Aging and vascular-related pathologies

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Abstract

Our aging population is set to grow considerably in the coming decades. In fact, the number of individuals older than 65 years will double by 2050. This projected increase of people living with extended life expectancy represents an inevitable upsurge in the presentation of age-related pathologies. However, our current understanding of the impact of aging on a number of biological processes is unfortunately inadequate. Cardiovascular, cerebrovascular and neurodegenerative diseases are particularly prevalent in the elderly population. Intriguingly, these pathologies are all associated with vascular dysfunction, suggesting that the process of aging can induce structural and functional impairments in vascular networks. Together with elevated cell senescence, pre-existing comorbidities and the emerging concept of age-associated inflammatory imbalance, impaired vascular functions can significantly increase one's risk in acquiring age-related diseases. In this short review, we highlight some current clinical and experimental evidence of how biological aging contributes to three vascular-associated pathologies: atherosclerosis, stroke, and Alzheimer's disease.

Introduction

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One thing is for certain, we cannot escape the process of aging. Population aging is expected to accelerate in the coming years, and along with it, comes new challenges. The last decade has seen vast advancements in public health, medical breakthroughs, and improvements in economic and social performance. All of these factors contribute to people living longer and healthier lives. According to data from the United Nations Population Division, the number of people aged >80 years is projected to triple from 137 million in 2017 to reach 425 million by 2050 [82]. In fact, by the middle of the twenty-first century, one in every five people will be aged 60 years or over [82].

A major challenge of population aging is the increased presentation of aged-related pathologies, especially in non-communicable diseases (NCDs). Unfortunately, it is estimated that 70% of global deaths are currently due to NCDs [90]. The main NCDs that affect the elderly include cardiovascular diseases, diabetes, neurodegeneration and cancer. Cardiovascular diseases, which includes coronary heart disease and stroke, formed the majority of deaths among older people in 2015 worldwide [82]. Immense research effort has been invested into understanding the aetiology of many NCDs in the hopes to find new therapeutic avenues. Recent findings indicate that age-related vascular abnormalities and dysfunction are key characteristics of cardiovascular, cerebrovascular and neurodegenerative diseases (Figure 1). Although many lifestyle factors such as diet and physical activity are known to influence vascular function, age is a non-modifiable risk factor. In this short review, we provide evidence to demonstrate that age-associated vascular changes can influence three key pathologies currently affecting the elderly population, specifically atherosclerosis, stroke, and Alzheimer's disease. While this review focuses on key age-related functional and structural vascular changes, it is important to recognise that these alterations are likely to overlap, or are an additive to vascular responses caused specifically by disease initiation and progression.

Atherosclerosis

Atherosclerosis is a leading cause of cardiovascular disease in the elderly, commonly manifesting as ischemic heart disease and ischemic stroke. It is a chronic inflammatory disease of the vasculature, characterised by the build-up of lipids within arterial walls. Over time, this hardened lipid plaque creates a blockage to blood flow, restricting oxygen supply to vital organs. Atherosclerosis occurs predominately in larger vessels first and they are usually more progressive with higher rates of rupture. With age however, the occurrence of lesions in

smaller vessels may increase [1]. It is suggested that aging, in combination with specific vascular risk factors such as hypertension, diabetes and dyslipidemia are more consistently associated with small vessel atherosclerotic disease [1,47]. Although the physiological and pathological mechanisms for this observation requires more understanding, it is known that endothelial cells of small vessels interact closely with neighbouring cells and circulating or tissue resident immune cells to shape microvascular outcomes during chronic injury. Accumulating evidence, as discussed below, suggest elevated vascular inflammation and immunosenescence within smaller vessels may be fundamental in mediating disease progression.

Recent studies have shown that healthy elderly individuals often exhibit dysregulation of cytokine homeostasis, frequently reflected as chronic low-grade inflammation. This state is maintained by elevated circulating levels of pro-inflammatory cytokines and chemokines, including interleukin (IL)-6, IL-12, IL-1 β , transforming growth factor beta (TGF- β), tumour necrosis factor alpha (TNF- α), monocyte chemoattractant protein-1 (MCP-1) and macrophage inflammatory protein (MIP)-1 α by various cell types [2,30,70,78,97]. It is speculated that vascular inflammation, which is intrinsic to the aging process, may amplify these responses, contribute to vessel injury and predispose elderly individuals to vascular disease. Supporting this notion, several clinical studies report that the levels of inflammatory markers in the blood are predictive of cardiovascular complications, in particular C-reactive protein (CRP) and IL-6 [64,72,73]. Below, we discuss some age-associated mechanisms that have been documented to contribute to vascular injury during atherosclerosis.

It is well accepted that the initiation and progression of atherosclerosis is predominantly monocyte-driven [89]. Circulating monocytes derive from hematopoietic precursor cells in the bone marrow and are key components of the innate immune response. As we age, haematopoietic stem cells (HSCs) exhibit bias towards long-lived myeloid differentiation, while reducing the repopulation of T- and B-lymphocytes [8,18]. Analysis of healthy volunteers showed that despite no change in total circulating monocytes with age, the proportion of phenotypically distinct subsets do alter [38,75]. More specifically, it was reported that CD14⁺CD16⁺ inflammatory monocytes significantly increases with age [38,75]. These aged CD14⁺CD16⁺ inflammatory monocytes show reduced HLA-DR, CXCR3, CD38 and CD62L phenotypic markers, but increased CD11b expression. Monocytes and macrophages from older individuals also display reduced expression levels of immune activating receptors, such as major histocompatibility (MHC) class II and toll-like receptors (TLRs). The lowered expression of these receptors have been shown to contribute to poor

adaptive immunity [40,53,69] and cytokine dysregulation [11,38,84]. It is conceivable that such alterations in monocyte phenotype and increased inflammatory capacity with age may exacerbate vascular inflammation, injury and remodelling. Indeed, increased CD11b expression by monocytes under elevated inflammatory MCP-1 conditions has been associated with increased atherosclerotic plaque formation and monocyte infiltration in advanced lesions in mice [85].

A critical step in the initiation of an atheroma lesion is the enhanced expression of adhesion molecules by endothelial cells and monocytes, particularly under inflammatory conditions [31]. These adhesion molecules enable the recruitment, adherence and transmigration of circulating monocytes to vessel walls [52]. Selectins (P, L and E) are involved in the rolling of monocytes under high shear stress exerted by vascular blood flow [52]. Firmer adhesion and transmigration of inflammatory cells at the vascular wall is subsequently mediated by integrins, intercellular adhesion molecules (ICAMs), vascular cell adhesion molecules (VCAM-1) and platelet endothelial cellular adhesion molecules (PECAM-1) [52]. Many studies using mouse models of atherosclerosis have shown that deficiencies in these adhesion molecules reduce monocyte cell recruitment and attachment, lesion formation in arterial vasculature and atherosclerotic fatty streaks [20,25,44,67]. Unfortunately, very few studies have examined how aging affects these processes. Of the few reported, the expression of aortic P-selectin and VCAM-1 was shown to increase with age, causing excessive leukocyte infiltration to vessel walls that could trigger prolonged or exaggerated inflammatory responses [56,99]. Older animals (20-22 months old) with higher VCAM-1 expression developed more atherosclerotic lesions in the aortic wall compared to their younger counterparts [56]. The underlying mechanism of enhanced VCAM-1 and P-selectin expression with age was shown to involve endothelial oxidative stress through NF- κ B signalling [99]. Another study showed that soluble E-selectin, P-selectin, ICAM-1 and VCAM-1 in the serum of aged rats (24-months) were all significantly higher compared to younger cohorts (6-months), suggesting the systemic expression of these adhesion molecules may contribute to increased risk of inflammatory vascular diseases [98]. Furthermore, peritoneum macrophages isolated from aged mice (10-months) exhibit higher adherence capacity and lower chemotactic ability *ex vivo* [29], both of these factors may impact on leukocyte accumulation at injured vascular sites.

Once adherent to the vascular surface, monocytes enter the intima and differentiate into macrophages that take up modified low-density lipoprotein (LDL) to form foam cells

[17]. A recent study elegantly demonstrated that senescent foam cells with reduced telomere length are vital for plaque build-up, and in later stages, plaque remodelling and rupture [16]. These senescent cells show heightened profiles of proatherogenic and proteolytic factors, including IL-1 α , TNF- α , metalloprotease (MMP)-3, MMP12, MMP13, MCP-1, and VCAM-1 [16]. Cellular senescence is a permanent state of cell cycle arrest, characterised by elevated activity of β -galactosidase, increased p16^{Ink4a}, p53, and p21 expression, and telomere erosion [83]. Importantly, shortened telomere length and markers of senescence are distinctive features of aged leukocytes [87]. Clinically, reduced leukocyte telomere length has also been reported to be a predictor of future coronary heart disease [13]. Collectively, these observations suggest that senescent aged cells could accelerate atheroma formation, and participate as key drivers of cardiovascular disease.

Ischaemic stroke

Ischaemic stroke occurs when blood flow to the brain is interrupted by i) formation of a blood clot on an atherosclerotic plaque within a cerebral blood vessel (atherothrombotic stroke); or ii) embolism of a clot or plaque that ruptured from an atherosclerotic lesion outside the brain. Without blood flow the brain tissue is deprived of oxygen and nutrients, subsequently causing ischaemic injury. Intracranial atherosclerotic disease represents a major cause of ischemic stroke worldwide, particularly prevalent in black, Asian and Hispanic populations. It was reported that hypertension is a major risk factor for intracranial atherosclerotic disease, while obesity and hyperlipidemia are believed to be more important for the development of extracranial atherosclerotic lesions [81]. Clearly the effects of age on atherosclerosis are extremely relevant to stroke.

According to the World Health Organization (WHO), stroke affects an estimated 15 million people worldwide each year, and of these people 5 million die [61]. In fact, the incidence of stroke increases dramatically with age, with the risk doubling every decade after the age of 55 [19]. In addition, several large prospective clinical studies showed that old age is a prognostic marker for poor long-term outcome in both minor and major strokes [3,23,48]. For instance, a recent prospective study of 43,163 ischemic stroke patients found age was a predictor of poor functional outcome, independent of stroke severity and other characteristics such as risk factors, acute stroke therapy, complications, and stroke aetiology [48]. Post-stroke complications are common, and can include dysphagia, infection, venous thromboembolism, gut dysfunction, delirium, immobility and seizures [76,88]. Similar to

clinical observations, experimental stroke studies have also highlighted the significance of age in worsening stroke severity and functional improvement [54,66,92]. So what can mediate this age-dependent effect in stroke prognosis? Although it remains uncertain, research suggests diverse morphological changes that occur naturally in the aging brain and neurovascular unit may compromise recovery after ischaemic brain damage.

Various cross-sectional and longitudinal volumetric studies using magnetic resonance imaging (MRI) provide evidence of significant decline in global and regional brain volumes with age [43,58,74]. Age-associated reduction in brain volume have been confirmed in regions such as the hippocampus, cerebral cortex, frontal lobe and temporal lobe [43,59,74]. It is estimated that between 30 and 90 years of age, volume loss averages 14% in the cerebral cortex, 35% in the hippocampus, and 26% in the cerebral white matter [43]. However, to date there is still no consensus among studies to indicate which specific brain regions are most likely to alter with age, and by how much. This is likely due to variations in the sensitivity of methods employed to detect brain volumetric changes, sex-related biological differences, as well as environmental and lifestyle factors (e.g. nutrition). Nevertheless, it is thought that age-related vascular degradation, combined with less neuronal proliferation contributes to reduced brain volume. Importantly, disruption of the brain vascular network could have significant implications for neurovascular repair (angiogenesis) and blood brain barrier permeability following stroke onset in the elderly (discussed below) [65,77].

Angiogenesis is a physiological process involving the growth of new blood vessels from pre-existing vessels and a key feature of post-stroke neuroregeneration. Studies indicate that angiogenesis has a crucial role in stroke recovery as it helps re-establish the cerebral microvasculature to stimulate blood flow and metabolism to ischaemic brain regions [6,37,55]. Although clinical studies are limited, analysis of post mortem brain tissues indicate stroke patients with greater microvessel density tend to have improved survival outcome and recovery [49]. Rodent ischaemic stroke models demonstrated that gene expression of angiogenesis-related genes are upregulated immediately after injury, which is accompanied by increased endothelial cell proliferation in the peri-infarcted regions [6,15,37]. Some key pro-angiogenic factors secreted by the brain milieu include vascular endothelial growth factor (VEGF), MMPs, angiopoietins, fibroblast growth factor (FGF) and platelet-derived growth factor (PDGF) [95].

Few studies have addressed how age affects angiogenesis in stroke, and there is no clear consensus [10,15,32,80]. A 60 patient cohort study found angiogenesis was evident 3-4 days after stroke onset [80]. When patients were further separated according to age, they

showed using immunocytochemical methods that the duration of penumbra neovascularisation decreased in older patients (70-92 years of age) compared to the younger group (48-69 years of age) [80]. In terms of experimental models, a recent in depth transcriptomic study identified key differences in gene expression of angiogenic factors in the aged brain after stroke [15]. Aged rats (18-20 months) showed delayed upregulation of genes involved in sprouting angiogenesis, tube formation, and maturation compared to younger animals (3-5 months) [15]. Despite these alterations, aged brains were still capable of mounting a vigorous angiogenic response after stroke onset, and at a comparable level as younger counterparts. Similarly, although aged mice showed attenuated VEGF and hypoxia inducible factor 1- α (HIF-1 α) expression in the cerebral cortex after prolonged hypoxia, the long-term angiogenic response was unaffected compared to young mice [10]. Furthermore, overexpression of VEGF in the mouse brain induced angiogenesis and neurogenesis in 3- and 12-month-old mice, but not in 24-month-old mice [32]. These studies highlight that aging can dampen angiogenesis and vascular remodelling, but how this affects long term functional recovery and overall brain plasticity after stroke warrants further investigation.

VEGF-monotherapy in particular has gained much attention as a therapeutic avenue in stroke. The infusion of VEGF into brain tissue has proven to enhance angiogenesis, reduce infarct size and improve neurological performance after cerebral ischemia damage in rodents [79,96]. However, it appears the timing of VEGF treatment after stroke is equally important to ensure a beneficial effect. One study showed that while late (48 hours) administration of VEGF to ischemic brains improved neurological recovery, early post-ischemic (1 hour) administration increased blood-brain barrier leakage, haemorrhagic transformation, and ischemic lesions in rats [96]. As such, we must further understand the mechanistic roles of pro-angiogenic stimuli during defined times post-stroke to ensure an effective therapeutic strategy. Care should also be taken when considering the use of VEGF-monotherapies in the elderly. For example, it would be difficult to predict the responses of aged patients whom often have various underlying conditions that is implicated by the VEGF pathway, including cardiovascular diseases, diabetes and hypertension.

Emerging evidence suggests that re-establishment of the cerebral microvasculature after stroke is also dependent on endothelial progenitor cells (EPCs). EPCs are immature endothelial cells found in peripheral circulation [4], which have the capacity to differentiate into mature endothelial cells for vessel repair and angiogenesis after vascular injury [26]. Clinically, circulating EPC levels are reported to either significantly decline [34,91], or remain unchanged with age [39,50]. A report from *Heiss et al.* demonstrated that despite no

change in numbers, EPCs isolated from healthy aged individuals (61 years old) show reduced proliferative ability and VEGF-induced migration when compared to EPCs from younger subjects (20 years old) [39]. Furthermore, bone-marrow derived EPCs from aged mice have reduced capacity to initiate angiogenic repair in models of cardiac injury [27] and atherosclerosis [68]. An elegant study by *Fan et al.* demonstrated that transplanted human EPCs migrated to the ischemic brain region of post-stroke mice within 24 hours via a stromal-derived factor (SDF)-1/CXCR4 mediated pathway [28]. Consequently, post-stroke mice that received EPC therapy showed reduced cortex atrophy, improved neurobehavioral outcomes and increased angiogenesis around ischemic boundaries [28]. Taking these findings into consideration, it is reasonable to speculate that aged EPCs are less effective at forming functional cerebral vessels after stroke, thereby attenuating blood flow and recovery after stroke.

The blood-brain barrier (BBB) is a major component of the neurovascular unit. It is mainly composed of endothelial cells closely bound together by tight junctions, including occludin, claudin, and junctional adhesion molecules (JAMs). Endothelial cells are further supported by astrocyte end-feet and pericytes. Together, this dynamic network of cells and junction proteins regulate the selective diffusion of molecules between the intravascular lumen/space and extravascular parenchyma to maintain homeostasis within the brain. Disruption of this barrier system has been implicated in numerous comprehensive stroke studies in patients and rodent models [9,21,33,45,93]. However, the underlying mechanisms whereby age affects BBB function after stroke is currently unknown. Although limited, studies do indicate that age exacerbates BBB permeability and worsens stroke outcomes [24,46]. For instance, aged animals (18 months) demonstrated elevated BBB permeability by almost 2-fold in the infarct brain hemisphere as compared to younger animals (3 months) at 20 minutes and up to 24 hours post-stroke [24]. Neurological damage in these aged rats post-stroke was also worse compared to the young cohorts at 24 hours, with the aged rats suffering larger infarct size, worse functional impairment and prolonged recovery time [24]. Enhanced BBB permeability with age may be due to changes in the phosphorylation status of tight junction proteins, including claudin 5 and occludin after stroke onset [46]. A recent study speculated on the use of insulin-like growth factor 1 (IGF-1) treatment in the aging brain to improve stroke outcome [5]. IGF-1 is considered neuroprotective, and middle-aged (9-11 month old) mice showed improved blood brain barrier integrity and reduced infarct volume after IGF-1 treatment [5]. Overall, while age appears to be an important factor in BBB dysregulation in stroke, it is often neglected in animal studies of ischemic stroke and hence

requires much more extensive investigation. In addition to the devastating consequences of stroke following acute disruption of blood flow to the brain, there is a growing body of evidence from epidemiological, neuroimaging and clinical studies to indicate chronic hypoperfusion is linked to risk factors of Alzheimer's disease [22].

Alzheimer's disease

Alzheimer's disease (AD) is the most common form of dementia in the elderly, clinically characterised by the progressive decline in memory and cognitive function. A key pathological feature of AD is the abnormal deposition of amyloid β -peptide ($A\beta$) that forms plaques in the brain parenchyma and cerebral blood vessels, as well as presence of neurofibrillary tangles. $A\beta$ deposition has been shown to initiate a cascade of events that culminates in neuronal loss, synaptic dysfunction and eventual cognitive decline [36]. Despite intense research efforts in the last decade, there is currently no cure for this complex disease, and the available pharmacological treatments only offer symptomatic relief by regulating neurotransmitter imbalance [94]. Interestingly, accumulating evidence suggests that vascular dysfunction may contribute to the development of AD - a factor currently not considered during diagnosis.

Early indications of vascular involvement in AD comes from large epidemiological studies [41,42,62,63,86]. The Rotterdam study, a prominent prospective population-based study that included over 7,000 participants over the age of 55, is one such early example. It was concluded from many years of patient follow-up that risk factors for vascular disease are strongly associated with AD in the elderly, including diabetes mellitus, atherosclerosis and atrial fibrillation [12,41,62,63]. Similar to these observations, a more recent study of 430 individuals aged >60 reported that age was a predictor for poor vascular health, and those with existing cardiovascular conditions had significantly greater AD neurodegeneration [86]. Furthermore, another recent study analysed over 7,700 multimodality brain images, in conjunction with plasma and cerebrospinal fluid biomarkers from 1,171 healthy and AD individuals, to understand the temporal order of disease progression [42]. The data-driven study concluded that intra-brain vascular dysregulation is the earliest and strongest pathologic factor associated with late-onset AD. This was followed in order by $A\beta$ deposition, glucose metabolism dysregulation, functional impairment, and grey matter atrophy [42].

The importance of vascular changes in the pathogenesis of AD was shown more conclusively in an eloquent experimental animal study by Meyer *et al.* [57]. Using APP23

transgenic (tg) mice, which display typical pathological hallmarks of AD, they found an age-dependent disruption of the brain microvasculature integrity with vascular corrosion casting techniques [57]. Specifically, vessels from aged tg mice (18-months) were often found to be truncated, constricted, and missing in areas of amyloid plaques. Using the same animal model, they previously showed these changes were associated with reduced cerebral blood flow [7]. Importantly, morphological and architectural alterations of the vasculature preceded deposition of amyloid plaques, supporting the idea that aged cerebral vasculature contributes to disease pathogenesis and progression [57]. One may speculate from these findings that AD is in fact an inevitable part of normal or 'unhealthy' vascular aging. Indeed, it is hard to ignore the many overlaps of vascular degenerative processes that occur in both the aged brain and in AD: capillary loss, reduced cerebral blood flow, BBB dysfunction, and lower glucose metabolism [14]. While more conclusive studies are required, it is clear from current studies there is a strong synergy between vascular aging and AD.

Outlook

From the clinical and experimental evidence reviewed here, it is fair to conclude that the process of aging elicits significant structural and functional impairments in vascular networks. It is important to remember that many age-related pathologies share similar risk factors and spectrum of underlying vascular dysfunction. For example, chronic hypertension is a major cause of atherosclerosis, which can lead to heart attacks and stroke. More recently, evidence suggests hypertension is a risk factor for cognitive decline, and can also act synergistically with vascular disease such as atherosclerosis to promote AD progression [60]. Together with proven inflammatory imbalance and elevated cell senescence with age, it is somewhat unsurprising that vascular-related pathologies arise more readily in elderly individuals. This raises the possibility that pharmacological approaches aimed at targeting/reversing age-associated impairments in vascular and immunological functions may delay the onset of disease in the elderly. Indeed, some studies have focused on the potential beneficial effects of anti-oxidant and anti-inflammatory therapies with promising results.

The results of the recent Canakinumab Anti-inflammatory Thrombosis Outcome Study (CANTOS) is one such example (NCT01327846) [71]. This randomised, double-blind trial showed that anti-inflammatory therapy targeting the IL-1 β innate immunity pathway with Canakinumab led to significantly lower rate of secondary cardiovascular events than placebo in patients with a history of myocardial infarction and persistent pro-inflammatory response, as defined by high-sensitivity C-reactive protein (median age 61) [71]. Similarly,

the JUPITER (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin) trial (NCT00239681) showed that healthy individuals above 50 years of age with high levels of basal inflammation, as indicated by high C-reactive protein levels, had significantly reduced occurrence of symptomatic venous thromboembolism after treatment with statin therapy (rosuvastatin) [35]. Statins are known to markedly lower LDL-cholesterol as well as reducing inflammation. Further, the JUPITER trial indicated that patient with the highest levels of persistent pro-inflammatory response showed the greatest absolute risk reduction of major vascular events. The Cardiovascular Inflammation Reduction Trial (CIRT; NCT02576067) is still currently ongoing to evaluate whether anti-inflammatory methotrexate (LDM) at low-doses can reduce rates of myocardial infarction, stroke, and cardiovascular death. If successful, this trial will open new directions for cardiovascular treatment. Besides drug based treatments, it is perhaps equally important to place more social focus on encouraging our aging population to maintain lifestyle changes and preventative measures that may attenuate the negative consequences of aging and preserve vascular integrity. For example, incorporation of a healthy diet and regular exercise have been well accepted to reduce risk of cardiovascular disease.

Although significant attention and efforts have been devoted into deciphering the effect of aging on many biological processes in recent years, there are still many caveats in the emerging field of aging research. Firstly, current experimental models of disease cannot recapitulate the spectrum of co-morbidities and vascular injury that often present in elderly patients. For example, the occlusion of the middle cerebral artery is the most frequently used model in stroke research. This model involves the transient or permanent insertion of a monofilament to induce a direct mechanical occlusion of blood flow to the brain and cause ischaemic injury. A disadvantage of such model is that co-morbidities that are known to contribute significantly to stroke with age, such as arterial hypertension, diabetes and atherosclerosis are not considered. In addition to this limitation, many preclinical studies examining age-related illnesses do not use aged animal models due to various logistical challenges. One of this being the resource, time and costs required to age experimental animals. According to the Jackson Laboratory, the biological measures of a mature adult mice of 3-6 months old equates to humans at 20-30 years old, while mice ranging from 18-24 months of age correlate with humans ranging from 56-69 years of age [51]. By omitting the age factor, this means that critical molecular and biological changes associated with aging are not considered, which could alter the efficacy of therapeutics being tested.

For some areas of neurodegenerative disorders such as Alzheimer's disease, preclinical models rely on using genetic mutations instead of naïve aged animals to initiate similar brain pathologies. Unfortunately, most of these existing transgenic models do not recapitulate the entire spectrum of lesions and cognitive decline observed in human. Additionally, transgenic mouse models are based on the expression of mutant genes implicated in causing pathology in a small subset of patients, and separating gene effects from those initiated by age remains difficult. A similar case exists with existing experimental models of atherosclerosis whereby studies employ the use Apolipoprotein E (*ApoE*) knockout or LDLR deficient mice. Development of pathology in these models do not rely on age and avoid the toxicity of long-term high fat diets. Nevertheless, these transgenic models have improved our understanding of disease pathogenesis, and will no doubt play a crucial role in the quest for novel therapeutic approaches.

Disclosure of potential conflicts of interest

The authors declare no potential conflicts of interest.

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Figure Legend

Figure 1. Key age-associated changes that contribute to the progression of atherosclerosis, stroke and Alzheimer's disease (Stock images sourced from Servier Medical Art; Creative Commons Attribution 4.0 International License).

References

1. Aboyans V, Lacroix P, Criqui MH. Large and small vessels atherosclerosis: similarities and differences. *Progress in cardiovascular diseases* **50**: 112-125, 2007.

2. Alvarez-Rodriguez L, Lopez-Hoyos M, Munoz-Cacho P, Martinez-Taboada VM. Aging is associated with circulating cytokine dysregulation. *Cellular immunology* **273**: 124-132, 2012.
3. Andersen KK, Andersen ZJ, Olsen TS. Predictors of early and late case-fatality in a nationwide Danish study of 26,818 patients with first-ever ischemic stroke. *Stroke* **42**: 2806-2812, 2011.
4. Asahara T, Murohara T, Sullivan A, Silver M, van der Zee R, Li T, Witzenbichler B, Schatteman G, Isner JM. Isolation of putative progenitor endothelial cells for angiogenesis. *Science* **275**: 964-967, 1997.
5. Bake S, Selvamani A, Cherry J, Sohrabji F. Blood brain barrier and neuroinflammation are critical targets of IGF-1-mediated neuroprotection in stroke for middle-aged female rats. *PloS one* **9**: e91427, 2014.
6. Beck H, Acker T, Wiessner C, Allegrini PR, Plate KH. Expression of angiopoietin-1, angiopoietin-2, and tie receptors after middle cerebral artery occlusion in the rat. *The American journal of pathology* **157**: 1473-1483, 2000.
7. Beckmann N, Schuler A, Mueggler T, Meyer EP, Wiederhold KH, Staufenbiel M, Krucker T. Age-dependent cerebrovascular abnormalities and blood flow disturbances in APP23 mice modeling Alzheimer's disease. *The Journal of neuroscience : the official journal of the Society for Neuroscience* **23**: 8453-8459, 2003.
8. Beerman I, Bhattacharya D, Zandi S, Sigvardsson M, Weissman IL, Bryder D, Rossi DJ. Functionally distinct hematopoietic stem cells modulate hematopoietic lineage potential during aging by a mechanism of clonal expansion. *Proceedings of the National Academy of Sciences of the United States of America* **107**: 5465-5470, 2010.
9. Belayev L, Busto R, Zhao W, Ginsberg MD. Quantitative evaluation of blood-brain barrier permeability following middle cerebral artery occlusion in rats. *Brain research* **739**: 88-96, 1996.

10. Benderro GF, Lamanna JC. Hypoxia-induced angiogenesis is delayed in aging mouse brain. *Brain research* **1389**: 50-60, 2011.
11. Boyd AR, Shivshankar P, Jiang S, Berton MT, Orihuela CJ. Age-related defects in TLR2 signaling diminish the cytokine response by alveolar macrophages during murine pneumococcal pneumonia. *Experimental gerontology* **47**: 507-518, 2012.
12. Breteler MM. Vascular risk factors for Alzheimer's disease: an epidemiologic perspective. *Neurobiology of aging* **21**: 153-160, 2000.
13. Brouillette SW, Moore JS, McMahon AD, Thompson JR, Ford I, Shepherd J, Packard CJ, Samani NJ, West of Scotland Coronary Prevention Study G. Telomere length, risk of coronary heart disease, and statin treatment in the West of Scotland Primary Prevention Study: a nested case-control study. *Lancet* **369**: 107-114, 2007.
14. Brown WR, Thore CR. Review: cerebral microvascular pathology in ageing and neurodegeneration. *Neuropathology and applied neurobiology* **37**: 56-74, 2011.
15. Buga AM, Margaritescu C, Scholz CJ, Radu E, Zelenak C, Popa-Wagner A. Transcriptomics of post-stroke angiogenesis in the aged brain. *Frontiers in aging neuroscience* **6**: 44, 2014.
16. Childs BG, Baker DJ, Wijshake T, Conover CA, Campisi J, van Deursen JM. Senescent intimal foam cells are deleterious at all stages of atherosclerosis. *Science* **354**: 472-477, 2016.
17. Chistiakov DA, Melnichenko AA, Myasoedova VA, Grechko AV, Orekhov AN. Mechanisms of foam cell formation in atherosclerosis. *Journal of molecular medicine* **95**: 1153-1165, 2017.
18. Cho RH, Sieburg HB, Muller-Sieburg CE. A new mechanism for the aging of hematopoietic stem cells: aging changes the clonal composition of the stem cell compartment but not individual stem cells. *Blood* **111**: 5553-5561, 2008.

19. Chong JY, Sacco RL. Risk factors for stroke, assessing risk, and the mass and high-risk approaches from stroke prevention. *CONTINUUM: Lifelong Learning in Neurology* **11**: 18-34, 2005.
20. Collins RG, Velji R, Guevara NV, Hicks MJ, Chan L, Beaudet AL. P-Selectin or intercellular adhesion molecule (ICAM)-1 deficiency substantially protects against atherosclerosis in apolipoprotein E-deficient mice. *The Journal of experimental medicine* **191**: 189-194, 2000.
21. Dankbaar JW, Hom J, Schneider T, Cheng SC, Bredno J, Lau BC, van der Schaaf IC, Wintermark M. Dynamic perfusion-CT assessment of early changes in blood brain barrier permeability of acute ischaemic stroke patients. *Journal of neuroradiology Journal de neuroradiologie* **38**: 161-166, 2011.
22. de la Torre JC. Alzheimer disease as a vascular disorder: nosological evidence. *Stroke* **33**: 1152-1162, 2002.
23. Denti L, Scoditti U, Tonelli C, Saccavini M, Caminiti C, Valcavi R, Benatti M, Ceda GP. The poor outcome of ischemic stroke in very old people: a cohort study of its determinants. *Journal of the American Geriatrics Society* **58**: 12-17, 2010.
24. DiNapoli VA, Huber JD, Houser K, Li X, Rosen CL. Early disruptions of the blood-brain barrier may contribute to exacerbated neuronal damage and prolonged functional recovery following stroke in aged rats. *Neurobiology of aging* **29**: 753-764, 2008.
25. Dong ZM, Chapman SM, Brown AA, Frenette PS, Hynes RO, Wagner DD. The combined role of P- and E-selectins in atherosclerosis. *The Journal of clinical investigation* **102**: 145-152, 1998.
26. Du F, Zhou J, Gong R, Huang X, Pansuria M, Virtue A, Li X, Wang H, Yang XF. Endothelial progenitor cells in atherosclerosis. *Frontiers in bioscience* **17**: 2327-2349, 2012.
27. Edelberg JM, Tang L, Hattori K, Lyden D, Rafii S. Young adult bone marrow-derived endothelial precursor cells restore aging-impaired cardiac angiogenic function. *Circulation research* **90**: E89-93, 2002.

28. Fan Y, Shen F, Frenzel T, Zhu W, Ye J, Liu J, Chen Y, Su H, Young WL, Yang GY. Endothelial progenitor cell transplantation improves long-term stroke outcome in mice. *Annals of neurology* **67**: 488-497, 2010.
29. Forner MA, Collazos ME, Barriga C, De la Fuente M, Rodriguez AB, Ortega E. Effect of age on adherence and chemotaxis capacities of peritoneal macrophages. Influence of physical activity stress. *Mechanisms of ageing and development* **75**: 179-189, 1994.
30. Forsey RJ, Thompson JM, Ernerudh J, Hurst TL, Strindhall J, Johansson B, Nilsson BO, Wikby A. Plasma cytokine profiles in elderly humans. *Mechanisms of ageing and development* **124**: 487-493, 2003.
31. Galkina E, Ley K. Vascular adhesion molecules in atherosclerosis. *Arteriosclerosis, thrombosis, and vascular biology* **27**: 2292-2301, 2007.
32. Gao P, Shen F, Gabriel RA, Law D, Yang EY, Yang GY, Young WL, Su H. Attenuation of brain response to vascular endothelial growth factor-mediated angiogenesis and neurogenesis in aged mice. *Stroke* **40**: 3596-3600, 2009.
33. Garbuzova-Davis S, Haller E, Williams SN, Haim ED, Tajiri N, Hernandez-Ontiveros DG, Frisina-Deyo A, Boffeli SM, Sanberg PR, Borlongan CV. Compromised blood-brain barrier competence in remote brain areas in ischemic stroke rats at the chronic stage. *The Journal of comparative neurology* **522**: 3120-3137, 2014.
34. Ghani U, Shuaib A, Salam A, Nasir A, Shuaib U, Jeerakathil T, Sher F, O'Rourke F, Nasser AM, Schwindt B, Todd K. Endothelial progenitor cells during cerebrovascular disease. *Stroke* **36**: 151-153, 2005.
35. Glynn RJ, Danielson E, Fonseca FA, Genest J, Gotto AM, Jr., Kastelein JJ, Koenig W, Libby P, Lorenzatti AJ, MacFadyen JG, Nordestgaard BG, Shepherd J, Willerson JT, Ridker PM. A randomized

trial of rosuvastatin in the prevention of venous thromboembolism. *The New England journal of medicine* **360**: 1851-1861, 2009.

36. Haass C, Selkoe DJ. Soluble protein oligomers in neurodegeneration: lessons from the Alzheimer's amyloid beta-peptide. *Nature reviews Molecular cell biology* **8**: 101-112, 2007.

37. Hayashi T, Noshita N, Sugawara T, Chan PH. Temporal profile of angiogenesis and expression of related genes in the brain after ischemia. *Journal of cerebral blood flow and metabolism : official journal of the International Society of Cerebral Blood Flow and Metabolism* **23**: 166-180, 2003.

38. Hearps AC, Martin GE, Angelovich TA, Cheng WJ, Maisa A, Landay AL, Jaworowski A, Crowe SM. Aging is associated with chronic innate immune activation and dysregulation of monocyte phenotype and function. *Aging cell* **11**: 867-875, 2012.

39. Heiss C, Keymel S, Niesler U, Ziemann J, Kelm M, Kalka C. Impaired progenitor cell activity in age-related endothelial dysfunction. *Journal of the American College of Cardiology* **45**: 1441-1448, 2005.

40. Herrero C, Sebastian C, Marques L, Comalada M, Xaus J, Valledor AF, Lloberas J, Celada A. Immunosenescence of macrophages: reduced MHC class II gene expression. *Experimental gerontology* **37**: 389-394, 2002.

41. Hofman A, Ott A, Breteler MM, Bots ML, Slooter AJ, van Harskamp F, van Duijn CN, Van Broeckhoven C, Grobbee DE. Atherosclerosis, apolipoprotein E, and prevalence of dementia and Alzheimer's disease in the Rotterdam Study. *Lancet* **349**: 151-154, 1997.

42. Iturria-Medina Y, Sotero RC, Toussaint PJ, Mateos-Perez JM, Evans AC, Alzheimer's Disease Neuroimaging I. Early role of vascular dysregulation on late-onset Alzheimer's disease based on multifactorial data-driven analysis. *Nature communications* **7**: 11934, 2016.

43. Jernigan TL, Archibald SL, Fennema-Notestine C, Gamst AC, Stout JC, Bonner J, Hesselink JR. Effects of age on tissues and regions of the cerebrum and cerebellum. *Neurobiology of aging* **22**: 581-594, 2001.
44. Johnson RC, Chapman SM, Dong ZM, Ordovas JM, Mayadas TN, Herz J, Hynes RO, Schaefer EJ, Wagner DD. Absence of P-selectin delays fatty streak formation in mice. *The Journal of clinical investigation* **99**: 1037-1043, 1997.
45. Kahles T, Luedike P, Endres M, Galla HJ, Steinmetz H, Busse R, Neumann-Haefelin T, Brandes RP. NADPH oxidase plays a central role in blood-brain barrier damage in experimental stroke. *Stroke* **38**: 3000-3006, 2007.
46. Kaur J, Tuor UI, Zhao Z, Barber PA. Quantitative MRI reveals the elderly ischemic brain is susceptible to increased early blood-brain barrier permeability following tissue plasminogen activator related to claudin 5 and occludin disassembly. *Journal of cerebral blood flow and metabolism : official journal of the International Society of Cerebral Blood Flow and Metabolism* **31**: 1874-1885, 2011.
47. Khan U, Porteous L, Hassan A, Markus HS. Risk factor profile of cerebral small vessel disease and its subtypes. *Journal of neurology, neurosurgery, and psychiatry* **78**: 702-706, 2007.
48. Knoflach M, Matosevic B, Rucker M, Furtner M, Mair A, Wille G, Zangerle A, Werner P, Ferrari J, Schmidauer C, Seyfang L, Kiechl S, Willeit J, Austrian Stroke Unit Registry C. Functional recovery after ischemic stroke--a matter of age: data from the Austrian Stroke Unit Registry. *Neurology* **78**: 279-285, 2012.
49. Krupinski J, Kaluza J, Kumar P, Kumar S, Wang JM. Role of angiogenesis in patients with cerebral ischemic stroke. *Stroke* **25**: 1794-1798, 1994.
50. Kunz GA, Liang G, Cuculi F, Gregg D, Vata KC, Shaw LK, Goldschmidt-Clermont PJ, Dong C, Taylor DA, Peterson ED. Circulating endothelial progenitor cells predict coronary artery disease severity. *American heart journal* **152**: 190-195, 2006.

51. Laboratory TJ. Life span as a biomarker [Online]. <https://www.jax.org/research-and-faculty/research-labs/the-harrison-lab/gerontology/life-span-as-a-biomarker>.
52. Ley K, Laudanna C, Cybulsky MI, Nourshargh S. Getting to the site of inflammation: the leukocyte adhesion cascade updated. *Nature reviews Immunology* **7**: 678-689, 2007.
53. Liang S, Domon H, Hosur KB, Wang M, Hajishengallis G. Age-related alterations in innate immune receptor expression and ability of macrophages to respond to pathogen challenge in vitro. *Mechanisms of ageing and development* **130**: 538-546, 2009.
54. Manwani B, Liu F, Xu Y, Persky R, Li J, McCullough LD. Functional recovery in aging mice after experimental stroke. *Brain, behavior, and immunity* **25**: 1689-1700, 2011.
55. Marti HJ, Bernaudin M, Bellail A, Schoch H, Euler M, Petit E, Risau W. Hypoxia-induced vascular endothelial growth factor expression precedes neovascularization after cerebral ischemia. *The American journal of pathology* **156**: 965-976, 2000.
56. Merat S, Fruebis J, Sutphin M, Silvestre M, Reaven PD. Effect of aging on aortic expression of the vascular cell adhesion molecule-1 and atherosclerosis in murine models of atherosclerosis. *The journals of gerontology Series A, Biological sciences and medical sciences* **55**: B85-94, 2000.
57. Meyer EP, Ulmann-Schuler A, Staufenbiel M, Krucker T. Altered morphology and 3D architecture of brain vasculature in a mouse model for Alzheimer's disease. *Proceedings of the National Academy of Sciences of the United States of America* **105**: 3587-3592, 2008.
58. Miyahira Y, Yu J, Hiramatsu K, Shimazaki Y, Takeda Y. [Brain volumetric MRI study in healthy elderly persons using statistical parametric mapping]. *Seishin shinkeigaku zasshi = Psychiatria et neurologia Japonica* **106**: 138-151, 2004.

59. Mu Q, Xie J, Wen Z, Weng Y, Shuyun Z. A quantitative MR study of the hippocampal formation, the amygdala, and the temporal horn of the lateral ventricle in healthy subjects 40 to 90 years of age. *AJNR American journal of neuroradiology* **20**: 207-211, 1999.
60. Nelson L, Gard P, Tabet N. Hypertension and inflammation in Alzheimer's disease: close partners in disease development and progression! *Journal of Alzheimer's disease : JAD* **41**: 331-343, 2014.
61. Organisation WH. Global burden of stroke [Online]. http://www.who.int/cardiovascular_diseases/en/cvd_atlas_15_burden_stroke.pdf?ua=1 [2018].
62. Ott A, Breteler MM, de Bruyne MC, van Harskamp F, Grobbee DE, Hofman A. Atrial fibrillation and dementia in a population-based study. The Rotterdam Study. *Stroke* **28**: 316-321, 1997.
63. Ott A, Stolk RP, van Harskamp F, Pols HA, Hofman A, Breteler MM. Diabetes mellitus and the risk of dementia: The Rotterdam Study. *Neurology* **53**: 1937-1942, 1999.
64. Pai JK, Pischon T, Ma J, Manson JE, Hankinson SE, Joshipura K, Curhan GC, Rifai N, Cannuscio CC, Stampfer MJ, Rimm EB. Inflammatory markers and the risk of coronary heart disease in men and women. *The New England journal of medicine* **351**: 2599-2610, 2004.
65. Petcu EB, Smith RA, Miroiu RI, Opris MM. Angiogenesis in old-aged subjects after ischemic stroke: a cautionary note for investigators. *Journal of angiogenesis research* **2**: 26, 2010.
66. Popa-Wagner A, Badan I, Walker L, Groppa S, Patrana N, Kessler C. Accelerated infarct development, cytogenesis and apoptosis following transient cerebral ischemia in aged rats. *Acta neuropathologica* **113**: 277-293, 2007.
67. Ramos CL, Huo Y, Jung U, Ghosh S, Manka DR, Sarembock IJ, Ley K. Direct demonstration of P-selectin- and VCAM-1-dependent mononuclear cell rolling in early atherosclerotic lesions of apolipoprotein E-deficient mice. *Circulation research* **84**: 1237-1244, 1999.

68. Rauscher FM, Goldschmidt-Clermont PJ, Davis BH, Wang T, Gregg D, Ramaswami P, Pippen AM, Annex BH, Dong C, Taylor DA. Aging, progenitor cell exhaustion, and atherosclerosis. *Circulation* **108**: 457-463, 2003.
69. Renshaw M, Rockwell J, Engleman C, Gewirtz A, Katz J, Sambhara S. Cutting edge: impaired Toll-like receptor expression and function in aging. *Journal of immunology* **169**: 4697-4701, 2002.
70. Riancho JA, Zarrabeitia MT, Amado JA, Olmos JM, Gonzalez-Macias J. Age-related differences in cytokine secretion. *Gerontology* **40**: 8-12, 1994.
71. Ridker PM, Everett BM, Thuren T, MacFadyen JG, Chang WH, Ballantyne C, Fonseca F, Nicolau J, Koenig W, Anker SD, Kastelein JJP, Cornel JH, Pais P, Pella D, Genest J, Cifkova R, Lorenzatti A, Forster T, Kobalava Z, Vida-Simiti L, Flather M, Shimokawa H, Ogawa H, Dellborg M, Rossi PRF, Troquay RPT, Libby P, Glynn RJ, Group CT. Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease. *The New England journal of medicine* **377**: 1119-1131, 2017.
72. Ridker PM, Hennekens CH, Buring JE, Rifai N. C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. *The New England journal of medicine* **342**: 836-843, 2000.
73. Ridker PM, Rifai N, Stampfer MJ, Hennekens CH. Plasma concentration of interleukin-6 and the risk of future myocardial infarction among apparently healthy men. *Circulation* **101**: 1767-1772, 2000.
74. Schill R, Frost C, Jenkins R, Whitwell JL, Rossor MN, Fox NC. A longitudinal study of brain volume changes in normal aging using serial registered magnetic resonance imaging. *Archives of neurology* **60**: 989-994, 2003.
75. Seidler S, Zimmermann HW, Bartneck M, Trautwein C, Tacke F. Age-dependent alterations of monocyte subsets and monocyte-related chemokine pathways in healthy adults. *BMC immunology* **11**: 30, 2010.

76. Smithard G. Stroke in Frail Older People. *Geriatrics* **2**, 2017.
77. Sohrabji F, Bake S, Lewis DK. Age-related changes in brain support cells: Implications for stroke severity. *Neurochemistry international* **63**: 291-301, 2013.
78. Starr ME, Saito M, Evers BM, Saito H. Age-Associated Increase in Cytokine Production During Systemic Inflammation-II: The Role of IL-1beta in Age-Dependent IL-6 Upregulation in Adipose Tissue. *The journals of gerontology Series A, Biological sciences and medical sciences* **70**: 1508-1515, 2015.
79. Sun Y, Jin K, Xie L, Childs J, Mao XO, Logvinova A, Greenberg DA. VEGF-induced neuroprotection, neurogenesis, and angiogenesis after focal cerebral ischemia. *The Journal of clinical investigation* **111**: 1843-1851, 2003.
80. Szpak GM, Lechowicz W, Lewandowska E, Bertrand E, Wierzba-Bobrowicz T, Dymecki J. Border zone neovascularization in cerebral ischemic infarct. *Folia neuropathologica* **37**: 264-268, 1999.
81. Uehara T, Tabuchi M, Mori E. Risk factors for occlusive lesions of intracranial arteries in stroke-free Japanese. *European journal of neurology* **12**: 218-222, 2005.
82. United Nations, Department of Economic and Social Affairs, Population D. *World Population Ageing 2017*. Report no. ST/ESA/SER.A/408, 2017.
83. van Deursen JM. The role of senescent cells in ageing. *Nature* **509**: 439-446, 2014.
84. van Duin D, Mohanty S, Thomas V, Ginter S, Montgomery RR, Fikrig E, Allore HG, Medzhitov R, Shaw AC. Age-associated defect in human TLR-1/2 function. *Journal of immunology* **178**: 970-975, 2007.
85. van Royen N, Hoefer I, Bottinger M, Hua J, Grundmann S, Voskuil M, Bode C, Schaper W, Buschmann I, Piek JJ. Local monocyte chemoattractant protein-1 therapy increases collateral artery

formation in apolipoprotein E-deficient mice but induces systemic monocytic CD11b expression, neointimal formation, and plaque progression. *Circulation research* **92**: 218-225, 2003.

86. Vemuri P, Lesnick TG, Przybelski SA, Knopman DS, Lowe VJ, Graff-Radford J, Roberts RO, Mielke MM, Machulda MM, Petersen RC, Jack CR, Jr. Age, vascular health, and Alzheimer disease biomarkers in an elderly sample. *Annals of neurology* **82**: 706-718, 2017.

87. Wang J, Geiger H, Rudolph KL. Immunoaging induced by hematopoietic stem cell aging. *Current opinion in immunology* **23**: 532-536, 2011.

88. Wen SW, Wong CHY. An unexplored brain-gut microbiota axis in stroke. *Gut microbes* **8**: 601-606, 2017.

89. Woollard KJ, Geissmann F. Monocytes in atherosclerosis: subsets and functions. *Nature reviews Cardiology* **7**: 77-86, 2010.

90. World Health Organization. *Global status report on noncommunicable diseases 2014* 2014.

91. Xiao Q, Kiechl S, Patel S, Oberhollenzer F, Weger S, Mayr A, Metzler B, Reindl M, Hu Y, Willeit J, Xu Q. Endothelial progenitor cells, cardiovascular risk factors, cytokine levels and atherosclerosis--results from a large population-based study. *PloS one* **2**: e975, 2007.

92. Yager JY, Wright S, Armstrong EA, Jahraus CM, Saucier DM. The influence of aging on recovery following ischemic brain damage. *Behavioural brain research* **173**: 171-180, 2006.

93. Yang GY, Betz AL. Reperfusion-induced injury to the blood-brain barrier after middle cerebral artery occlusion in rats. *Stroke* **25**: 1658-1664; discussion 1664-1655, 1994.

94. Yiannopoulou KG, Papageorgiou SG. Current and future treatments for Alzheimer's disease. *Therapeutic advances in neurological disorders* **6**: 19-33, 2013.

95. Yin KJ, Hamblin M, Chen YE. Angiogenesis-regulating microRNAs and Ischemic Stroke. *Current vascular pharmacology* **13**: 352-365, 2015.
96. Zhang ZG, Zhang L, Jiang Q, Zhang R, Davies K, Powers C, Bruggen N, Chopp M. VEGF enhances angiogenesis and promotes blood-brain barrier leakage in the ischemic brain. *The Journal of clinical investigation* **106**: 829-838, 2000.
97. Zheng MM, Zhang Z, Bemis K, Belch AR, Pilarski LM, Shively JE, Kirshner J. The systemic cytokine environment is permanently altered in multiple myeloma. *PloS one* **8**: e58504, 2013.
98. Zou Y, Jung KJ, Kim JW, Yu BP, Chung HY. Alteration of soluble adhesion molecules during aging and their modulation by calorie restriction. *FASEB journal : official publication of the Federation of American Societies for Experimental Biology* **18**: 320-322, 2004.
99. Zou Y, Yoon S, Jung KJ, Kim CH, Son TG, Kim MS, Kim YJ, Lee J, Yu BP, Chung HY. Upregulation of aortic adhesion molecules during aging. *The journals of gerontology Series A, Biological sciences and medical sciences* **61**: 232-244, 2006.

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