as a group, rather than one at a time thereby facilitating healthful life span extension in humans.

Keywords: *Senescence; Diabetes; Cardiovascular Diseases*

Human have always aspired to having longer lives. Eternal life was the subject of many folk tales and anecdotes. It is believed by some that the biblical figure of Adam was persuaded to eat the forbidden fruit tree in paradise for that same goal. The legend of the youth of fountain is again another reflection of that much sought after desire.

Aging is currently looked at as a major independent risk factor associated with many diseases that may cluster and occur insidiously and simultaneously (Figure 1). As people reach advanced age, they often face increasing disability accompanied by the prevalence and worsening of multiple chronic diseases, frailty, and loss of independence [1]. Premature aging ensues due to disruption of the cell cycles leading to arrest of their replication and regeneration and subsequently amelioration of their function. Diabetes is a clear evident example of premature aging in humans.

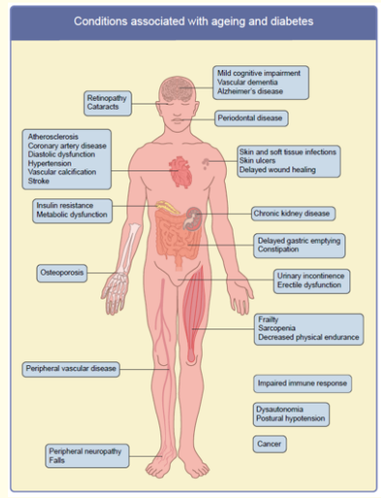

Figure 1: *Source: Palmer., et al. (2019) Diabetologia DOI 10.1007/s00125-019-4934-x.*

A recently published article explored the impact of intermittent fasting on general health, morbidity and mortality [2] and the results of that observation is in harmony with the hypothesis that treating chronic diseases one at a time does not suffice and that Calculations based on mortality data in the United States surprisingly predicts that: if cancer was eliminated as a cause of death, average human life span would increase only by 3% - 4% [1,3]. The same is true were ischemic heart disease to be "cured". Yet caloric restriction, which retards broad basic aging processes by as yet incompletely understood mechanisms [4], extends life span in animal models, including mice, by much larger increments (Figure 2).

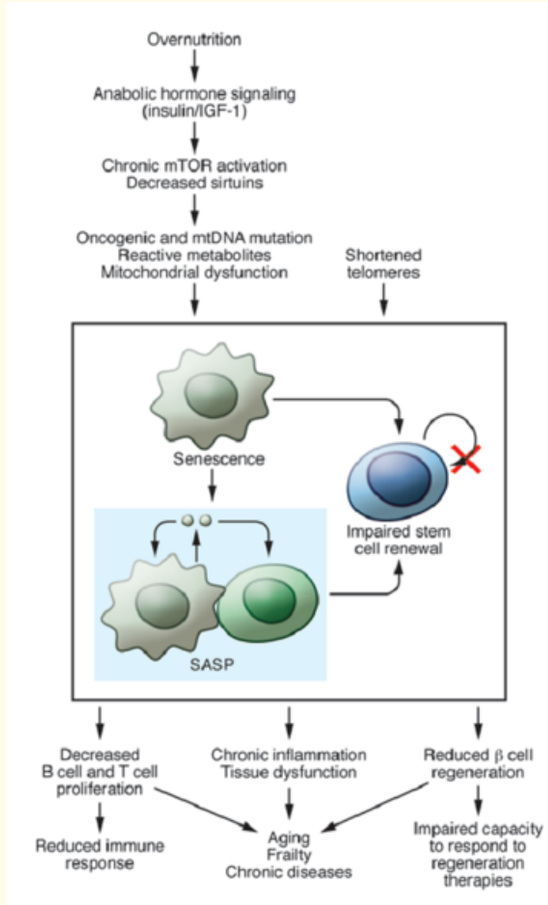

Figure 2

Until recently, the powerful association between age and chronic disease has mainly been noted with little hope of intervention. A critical roadblock to enhancing health span is the lack of effective treatments for age-related frailty and chronic diseases as a group. Currently available treatments are not directed at the root causes of age-related dysfunction. The study of the phenomenon of senescence of human cells highlighting its causes and mechanisms had opened new horizons in the field of defeating aging-related disorders.

Senescent cells by definition are those cells when exposed to factors leading to their death e.g. oncogenic insults, telomere erosion or oxidative stress, they resist the process of apoptosis and survive senescently and metabolically active secreting what is known as SASP "Senescence Associated Secretory Phenotypes", which in turn causes senescence to other cells in other organs either endocrinologically or paracrinologically. Senescent cells also show alterations in subcellular signaling pathways and expression levels of specific genes.

Cellular senescence is not always that bad, it is considered to be beneficial in a number of other processes, including wound healing [5,6], embryogenesis [7], cancer prevention [8], tissue regeneration [7,8] and the promotion of insulin secretion by pancreatic β-cells during aging (Table 1) [9]. In fact, senescence is a normal biologic process that occurs in all organs in a balanced way that keeps with the regenerative capacity of the organ, however when this balance is disrupted by accumulation of senescent cells beyond the clearance capacity of the immune system.

	Pediatric medication (n = 66) [1]	Adult medication (n = 267) [2]	Adult surgery (n = 88) [3]	All adults (n = 355) [4]	P (ANOVA) (1 vs. 2 vs. 3)	P (all adults vs. pediatric) (1 vs. 4)
Demographic characteristics						
Age (years)	14.2 ± 2.0	53.9 ± 8.9	49.1 ± 9.8	52.7 ± 9.4	<0.001	<0.001
Female, n (%)	47 (71.2)	114 (42.7)	69 (78.4)	183 (51.5)	<0.001	0.005
Race/ethnicity, n (%)					<0.001	<0.001
White	19 (28.8)	141 (52.8)	25 (28.4)	166 (46.8)		
Black	14 (21.2)	81 (30.3)	16 (18.2)	97 (27.3)		
Hispanic	25 (37.9)	28 (10.5)	40 (45.5)	68 (19.2)		
Asian	2 (3.0)	11 (4.1)	7 (8.0)	18 (5.1)		
American Indian	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.3)		
Mixed	6 (9.1)	4 (1.5)	0 (0.0)	4 (1.1)		
Other	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.3)		
Weight (kg)	98.9 ± 22.6	102.1 ± 19.8	96.8 ± 11.4	100.8 ± 18.2	0.057	0.454
BMI (kg/m^2)	36.6 ± 6.0	35.0 ± 5.7	35.4 ± 2.8	35.1 ± 5.1	0.093	0.035
Triponderal index (kg/m^3)	22.4 ± 3.5	20.6 ± 3.6	21.5 ± 2.0	20.8 ± 3.3	<0.001	<0.001
Waist circumference (cm)	109.0 ± 14.2	111.8 ± 13.5	105.8 ± 7.5	110.3 ± 12.6	<0.001	0.475
Glycemic characteristics						
HbA_{1c} (mmol/mol)	38.54 ± 6.11	39.30 ± 4.24	40.66 ± 4.55	39.64 ± 4.35	0.012	0.080
IGT, n (%)	53 (80.3)	197 (73.8)	54 (61.4)	251 (70.7)	0.022	0.147
Hyperglycemic clamp parameters						
Fasting glucose (mmol/L)	6.03 ± 0.97	6.09 ± 0.56	6.18 ± 0.83	6.11 ± 0.63	0.416	0.430
Fasting C-peptide (nmol/L)	1.67 ± 0.53	1.22 ± 0.47	1.23 ± 0.38	1.22 ± 0.45	<0.001	<0.001
Fasting insulin (pmol/L)	214.1 (62.2, 736.7)	103.6 (36.6, 293.5)	112.9 (39.9, 319.0)	105.8 (37.3, 299.9)	<0.001	<0.001
$ACPR_g$ (nmol/L)	1.24 (0.14, 11.18)	0.57 (0.10, 3.25)	0.49 (0.07, 3.46)	0.55 (0.09, 3.31)	<0.001	<0.001
AIR_g (pmol/L)	499.3 (55.4, 4,501.5)	174.4 (23.7, 1,281.3)	135.2 (11.0, 1,657.4)	163.8 (19.3, 1,390.6)	<0.001	<0.001
Steady-state (second-phase) C-peptide response (nmol/L)	5.19 (2.50, 10.74)	3.95 (1.96, 7.98)	3.55 (1.60, 7.84)	3.85 (1.85, 7.99)	<0.001	<0.001
Steady-state (second-phase) insulin response (pmol/L)	1,370.3 (298.6, 6,288.0)	636.3 (157.4, 2,572.8)	539.1 (123.4, 2,355.7)	610.7 (147.4, 2,530.4)	<0.001	<0.001
$ACPR_{max}$ (nmol/L)	7.85 (3.7, 16.66)	4.89 (2.03, 11.78)	4.72 (1.6, 13.93)	4.85 (1.91, 12.32)	<0.001	<0.001
AIR_{max} (pmol/L)	5,409.4 (2,196.2, 13,323.6)	3,144.1 (1,113.4, 8,878.5)	3,084.2 (897.1, 10,603.7)	3,129.1 (1,053.4, 9,295.3)	<0.001	<0.001
Glucose disposal rate (mmol/kg/min)	0.025 ± 0.010	0.022 ± 0.010	0.021 ± 0.012	0.021 ± 0.010	0.020	0.007
M/I ($\times 10^{-5}$ mmol/kg/min per pmol/L)	1.69 (0.37, 7.69)	3.06 (0.72, 12.97)	3.35 (0.89, 12.53)	3.13 (0.76, 12.87)	<0.001	<0.001
Fasting C-peptide/fasting insulin ($\times 10^{-2}$ nmol/pmol)	0.75 (0.31, 1.81)	1.1 (0.61, 1.99)	1.04 (0.61, 1.76)	1.09 (0.61, 1.93)	<0.001	<0.001

Table 1: *Select baseline physical and demographic characteristics, insulin sensitivity, and β-cell responses from the hyperglycemic clamp for youth and all adults.*

Data are mean ± SD or geometric mean (95% CI) unless otherwise indicated. P values for nonnormally distributed data based on log-transformed values. "Other" for race/ethnicity includes mixed, Asian, American Indian, and other.

In diabetes, the beta cells suffer from continuous loss by contributary effect of glucotoxicity, lipotoxicity, deposition of islet amyloid polypeptide, chronic exposure to oxidative stress, toxins, inflammation, and ultraviolet radiation all of which leads to stress-induced premature senescence (SIPS). However, aging alone is an independent factor for beta cell loss [7,8]. Besides a lower number of β-cells, senescence of β-cells can also lead to a decrease in insulin production in T2DM. However, the pathophysiology of pancreatic β-cell senescence appears to be complex, as it has been shown recently that induction of senescence in β-cells could also lead to increased insulin production.

Senescence also is condemned in the development of diabetes complications, recently, it was shown that Exposure of human aortic endothelial cells to high glucose levels leads to increased β-galactosidase expression and decreased telomerase activity, both markers of cellular senescence. In myocardial tissue of rodents with T1DM and diabetic cardiomyopathy, abundant cellular senescence is observed in cardiomyocytes and cardiac microvascular endothelial cells [10,11]. Hyperglycemia leads to p53 activation in cardiomyocytes, which upregulates the renin-angiotensin system [10]. Increased angiotensin II production leads to an increase in ROS formation and an increase in intracellular Ca^{2+} current, which both initiate telomere shortening, cellular senescence, and cell death [11]. In the arterial system, streptozotocin-induced T1DM in mice leads to cellular senescence in both endothelial cells and VSMCs [12,13].

Cellular senescence in the cardiovascular system seems to have different phenotypes depending on the causative factor being aging or diabetes. For instance, cellular senescence when induced by aging in both heart and vessels is mostly limited to endothelial cells, whereas when induced by diabetes it occurs in endothelial cells, VSMCs, and cardiomyocytes. Furthermore, the SASP has been shown to differ depending on the senescence-initiating stimulus being aging or disease [14].

Thus, senescent cells might be part of a pathogenic loop in diabetes and cardiovascular diseases, as both a cause and consequence of metabolic changes and tissue damage.

Therapeutic targeting of a basic aging mechanism such as cellular senescence may have a large impact on disease pathogenesis and could be more effective in preventing the progression of diabetes complications than currently available therapies that have limited impact on already existing tissue damage [15]. The paradigm that senescence and the SASP is at the center of different age-associated pathologies including diabetes [16] may lead to the discovery of new therapeutic avenues [17].

Some of the antidiabetic drugs can affect senescence, a recent study linked metformin antineoplastic activity to inhibition of the SASP by interfering with proinflammatory nuclear factor-kB signaling [18].

Senolytic therapy

Therapeutic clearance of cellular senescence is an active area of research in which there is much opportunity for progress. Senescent cell clearance may prove valuable in slowing progression of general age-related dysfunction and is also worth testing in diseases correlated with increased senescent cell burden, such as diabetes. Therapies could be developed either to target and eliminate senescent cells directly or to alleviate local and systemic effects of the SASP. This issue is further complicated by cell-type, tissue-type, and organismal differences in the composition of the SASP, as well as the multiple effects that SASP factors can play in inflammation, immunity and normal physiology. It is unclear whether senescent cell removal or SASP inhibition would be more beneficial, and this may depend on organ system and disease pathogenesis [19].

At least two approaches can be envisaged for removing senescent cells: the use of antibodies to specifically target senescent cells or the development of small molecules to selectively kill them. Developing interventions to target senescent cells or the SASP will be a tall order. Possibly, combinations of approaches will be required to address senescent cells in different tissues and specific for the SASP phenotype.

Recently senolytics were tried in different situations aiming to get rid of senescent cells and SASP. In diabetic chronic kidney disease, using the combination of Dasatinib and Quercetin (D + Q), which selectively eliminated senescent cells by transiently disabling pro-survival networks that defend them against their own apoptotic environment [20].

The new senolytic molecules navitoclax and ABT-737 could occupy the inhibitory pathways which counteract their antiapoptotic functions and initiate apoptosis in senescent cells [20]. Notably, a recent finding shows that bromodomain containing protein 4 (BRD4) inhibitors could modulate SASP with high specificity in senescent cells without influencing healthy subjects [21,22].

Surprisingly, senolytics had been shown to prevent T1DM, Senescent beta cells upregulated pro-survival mediator Bcl-2, and treatment of NOD mice with Bcl-2 inhibitors selectively eliminated these cells without altering the abundance of the immune cell types involved in the disease. Significantly, elimination of senescent beta cells halted immune-mediated beta cell destruction and was sufficient to prevent diabetes. The authors said that their findings demonstrate that beta cell senescence is a significant component of the pathogenesis of T1D and indicate that clearance of senescent beta cells could be a new therapeutic approach for T1D [23].

Palmer K., *et al.* showed that reducing senescent cell burden in obese mice, either by activating drug-inducible "suicide" genes or by treatment with senolytic agents, alleviates metabolic and adipose tissue dysfunction. These senolytic interventions improved glucose tolerance, enhanced insulin sensitivity, lowered circulating inflammatory mediators, and promoted adipogenesis in obese mice. Elimination of senescent cells also prevented the migration of transplanted monocytes into intra-abdominal adipose tissue and reduced the number of macrophages in this tissue. In addition, microalbuminuria, renal podocyte function, and cardiac diastolic function improved with senolytic therapy [24].

Ogrodnik., *et al.* [25] showed that the accumulation of senescent cells promotes hepatic fat accumulation and steatosis. They reported a close correlation between hepatic fat accumulation and markers of hepatocyte senescence. The elimination of senescent cells by suicide gene-meditated ablation of p16Ink4a-expressing senescent cells in INK-ATTAC mice or by treatment with a combination of the senolytic drugs dasatinib and quercetin (D+Q) reduces overall hepatic steatosis.

Roos M., *et al.* demonstrated that chronic clearance of senescent cells with dasatinib and quercetin improves established vascular phenotypes associated with aging and chronic hypercholesterolemia and may be a viable therapeutic intervention to reduce morbidity and mortality from cardiovascular diseases [26].

A large number of senolytic drugs are under research with preliminary promising results raising new hopes for a better control of age-related multiorgan disorders [27-29].

Conclusion

Aging is a major independent risk factor for the development of several multi-organ diseases, including diabetes, stroke, myocardial infarction, Alzheimer's disease, and several types of cancer. Cellular senescence can be defined as a permanent arrest of cellular growth. Although senescent cells do not proliferate, they have the capacity to produce and secrete soluble factors that can influence neighboring cells and tissues by induction of a state of chronic inflammation (inflammaging). Senescence can be the missing link between aging and chronic diseases. Senolytic therapy had been shown to ameliorate effects of aging on different pathologies including diabetes and its complication, cardiovascular atherosclerotic diseases, osteoporosis and Alzheimer's disease. If the premise proves to be true then a great transformation of medical care could be expected.

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