PERSPECTIVES

Autophagy, Senescence, and Arterial Inflammation: Relationship to Arterial Health and Longevity

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One essential element to longevity is maintaining the wellness of our vascular system. Our microhealth and macrohealth require an adequate supply line of nutrients. Cells and organs perish without arterial support. In order to maintain an excellent stream of sustenance, we must avoid serious impairment to the approximate 60 000 miles (96 560 km) of vessels in our body.

Arterial wellness demands mitigation of systemic inflammation. It has been proposed for over 3 decades that arterial disease is an inflammatory condition. In a more recent publication it was stated that inflammation plays a key role in the initiation and progression of atherosclerosis along with triggering cardiovascular events.[1] *The Lancet* in March 2012 published two genetically-based studies that indicate inflammation is causal of cardiovascular disease (CVD).[2,3] This concept fits well with published data that indicates there are numerous pathologies beyond cholesterol associated with CVD. These pathologies not only include dyslipidemia but also issues such as insulin resistance, nicotine, sleep disturbance, obesity, physical inactivity, poor diet, psychosocial issues, inflammatory diseases such as rheumatoid arthritis, and oral infections. All of these conditions are known to potentially increase systemic inflammation. The cause of arterial disease viewed through a lens of inflammation meshes well with existing information. Realizing the critical factor is inflammation erases paradoxes such as: half the people with cardiovascular (CV) events have normal or low cholesterol,[4] and excellent control of cholesterol with high dose statins still leaves many of those individuals at risk for a CV event.[5] To maintain the wellness of our arteries we need to discard the mono-focused concept of dyslipidemia as the driver of arterial disease and adopt inflammation as the cause, recognizing numerous conditions can produce inflammation. Maintaining the health of our CV system demands a holistic approach designed to stave off systemic inflammation.

A critical step in arterial health is augmentation of autophagy. Systemic cell wellness and longevity also depend on autophagy. The interiors of cells continuously develop damaged proteins and organelles. Cells are also bombarded by harmful material such as toxins from the environment and infectious agents. Cellular health depends on the ability to isolate these injurious substances and then break them down into innocuous basic biological elements. This process is known as autophagy, or "self-eating." When autophagy is impaired, inflammation develops, which can increase the risk of arterial disease.[6] In addition, some of the harmful proteins not destroyed can stimulate cancer and insulin resistance. An increase in reactive oxygen species (ROS) also develops within the cell. This can result in premature senescence. The net effect will be a negative influence on longevity, as well as arterial health. Augmenting autophagy is pivotal in living long and preserving fit arteries.

There are known safe therapies for improving autophagy. The biochemical pathways, which impair and enhance autophagy, are well defined. When a substance known as sirtuin 1 (SIRT-1) is increased, autophagy improves. When insulin like growth factor 1 (IGF-1) is increased, autophagy is impaired. One simple measure that will affect both of these issues in a way to improve autophagy is caloric restriction (CR). CR without starvation has been shown to increase life span.[7] There is indirect evidence of this with BMI data. Maintaining a BMI between 20 and 25 kg/m^2 in any developed country demands some CR. All-cause mortality risk is the lowest in this BMI group.[8] The study demonstrating that

the Mediterranean diet significantly reduced CV risk also supports the concept of reducing mortality risk with CR. Despite having a significant impact on decreasing CV risk, neither arm of the Mediterranean diet reduced overall mortality risk compared to the low fat dietary arm.[9] One explanation for this might be that there was no CR in any of the dietary arms. This study points out prolonging life involves more than just maintaining a balanced diet for a healthy vascular system. CR without starvation is an excellent treatment to assist in arterial wellness and to increase life span by enhancing autophagy.

IGF-1 impairs autophagy so lowering the level will cause enhancement. IGF-1 is increased with endogenous insulin. Therefore, keeping low insulin levels will decrease IGF-1. To maintain low insulin levels, individuals need to remain sensitive to insulin by reducing central adiposity, remaining physically active and avoiding metabolic syndrome. Type 2 diabetes is the end result of being insulin resistant for many years. It is known that becoming a type 2 diabetic by age 50 reduces life span by about 25% to 30%.[10] Exercise and weight loss have been shown to decrease IGF-1 levels.[11] These measures are safe lifestyle issues that will also enhance autophagy.

Exercise induces autophagy by an additional mechanism. Interruption of beclin 2–beclin 1 complex is crucial for stimulus-induced autophagy in mammals. During physical exercise, beclin 2 is phosphorylated, which separates it from beclin 1. This disruption causes activation of adenosine 5'-monophosphate-activated protein kinase (AMPK) by phosphorylation and the induction of autophagy.[12] In the Women's Health Study the reasons for reduced CV risk with exercise were explored. It was discovered that the number one reason exercise was beneficial to arterial wellness was reduction of inflammation.[13] Enhancement of autophagy through exercise would mitigate inflammation. It is well known that exercise improves longevity. Daily exercise that results in generating ≥25 MET-hours/week reduces the risk of dying by about 50%.[14] The Mayo Clinic reported in 2012 that people who exercise regularly versus the physically inactive live a mean of 7 years longer. The remarkable improvement in longevity and CV health with exercise is at least partially explained through enhanced autophagy.

There are several known chemicals that can enhance autophagy, but they can cause adverse off-target effects. Resveratrol will improve autophagy by activating SIRT-1. However, one issue with resveratrol is its poor bioavailability. Red wine, for example, is known to contain this substance, but only trace amounts are found after ingesting 177 mL of red wine. When higher doses of resveratrol are delivered, side effects involving diarrhea, potassium, and hepatic function surface.[15] GlaxoSmithKline terminated a trial in 2010 with resveratrol for safety reasons. Chemical activation of SIRT-1 still appears to be a viable option for improving autophagy. Investigation with formal clinical trials is underway with more potent and selective SIRT-1 activators.[16] The antibiotic and immunosuppressant, rapamycin (RAP), improves autophagy by reducing (mammalian) target of RAP (mTOR). In a study with mice, matched for the equivalent to a 60-year-old human, RAP prolonged life by around 30%. A recent study in mice demonstrated RAP therapy delivered to ischemic myocardium enhanced autophapy. Furthermore, this improvement in autophagy significantly reduced myocardial apoptosis 23% and infarction size 45%.[17] It remains to be seen if the off-target issues of lung toxicity, insulin resistance, and potential cancer risk will prevent this drug from being used to improve autophagy. Research is ongoing to identify autophagy enhancing pharmaceutical agents that are safe.

There is one natural substance that improves autophagy by upregulating expression of the ATG gene, which generates the ATG protein necessary for autophagy induction. So far no adverse effects have been reported with this substance, spermidine. It is found in many foods with the best concentrations being in legumes such as beans, sunflower seeds, and peas. Mussels, maize, oats, and rye are also moderately rich in spermidine. There is considerable hype in some circles about semen being very beneficial for health due its concentration of spermidine. Many individuals will find comfort in the fact that the legumes are three to six times more concentrated with spermidine than is semen.[18] Perhaps one of the reasons the Mediterranean diet demonstrated significant CV risk reduction is due to its containment of many foods rich in spermidine. At this time, spermidine does seem to be a safe enhancer of autophagy.

Senescence is the loss of a cell's ability to replicate. This can happen two ways: aging and oxidative stress. As we age, telomeres shorten. They can eventually get so short that they preclude cell replication, which is known as senescence of aging. The other mechanism involves oxidative stress resulting in senescence and this is not related to telomere length. This is known as premature senescence. Cells that develop senescence from either mechanism become inflammatory. When this occurs with endothelial cells, vascular smooth muscle cells, or macrophages, the resulting inflammation can promote arterial disease.[19] The most significant traditional risk factor for CV risk is age. The reason for this is probably, to a large degree, senescence of aging. There is a lot of active research to identify safe treatments to halt telomere shortening. There are numerous measures available to mitigate premature senescence. Numerous lifestyle measures can reduce oxidative stress and, therefore, premature senescence. Nicotine generates significant oxidative stress. Avoidance of tobacco exposure is very important in lessening premature senescence. Maintaining a BMI less than 30 kg/m^2 along with a waist under the metabolic syndrome cut points is important, as obesity with central adiposity causes oxidative stress. Moderate physical activity and maintaining diets high in antioxidants are excellent ways to reduce oxidative stress. Some commonly used CV drugs such as statins and renin-angiotensin-aldosterone system medications are known antioxidants. Eliminating oxidative stress will prevent premature senescence, which will improve arterial health and longevity. A report presented at the American College of Cardiology's

Scientific Session on March 9, 2013 indicates the survival rates of patients with known coronary artery disease can be predicted by the length of their telomeres. However, the study demonstrated telomere length did not predict heart attack and stroke risk after adjusting for age. This finding is not a surprise, as telomere length does not indicate the degree of premature senescence, which will also impact CV risk. Fortunately, we have some medications and safe lifestyle measures to reduce premature senescence. Senescence (regardless of its cause) will impact arterial wellness and longevity.

The wonderful news is there are numerous benign therapies for autophagy and senescence. Their application should result in reduction of CV risk and increased longevity. One could argue that all antiaging programs should have these elements as essential recommendations. They are remarkably similar to the lifestyle essentials for heart health, which were recently demonstrated to also significantly reduce cancer risk.[20] This news should not be shocking since autophagy is enhanced with these "essentials." Autophagy allows cells to potentially eliminate cancer-stimulating proteins prior to formation of cancer. Advice in virtually all antiaging practices should include (1) no nicotine exposure; (2) daily physical activity; (3) a diet rich in antioxidants and spermidine coupled with CR to maintain a BMI of 20 to 25 kg/m^2; and (4) avoidance of central adiposity and insulin resistance. These recommendations are applicable to all individuals. There is tremendous opportunity in these arenas as recently published studies show almost 80% of adults are not at the combined aerobic and resistive physical activity goals; approximately 66% of adults are either overweight or obese; type 2 diabetes is the fastest growing disease in the United States; and a significant number of adults still smoke. Antiaging programs incorporating these lifestyle concerns as critical elements of care can have a large impact transforming our health care system to where the central goal is maintaining wellness.

It would be helpful to have an objective measurement for autophagy and senescence. At the present time, there is none except mortality. However, oxidative stress is strongly related to both autophagy and senescence. Oxidative stress increases with impaired autophagy and it drives premature senescence. There is an excellent urinary measurement for oxidative stress: F2-isoprostane.[21] In our work, we have nicknamed it the "lifestyle lie detector" and the test that tells us how "rusty" someone is, which translates to how fast they are aging. There are a few caveats to the measurement, but for the most part a high level indicates poor compliance with the essential therapies mentioned above for autophagy and senescence. This test does provide some objectivity in accessing two natural phenomena highly related to the maintenance of arterial wellness and longevity. At the moment, F2-isoprostane can be considered a surrogate measure of autophagy and senescence.

A Chinese statement from 4000 years ago proclaimed: "Superior health care providers prevent disease; mediocre health care providers treat disease before it is full-blown; inferior health care providers treat the full-blown disease." Our current system is set up to provide the most rewards to those treating end stage or full-blown disease. This has led to the bankruptcy of our health care system financially, emotionally, and physically. We must migrate to a platform of maintaining wellness and preventing disease. Autophagy and senescence are key biological processes to facilitate this movement. Antiaging medicine is in a position to lead the charge! May we all have enhanced autophagy and avoidance of premature senescence!

AUTHOR DISCLOSURE STATEMENT

Both authors are consultants and speakers for the Cleveland HeartLab.

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