Review

Inflammaging (inflammation + aging): A driving force for human aging based on an evolutionarily antagonistic pleiotropy theory?

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Summary **Aging, and especially human aging, can be explained by the emerging concept of para-inflammation-driven inflammaging, *i.e.* a combination of inflammation and aging. Inflammaging posits that aging either physiologically or pathologically can be driven by the pro-inflammatory cytokines and substances produced by the innate immune system. Animals must maintain homeostasis as they age despite incessant attack from both intrinsic and extrinsic stimuli/antigens. These potentially harmful pro-inflammatory signals at a later stage of life may act antagonistically to the beneficial role they had in an earlier stage of life, like serving as developmental engines for body system formation. The concept of inflammaging is based on an antagonistic pleiotropy theory programmed during evolution. Clinical trials including caloric restriction, sirtuin activators, and p38 MAPK inhibitors against both pathological aging such as metabolic syndrome, diabetes mellitus, rheumatoid arthritis, and Werner syndrome and physiological aging have been proposed.**

Keywords: Aging, Antagonistic pleiotropy, Caloric restriction, Cytokine, Evolution, Inflammaging, Inflammation, Innate immunity, Metabolic syndrome, Rheumatoid arthritis, Sirtuin, Werner syndrome

1. What is aging?

Bernard Strehler proposed the classical definition of aging 30 years ago (*1*) according to the following four characteristics. Although these criteria are generally accepted, recent progress in the fields of evolutionary science, gerontology, and inflammation research in a variety of models have led to slight modifications of this view, as are noted in comments here:

1. Universality: Changes should occur in all older members.
2. Intrinsicality: Aging does not result from modifiable, environmental variables.
   Comment: Recent experiments suggest the significantly modifiable effect of environmental factors such as caloric restriction on aging in a variety of species (*2-6*).
3. Progressiveness: Aging begins with a gradual and cumulative occurrence of onset like development and maturation.
   Comment: Aging begins immediately after maturity. The basic mechanism of aging may different from development and maturation, which are heavily controlled genetically. Restoration and repair of decreased function and damaged tissue can be interventionally obtained, for example, by caloric restriction (*2-7*).
4. Deleteriousness: The most characteristic change that differentiates aging from development and maturation is its deleteriousness; minute, but progressive decline of the whole aspect of physiological functions in a concerted fashion.
   Comment: As the term 'aging' basically means concerted changes in an organism over time and does not solely mean senescence with weakness, aging should include all stages of an organism's life: development, maturation, and senescence from birth until death. Some physiological functions such

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as those of the nervous system and psychological system may remain unchanged if pathological dysfunctions can be prevented or repaired (*8-15*). However, most functions/systems in the human body tend to deteriorate slowly and progressively with age like machines, and the terms "aging" and "senescence" are used interchangeably even in the field of gerontology.

Human aging has been viewed as the declining function of most body systems as the result either of the progressive accumulation of damaged tissue and substances or the progressive loss of normal tissue and substances either by intrinsic or extrinsic mechanisms. As no older individuals can escape from age-related pathologies like atherosclerosis, osteoporosis, insulin resistance, and sarcopenia, defining the elderly as healthy is problematic. In practice, elderly who live independently in relatively good health are considered healthy or normal, even if they have a certain degree either of hypertension, osteoporosis, sarcopenia, insulin resistance, cognitive dysfunction, or other age-related organ dysfunctions according to standards for healthy young adults. Thus, the term "successful aging or better aging" has been proposed. Theoretically, aging can be divided into two categories: physiological (normal/intrinsic) aging and pathological (diseased/extrinsic) aging, though a clear-cut separation between the two is difficult.

The four major theories on the mechanisms of aging that have been proposed are listed in Table 1.

1. Wear & tear theory was the historically accepted theory; all living things that exist under the control of time may be damaged either by extrinsic environmental damage such as radiation, free radicals, infections, and attacks from the predators or by intrinsic environmental damage such as free radicals and metabolites. This damage may induce somatic mutations leading to malignancy: the acceleration of aging. This mechanism may not be genetically inherited.
2. Wear & repair theory has been proposed as a variation of wear & tear theory. This theory suggests the mechanisms of inheritable maintenance and repair.
3. Mutation accumulation theory is widely supported by oncologists and cell biologists and includes the idea that oncogene-induced senescence is part of the barrier to tumorigenesis (*16,17*).
4. Antagonistic pleiotropy theory has been favored in the form of the term "evolutionarily antagonistic pleiotropy."

2. Evolutionarily antagonistic pleiotropy

Natural selection that includes a "struggle for existence" and "survival of the fittest" as proposed in evolutionary theory has been widely accepted as the basic driving force leading to major biological changes (*18,19*). Aging has generally been believed to be time-dependent reduced Darwinian fitness resulting in a growing risk of disease and death that all living things inevitably experience in the later stage of life. It is also usually accompanied by a decline in fertility. Historically, aging has never been welcomed, especially among evolutionists, as they had difficulty in finding the merit of aging as an organism (*20*).

The advantages of programmed aging may be that:

1. It benefits the species/groups by preventing overcrowding and/or facilitating further evolution by securing a turnover of generations (*21*). This theory may explain the benefit of the species or group but supersedes the contrary interests of the individuals (*22*).
2. Aging stops cells that have escaped from normal control from dividing indefinitely, such as cancer and atherosclerotic plaques as cited by cell biologists (*23-25*).
3. Aging-associated declining function/metabolism with low/no fertility may provide benefits under stress such as starvation (*26,27*).

According to conventional evolutionary theory, aging as a non-adaptive process has been explained as the result of the weakening force of natural selection and reduced genetic effects with age (*28,29*).

This theory offered the following explanations for the apparent disadvantage to the individual:

1. Detrimental mutations acting only post-maturity may not be a reproductive disadvantage to individuals and thus can spread through populations.
2. Although the risk of death that individuals experience from environmental attack can increase with aging,

Table 1. The major mechanistic theories of aging

Theory	Cause of aging	Inheritance
1. Wear & tear	Radiation, Free radicals, Mechanical damage, Somatic mutation	No
2. Wear & repair	Radiation, Free radicals, Mechanical damage, Somatic mutation	Yes/No
3. Mutation accumulation	Deleterious mutation late in life	Yes
4. Antagonistic pleiotropy	Genes with beneficial effects early in life and detrimental effect later	Yes

the individual's genes can be inherited and spread to the next generation and the chance of evolutional mutations may be enhanced before senescence by fragility and death.

Recent reports on wild red deer and sheep suggested genotype-by-age interactions (age-specific additive genetic covariance matrices across all ages without the dramatic loss of power associated with subdividing the data into age classes), which the evolutionary theory of aging already predicted. However, an increasing genetic variation with aging (additive genetic variation in individual aging rates) was observed (*30*,*31*).

According to antagonistic pleiotropy theory, the effects of aging should be beneficial in early life, when natural selection is strong, but harmful in later life, when selection is weak. Antagonistic pleiotropy theory in regard to the evolution of aging predicts that increased early-life performance should be accompanied by earlier (or faster) aging (*27*,*32*,*33*). Quantitative genetic pedigree analyses in wild swans indicate that traits from groups at the age of first reproduction and at the age of last reproduction had additive genetic variance, but both were positively genetically correlated (*34*). Thus, both traits show heritable variation and are under opposing directional selection, but their evolution may be constrained by a strong evolutionary trade-off. These results are consistent with the theory that increased early-life performance comes with faster aging because of genetic trade-offs.

Although Csete *et al*. proposed against evolutionary antagonistic pleiotropy in that the enormous complexity of organismal systems is the result of an evolutionary trade-off between robustness, feedback, and fragility (*35*), the randomness of the evolutionary process may retain the characteristics of antagonistic pleiotropy: beneficial events in earlier stages despite their later potential drawbacks. Evolution may not see into the future (*36*,*37*).

However, recent papers have proposed a new concept, programmed and altruistic aging (*38*). They proposed two altruistic reasons for the evolutional advantage of aging and death:

1. Programmed and altruistic aging benefits closely related organisms that have acquired mutations that increase their ability to grow and survive.
2. Programmed and altruistic aging benefits the species/group as a whole.

Recent studies of unicellular organisms have raised the controversial possibility that programmed and altruistic aging might occur, and that this might be an adaptive process that benefits small sub-populations of closely related mutants (*39-41*).

Evolutionary theory has not dealt primarily with individuals but with population/species using the concept of natural selection as a driving force for the "struggle for existence" and "survival of the fittest" (*18*,*19*). Although aging is a nearly universal feature of multicellular organisms, aging, and especially human aging, involves a purely individual phenomenon occurring after the reproductive stage and may involve freedom from the forces of natural selection.

Evolutionary theory with regard to aging is still in the formative stages because experimental evidence on aging, and especially among human beings, may be difficult to obtain. In addition, aging may not be a simple straight road to longevity or the end of life; aging may also fine tune organismal systems in a sophisticated concerted manner with a 'longevity' gene(s) and environmental stress, as was observed in the coagulatory systems of centenarians (*42*,*43*). Aging may be a new battlefield for evolution.

3. What is inflammation?

Inflammation, triggered by harmful stimuli and agents like infection and tissue injury, is defined as a wide variety of adaptive physiological and pathological processes to avoid infection and repair damage, restoring the organism to the usual state of homeostasis (*44*).

As Medzhitov mentioned in his review article in Nature, pathological aspects of many types of inflammation, either of acute or chronic, have been well documents, though most physiological functions of inflammation have not been fully studied (*45*). He explained three modes of adaptation and maintenance of tissue/cell homeostasis in relation to inflammation.

1. Under baseline conditions, tissues/cells maintain homeostasis. Apoptosis is a type of homeostatic mechanism during development, growth, and also aging.
   However, recent study of lymphoid tissue genesis induced by bacterial flora commensals through innate receptors suggests a countercurrent modification of homeostasis (*46*).
2. If damaged or infected, tissues/cells respond & repair as a result of acute/chronic inflammation.
3. If conditions waver in between homeostasis and infection, such as mild/slowly progressive stress or modest malfunction, the tissue/cells tend to finely adapt to the slightly changed conditions and restore tissue/cell functionality by inducing para-inflammation, sub-inflammation, low-level of inflammation, sterile inflammation, physiological inflammation, or inflammaging as Franceschi proposed (*47*).

Dysregulated para-inflammation may be responsible for mild chronic inflammatory conditions in age-related diseases like insulin resistant type II diabetes mellitus, atherosclerosis, cancer, and Alzheimer's disease (*48-52*).

Traditional evolutionary theory predicts the existence of genes with antagonistic functions on development, maturation, and aging.

4. What is inflammaging?

The term "inflammaging" is a coinage of "inflammation" and "aging" by Italian immunology researchers (*47,53*). For the immune system, the characteristic consequence of aging, they posited, is the progressive filling of the immunological system by activated lymphocytes, macrophages, and dendritic cells in response to chronic/continuous subtle stress either from pathological or physiological antigens/toxins. Thus, the condition of inflammaging provides a continuous mild antigenic challenge leading to a pro-inflammatory condition associated with the progressive stimulation/depletion of the immune system and other organismal systems (*14,29,53,54*). On the whole, immunosenescence can be taken as proof that the beneficial effects of the immune system, devoted to the neutralization of dangerous/harmful agents early in life and to better development and maturation leading to the prosperity of future generations and species in adulthood, become detrimental late in life, in a period largely not foreseen by evolution (*37*). This perspective fits with basic assumptions of evolutionarily antagonistic pleiotropy theory in regard to aging, which suggests that a trade-off between early beneficial effects and late negative outcomes can occur at the genetic and molecular level.

Inflammaging can be defined by:

1. Low-grade.
2. Controlled.
3. Asymptomatic and not pathological.
4. Chronic.
5. Systemic inflammatory state (*54*).
6. Beneficial effects in early life but detrimental effects in later life for individuals.

Although several groups from different research backgrounds have studied the inflammatory process in human aging (*55-58*), the inflammaging theory of human aging fails to clearly explain the "true" physiological aging process as a whole, despite a fairly large amount of evidence for pathological aging associated with the natural aging process (*48-52,59*). This is because of difficulty in separating "true" physiological aging and "true" pathological aging during the natural aging process, as mentioned in the previous section.

The contribution of inflammatory/infectious processes to the pathogenesis of age-associated diseases ("true" pathological aging) has been frequently discussed in terms of atherosclerotic cardiovascular diseases (*60-64*). Although atherosclerotic cardiovascular diseases such as myocardial infarction and cerebral bleeding are unquestionably diseases that are closely related to the aging process, one would be hard-pressed to distinguish whether atherosclerosis itself, and especially at the sub-clinical level, is the "true" pathological process of age-associated disease or just the accumulation of subtle but continuous physiological processes of natural aging. In the pre-clinical stage, other aging-associated diseases such as osteoporosis, type II diabetes mellitus, sarcopenia, osteoarthritis, Alzheimer's disease, and hypogonadism are also difficult to clearly differentiate as a diseased state or a non-normal state.

This difficulty may exist because of the following reasons:

1. Individuals develop, mature, and successively age with senescence after being born as an infant, and individuals maintain the consistency of their own systems as an organism throughout their lives.
2. According to the traditional point of view, diseases are an abnormal state that is detrimental to one's quality of life or that cannot be readily survived without medical intervention.
3. In modern society, a "diseased state" may not be apparent in an individual and extremely sophisticated medical examinations can easily detect minute changes in bodily constituents that may not impact the individual's life in the immediate future. And yet a doctor may consider the individual to have a "disease". However, a "diseased state" or an accumulation of physiological aging may be a prologue to age-associated diseases leading to an organism's death in the distant future.
4. Thus, distinguishing between a non-normal state and a true diseased state, and especially one that is age-associated, is difficult.

5. Clinical trials of drugs to treat pathological inflammaging

Several suggestions have been provided by clinical trials using anti-inflammatory interventions. The first evidence was reported in the field of atherosclerosis (*48,49,65*). A low dose of aspirin can prevent angina pectoris and myocardial infarction and extend the life-span of the patient. In addition, the important point is that intervention can significantly reduce the risk of cardiovascular disease even in apparently healthy individuals. This study suggests the potentially modifiable role of medical intervention in physiological aging in addition to that in pathological aging.

In cancer treatment, targeted inhibition of the cyclooxygenase-2 pathway may be effective in the treatment of colorectal cancer and other types of cancer through a reduction in tumor-associated inflammation (*66*). Osteoporosis, characterized by low bone mass and increased bony fragility, is not recognized as a disease

prior to an examination of bone mineral density or actual fracture. A recent study suggests an influential effect of inflammation on the occurrence of osteoporosis (*50*). Non-steroidal anti-inflammatory agents were found to have a protective with respect to the development of Alzheimer's disease (*51,67*), though a disagreement with this finding was also reported (*68*).

Caloric reduction is another type of anti-inflammatory intervention for aging and type II diabetes mellitus (*2-7,59*). In addition, the successful treatment of insulin-resistant diabetes mellitus by several pharmacological interventions has been reported in inflammatory pathways such as pioglitazone, high-dose aspirin, PPARα and γ ligands, and anti-TNFα (*69-71*).

6. What drives inflammaging?

The potential forces that drive inflammaging are pro-inflammatory cytokines and substances as are listed in Table 2. CRP and fibrinogen, the major clinical markers of inflammation, have been significantly associated with coronary disease, myocardial ischemia, and myocardial infarction, in association with IL-1, IL-1 receptor antagonist, IL-6, soluble IL-6 receptor, IL-18, TNFα, serum amyloid A, and soluble ICAM-1 (*56,72-74*).

Table 2. Associated changes of inflammation with aging

Agents	Inflammation	Aging
Inflammatory proteins		
CRP	↑*	↑
SAA	↑	↑
Proinflammatory mediators		
IL-1α, β	↑	↑
IL-4	↑	?***
IL-6	↑	↑
IL-12	↑	↑
IL-15	↑	↑
IL-18	↑	↑
TNFα, β	↑	↑
IFNγ	↑	↑
TGFβ1	↑	↑
sIL-2R	↑	↑
sIL-6R	↑	↑
MCSF	↑	↑
GM-CSF	↑	↑
Chemokines		
IL-8	↑	↑
MCP-1	↑	↑
Anti-inflammatory mediators		
IL-1ra	↑	↑
sTNFR	↑	↑
IL-10	↑	↓
Proinflammatory enzymes		
iNOS	↑	↑
COX2	↑	↑
PGE2	↑	↑
Adhesion molecules		
ICAM-1	↑	↑
VCAM-1	↑	↑
Hypoxic markers		
HIF-1α	↑	↑
VEGF	↑	↑
Redox state		
ROS	↑	↑
SOD	↓**	↓

* ↑, increased; ** ↓, decreased; *** ?: conflicting results.

Cancer-related inflammation is reported under the conditions described below (*75,76*):

1. Growth of tumor cells associated with leukocyte recruitment and survival is initiated by G-CSF, GM-CSF, M-CSF, TGF-β, PDGF, IGF-1 and bFGF.
2. Monocyte recruitment and angiogenesis are activated by chemokines such as IL-8, CC-chemokine ligand 2/MCP-1, and CCL20 and modulated by IL-4 and IL-12.
3. Tumor cell homing to lymph nodes is promoted by chemokines, chemokine receptors, and adhesion molecules including CXC-chemokine receptor 4, CXC ligand 12, and L-selectin.
4. Tumor cell invasion and dissemination may be promoted by proteases including MMPs 7, 9, and 10 and urokinase-type plasminogen activator.
5. Fibrosis as the result of tissue repair was accelerated by TGF-β, PDGF, IL-1, IL-4, and mast cell tryptase.

However, whether an age-associated "pro-inflammatory condition" is the result of the primary impairment of the mechanisms that induce the inflammatory response or is the net result of cardiovascular risk factors including smoking, obesity, alcohol consumption, sedentary lifestyle, and excessive stress is still unclear (*74*).

Several lines of basic research suggest the important roles of inflammation and perhaps chronic infection in the initiation and progression of atherosclerosis (*5,44,47,49,61*). For example, prior exposure to *Chlamydia pneumoniae*, cytomegalovirus, and *Helicobacter pylori* has been detected in atherosclerotic tissue in humans (*62,77-81*). Cytomegalovirus infection can also induce atherosclerosis with endothelial lesions in animal experiments (*63,82*). These findings suggest that these microorganisms may activate vessel-associated leukocytes or lymphocytes or induce the transformation of vascular muscles or vascular endothelial cells (*81*).

As summarized in Table 3, an association between inflammation/infection and cancer risk has been proposed (*76,77,82,83*) and the successful prevention and treatment of colon cancer both in humans and mice by cyclooxygenases and stomach cancer by

Table 3. Cancer risk associated with infections

Cancer	Infections
Baldder/colon cancer	*Schistosoma haematobium*
Cervical cancer	Papilloma virus
Stomach cancer	*Helicobacter pylori*
MALT lymphoma	*Helicobacter pylori*
Hepatocellular carcinoma	Hepatitis virus B, C
Kaposi's sarcoma	Herpes virus
Nasopharyngeal carcinoma	Epstein Barr virus
Burkitt's lymphoma	Epstein Barr virus
Rous sarcoma	Rous sarcoma virus

antibiotics is widely accepted (*83-85*). Sarcopenia and frailty syndrome leading to accelerated mortality may be caused by the apoptotic death of muscle cells mediated by TNFα (*86*). Inflammatory cytokines including TNFα, IL-1, and IL-6 have been reported to be associated with cognitive decline with aging and Alzheimer's disease (*86*).

7. Innate immunity

The physiological aging process and many age-associated diseases are likely orchestrated with pro-inflammatory cytokines and chemokines by reactive oxygen species and reactive nitrogen species reactions through the activation of NFκB, which has a central position in the inflammatory reaction (*56,57*). However, what and how bodily defense systems including the immune system cope, modulate, and respond to a time-dependent environmental attack either from the inside or outside is still unclear.

The immune system operates in concert with two evolutionarily different branches: innate (natural) immunity and adaptive (acquired) immunity. The host immune system recognizes and differentiates between different inflammatory triggers such as tissue injury, bacterial/viral/parasitic infections, food, drugs, and mutant cells using specific receptors. Most microbial infection and some fragmented tissue products can be detected by innate immune receptors known as Toll-like receptors (TLR) on the surface of macrophages, polymorphonuclear cells, dendritic cells, and mast cells (*87-90*). Microbes and fragmented tissue products that may be recognized by TLR are listed in Table 4.

Cells dying as the result of asterile tissue injury such as ischemia-reperfusion or apoptosis during normal development can trigger an inflammatory cytokine response mimicking the features of infection-induced inflammation (*91-94*).

A decreased ability to maintain homeostasis in response to external stress in association with an increased risk of age-associated diseases and death has been studied in the elderly (*95,96*). At over 60 y.o., individuals have a mortality up to 25 times that of the individuals between 25 and 44 y.o.; when compared to the individuals between 25 and 44 y.o., specific mortality rates in people over 65 y.o. are much higher as a result of the following factors: ~90-fold for heart disease and pneumonia/influenza, 43-fold for cancer, and more than 100-fold for stroke and chronic lung diseases. As resistance to/defense against these age-associated pathologies may depend on the immune system, these data suggest that aging and innate immunity play a pivotal role of in controlling longevity of the elderly.

Accumulating evidence indicates the possible role of innate immunity-mediated inflammaging in human aging process.

However, there are still a number of unanswered questions (*97-100*).

1. How does the innate immune system recognize the degree of harmful inflammation that may lead to the following outcomes: homeostasis (complete repair), partial repair, modified repair, additional/collateral damage or death?
2. In addition, do qualitatively different types of insults to the host such as sterile tissue injury and infection produce similar inflammation since the ligands that lead to subsequent signals may follow similar innate immune pathways?
3. What are the mechanisms to resolve innate immunity-mediated inflammation as accompanies aging?
4. How do aging organisms confront, *via* innate immunity, the continuous attack of inflammaging and maintain a slightly changed/aged state?

According to the general theory of hormesis (*101,102*), the beneficial effects of extremely low doses of agents including those from apoptotic cells and fragmented matrix components during normal development and maturation are otherwise toxic at higher doses that can not be fully cleared from the tissues and cells, and accumulate with aging within the organism (*85,103-106*).

Several groups of researchers have suggested that inflammaging may be an auto-innate immunity subclinical syndrome induced by self-constituents released from apoptotic cells or degraded products during physiological development and daily tissue

Table 4. Toll-like receptor and ligands

TLR	Ligand
TLR1	Bacterial triacyl lipopeptides, Peptidoglycan, Lipoteic acid, Zymozyan, Hemagglutinin, Virus
TLR2 (cell surface)	Triacyl lipopeptides, Peptidoglycan, Lipoteic acid, Zymozyan, Hemagglutinin, Virus
TLR3 (endosome)	Viral dsRNA, Poly (I:C), Endogenous RNA from necrotic cells
TLR4 (cell surface)	LPS (gram(-)), Hsps, Hyaluronan, Fibronectin
TLR5	Bacterial flaggellin
TLR6	Bacterial diacyl lipopeptides
TLR7/TLR8 (endosome)	Viral ssRNA
TLR9 (endosome)	Bacterial/viral CpG DNA, Chromatin IgG complexes, HMGB1
TLR10	not yet identified
TLR11	not yet identified in humans

damage (*54,105,106*).

Evolutionary programming of the innate immune system leading to inflammation may act beneficially before maturation as a driving force for physiological development linked, for example, to apoptosis, but act detrimentally after maturation as a harbinger of both the physiological and pathological aging. Thus, this programming may act *via* evolutionary selection of these genetic traits.

8. Models of human inflammaging

Three different types of potential disease models for human inflammaging are 1) metabolic syndrome, 2) rheumatoid arthritis, and 3) Werner syndrome. The similar but accelerated clinical aspects of these diseases in response to natural aging are summarized in Table 5.

8.1. *Metabolic syndrome*

Metabolic syndrome consists of a combination of abdominal fat deposition, hypertriglyceridemia, low high density lipoprotein, hypertension, and fasting hyperglycaemia that can lead to diabetes mellitus and atherosclerosis (*96*). Diabetes mellitus has been proposed as a model for an accelerated form of human aging (*107-109*). Recent accumulated evidence suggests a pivotal role for inflammation in the pathogenesis of diabetes mellitus, obesity, and metabolic syndrome resulting from an overeating and inactivity in postindustrial societies (*2,4,57*). Obesity is closely associated with a series of sequentially appearing health problems including insulin-resistant type II diabetes mellitus, fatty liver, atherosclerosis, hypertension, neurodegenerative Alzheimer's disease, chronic obstructive lung disease, and even some cancers (*69*). As indicated in Table 5, some of the major clinical manifestations usually noted in the natural aging process such as secondary dwarfism, cataracts, and loss of hair are not usually encountered in metabolic syndrome. In addition, although the data on the aging-related immunological dysfunctions are, except for an elevation of pro-inflammatory cytokines, lacking, several endocrine-metabolic disorders in an accelerated fashion are consistent hallmarks of metabolic syndrome (*110-112*). Caloric restriction along with appropriate exercise has been suggested as an effective treatment for metabolic syndrome (*1-6,69,71*).

8.2. *Rheumatoid arthritis*

Rheumatoid arthritis is not usually recognized as a type of accelerated aging disorder (*113*). Patients with rheumatoid arthritis do not usually experience a higher incidence of cancer except lymphoma, but do exhibit a significantly higher incidence of atherosclerotic diseases, sarcopenia, sleep disorders, and osteoporosis in comparison to the general population (*114-117*). In spite of substantial recent medical progress, the average life-span of patients with rheumatoid arthritis remains far lower than that of general population (*118-121*). They show some signs of metabolic syndrome as listed in Table 5, though disease-specific therapy may contribute to the development of age-associated pathologies to a certain degree. In addition, immunological hallmarks usually observed in rheumatoid arthritis can be viewed as the result of an accelerated immunological state due to aging such as increased serum immunoglobulin levels, positivity for rheumatoid factor and anti-nuclear antibodies, increased

Table 5. Clinical aspects of inflammation-associated diseases

Signs & symptoms	Natural aging	Metabolic syndrome	Rheumatoid arthritis	Werner syndrome
Connective tissue disorder				
Dwarfism	+	+	++	++
Gary hair/alopecia	+	+	++	++
Skin atrophy	+	+	++	++
Sarcopenia	+	++	++	++
Arthropathy	+	++	++	++
Cataract	+	++	++	++
Osteoporosis	+	+	++	++
Endocrine-metabolic disorder				
Diabete mellitus	+	++	++	++
Hypogonadism	+	++	++	++
Hyperlipidemia	+	++	++	++
Hyperuricemia	–	++	++	++
Central obesity	+	++	++	++
Immune disorder				
Autoantibody production	+	+	++	++
Recurrent infection	+	+	+	+
Pro-inflammatory cytokines ↑	+	++	++	++
Neurodegenerative disorder	+	++	–	–
Cancer	+	++	++	++
Atherosclerosis	+	++	++	++
Hypertension	+	++	+	+

production of pro-inflammatory cytokines, decreased DTH reaction to BCG, and decreased production of IL-2 and γIFN (*113,122-124*). As recommended by the American College of Rheumatology, the standard treatment protocol for rheumatoid arthritis involves treating chronic autoimmune-mediated inflammation (*125,126*). Recent anti-TNFα therapy is reported to improve both age-related conditions such as insulin resistance and arthritic inflammation in patients with rheumatoid arthritis (*127*). Interestingly, the traditional use of hydroxychloroquine and sulphasalazine can improve insulin resistance in parallel with an improvement in condition (*128-130*).

8.3. *Werner syndrome*

Werner syndrome has been recognized as typical progeroid syndrome mimicking accelerated human aging (*131*). As listed in Table 5, patients with Werner syndrome manifest a wide variety of aging phenotypes immediately after maturity (*132-134*). Werner syndrome is an autosomal recessive disease involving mutation of the RecQ3 helicase and a shorter life-span (*134-137*). Dysfunction of the RecQ3 helicase, resulting in the unwinding of the double helices of DNA and RNA unquestionably leads to the typical Werner syndrome symptoms of metabolic syndrome (*131-133,138-140*). The major causes of death are myocardial infarction and cancer in concert with causes of death in the general population. A reason for interest in Werner syndrome is the constant presence of immunological and metabolic abnormalities that usually overlap normal aging (*141-146*). Although patients with Werner syndrome usually do not manifest apparent inflammatory symptoms such as recurrent infection and chronic inflammatory diseases, elevated serum levels of inflammatory cytokines including IL-6, TNFα, adipocytokines, and TGFβ have been frequently detected in addition to elevated levels of soluble Fas ligand, MMP1 and 9, hyaluronan, and fibronectin (*138-140,144,147,148,* unpublished data). There is no clear association between these inflammatory markers and age-related phenotypes in Werner syndrome except as regards diabetes mellitus. In patients with Werner syndrome, levels of plasma adipocytokines, *i.e.* significantly elevated TNFα and decreased adiponectin, can return to normal after treatment with pioglitazone (*139*).

9. Caloric restriction: Clues to support the concept of inflammaging as a form of evolutionarily antagonistic pleiotropy

Inflammaging is a low-grade (mild and subtle), controlled (easily adjusted to a homeostatic state), asymptomatic (not pathological or unrecognizable), chronic (near-steady state), and systemic inflammatory state. The concept of inflammaging coincides with antagonistic pleiotropy theory in regard to the evolution of aging, postulating that aging is the late deleterious effect of genes (pro-inflammatory *vs.* anti-inflammatory) that are beneficial at an earlier stage of life for the development and maintenance of body systems (*47*). Restriction of food intake (caloric restriction) can extend the maximum and average life span of laboratory animals by delaying natural aging processes (*2-6,149*). Although the evidence on an underlying mechanism of countering natural aging is scarce, a hypothesis, in line with hormesis theory (*101,102*), that links the alteration of glucose-IGF1 and growth hormone has recently gained support (*4,6*).

In addition, the crucial role of hypothalamic energy-sensing neurons in the control of energy metabolism-derived inflammation has been suggested (*4,6*). A recent paper by Sinclair indicated that resveratrol (3,5,4'-trihydroxy stilbene) is an effective drug for maintaining the health and extending the life span of laboratory mice (*150*). Resveratrol, a small polyphenolic SIRT1 activator found in red wine, can modulate energy metabolism by enhancing insulin sensitivity, decreasing plasma IGF-1 levels, increasing AMP-activated protein kinase and peroxisome proliferator-activated receptor-γ coactivator 1α (PGC-1α) activity, and increasing the number of mitochondria with improved motor function (*150*). Resveratrol, a sirtuin activator, has been implicated in several important cellular processes, including DNA repair, p53-mediated apoptosis, and adipogenesis and is reported to extend life-span in many animal models like those involving caloric restriction (*150-153*). With the birth of life on Earth millions of years ago, life had to evolve to maximize its metabolic efficiency to obtain as much energy as possible in a severely nutrient-scarce environment. Thus, life must acquire better metabolic systems during evolutionary processes. Consequently, an organism can accumulate an excess amount of fat/energy resources in a relatively rich environment like in today's postindustrial societies (*2,4,6*). A "hyper-adapted" system of energy metabolism (based on the 'thrifty gene' hypothesis) (*154*) may act beneficially as a driving force for physiological development and maturation but may induce and accelerate aging after maturity through inflammaging as a result of natural selection (*96*).

10. Future perspective

Along with the recent concept of linking inflammaging to innate immunity to explain aging, several lines of anti-inflammatory intervention such as caloric restriction, SIRT1 activators, and p38 MAPK inhibitors for diabetes mellitus, sarcopenia, arthritis, and life-extension have been proposed for a variety of species (*2-7,71,150,155-158*). However, the relatively complex functional mechanisms of the SIRT1/SIR2 pathway that

regulate the p38 MAPK, p53, and energy metabolism pathways require extensive study in future clinical trials (*159-162*).

Science has developed and progressed based on strictly logical evidence according to current standards. Although science demands a rational answer for every phenomenon, such inquiry is irrelevant to most animals, and current scientific standards fail to explain why they experience decay and death.

"Aging", a term for a mechanism of inflammaging based on antagonistic pleiotropy theory, may represent a transitional indicator of unceasing evolutionary dynamics. Neither man nor even evolutionary theory can unfalteringly predict the future.

References

1. Strehler BL. Time, Cells, and Aging. Academic Press, New York, USA, 1977.
2. Weindruch R, Sohal RS. Caloric intake and aging. N Eng J Med 1997; 337:986-994.
3. Shelke RR, Leeuwenburgh C. Lifelong caloric restriction increases expression of apoptosis repressor with a caspase recruitment domain (ARC) in the brain. FASEB J 2003; 17:494-496.
4. Masoro EJ. Overview of caloric restriction and ageing. Mech Age Dev 2005; 126:913-922.
5. Baur JA, Pearson KJ, Price NL, *et al*. Resveratrol improves health and survival of mice on a high-calorie diet. Nature 2006; 444:21-26.
6. Bishop NA, Guarente L. Genetic links between diet and lifespan: shared mechanisms from yeast to humans. Nature Rev Genet 2007; 8:835-844.
7. Chung HY, Kim HJ, Shim KH, Kim KW. Dietary modulation of prostanoid synthesis in the aging process: role of cyclooxygenase-2. Mech Age Dev 1999; 111:97-106.
8. Langer EJ, Rodin J. The effects of choice and enhanced personal responsibility for aged: A field experiment in an institutional setting. J Personality Soc Psychol 1976; 34:191-198.
9. Lindenberger U, Baltes PB. Sensory functioning and intelligence in old age: A strong correlation. Psychol Aging 1994; 9:339-355.
10. Salthouse TA, Hancock HE, Meinz EL, Hambrick DZ. Interrelations of age, visual acuity, and cognitive functioning. J Gerontol: Psychol Sci 1996; 51B:317-330.
11. Kempermann G. Adult neurogenesis. Oxford University Press, New York, USA, 2006.
12. Kramer AF, Hahn S, Cohen NJ, Banich MT, McAuley E, Harrison CR, Chason J, Vakil E, Bardell L, Boileau RA, Colcombe A. Ageing, fitness and neurocognitive function. Nature 1999; 400:418-419.
13. Perls TT. The oldest old. Sci Am 1995; 272:70-75.
14. Franceschi C, Bonafe M. Centenarians as a model for healthy aging. Bio- chemical Soc Trans 2003; 31:457-461.
15. Christensen K, McGue M, Petersen I, Jeune B, Vaupel JW. Exceptional longevity does not result in excessive levels of disability. Proc Natl Acad Sci U S A 2008; 105:13274-13279.
16. Hughes KA, Alipaz JA, Crnevich JM, Reynolds RM. A test of evolutionary theories of aging. Proc Natl Acad Sci U S A 2002; 99:14286-14291.
17. Bartkova J, Rezaei N, Liontos M, *et al*. Oncogene-induced senescence is part of the tumorigenesis barrier imposed by DNA damage checkpoints. Nature 2006; 444:633-637.
18. Darwin C. On the origin of species by means of natural selection, or the preservation of favoured races in the struggle for life. John Murray, London, England, 1859.
19. Richardson MK. Vertebrate evolution: the developmental origins of adult variation. BioEssays 1999; 21:604-613.
20. Orgel LE. Ageing of clones of mammalian cells. Nature 1973; 243:441-445.
21. Weismann A. Essays upon heredity and kindred biological problems. Vol. 1, Clarendon Press, Oxford, England, 1889.
22. Kirkwood TB. Understanding the odd science of aging. Cell 2005; 120:437-447.
23. Hayflick L, Moorhead PS. The serial cultivation of human diploid cell strains. Exp Cell Res 1961; 25:585-621.
24. Martin GM, Sprague CA, Epstein CJ. Replicative life-span of cultivated human cells. Effects of donor's age, tissue, and genotype. Lab Invest 1970; 23:86-92.
25. Dykhuizen D. Evolution of cell senescence, atherosclerosis and benign tumors. Nature 1974; 251:616-618.
26. Williams SC. Adaptation and natural selection. Princeton University Press, Pinceton, USA, 1966.
27. Rose MR. Evolutionary Biology of Aging. Oxford University Press. New York, USA, 1991.
28. Comfort A. Ageing, The Biology of Senescence. Routledge and Kegan Paul, London, England, 1964.
29. Kirkwood TB. Evolution of ageing. Nature 1977; 270:301-304.
30. Wilson AJ, Nussey DH, Pemberton JM, Pilkington JG, Morris A, Pelletier F, Clutton-Brock TH, Kruuk LE. Evidence for a genetic basis of aging in two wild vertebrate populations. Curr Biol 2007; 17:2136-2142.
31. Foerster K, Coulson T, Sheldon BC, Pemberton JM, Clutton-Brock TH, Kruuk LEB. Sexually antagonistic genetic variation for fitness in red deer. Nature 2007; 447:1107-1110.
32. Williams CG. Pleiotropy, natural selection, and the evolution of senescence. Evolution 1957; 11:398-411.
33. Wright A, Charlesworth B, Rudan I, Carothers A, Campbell H. A polygenic basis for late-onset disease. Trends Genet 2003; 19:97-106.
34. Charmantier A, Perrins C, McCleery RH, Sheldon BC. Quantitative genetics of age at reproduction in wild swans: Support for antagonistic pleiotropy models of senescence. Proc Natl Acad Sci U S A 2006; 103:6287-6592.
35. Csete ME, Doyle JC. Reverse engineering of biological comolexicity. Science 2002; 295:1664-1669.
36. Kelley L, Scott M. The evolution of biology. EMBO Reports 2008; 9:1163-1167.
37. Franceschi C, Valensin S, Fagnoni F, Barbi C, Bonafe M. Biomarkers of immunosenescence within an evolutionary perspective: the challenge of heterogeneity and the role of antigenic load. Exp Gerontol 1999; 34:911-921.
38. Longo VD, Mitteldorf J, Skulachev VP. Programmed and altruistic ageing. Nature Rev Genet 2005; 6:866-872.
39. Herker E, Jungwirth H, lehmann KA, Maldener C, Frohlich KU, Wissing S, Buttner S, Fehr M, Sigrist S, Madeo F. Chronological aging leads to apoptosis in

yeast. J Cell Biol 2004; 164:501-507.
40. Fabrizio P, Battistella L, Vardavas R, Gattazzo C, Liou LL, Diaspro A, Dossen JW, Gralla EB, Longo VD. Superoxide is a mediator of altruistic aging program in saccharomyces cervisiae. J Cell Biol 2004; 166:1055-1067.
41. Longo VD, Ellerby LM, Bredesen DE, Valentine JS, Gralla EB. Human Bcl-2 reverses survival defects in yeast lacking superoxide dismutase and delays death of wild-type yeast. J Cell Biol 1997; 137:1581-1588.
42. Mari D, Mannucci PM, Coppola R, Bottasso B, Bauer KA, Rosenberg RD. Hypercoagulability in centenarians: The paradox of successful aging. Blood 1995; 85:3144-3149.
43. Baggio G, Donazzan S, Monti D, Mari D, Martini S, Gabelli C, Vestra MD, Previato L, Guido M, Pigozzo S, Cortella I, Crepaldi G, Francheschi C. Lipoprotein(a) and lipoprotein profile in healthy centenarians: a reappraisal of vascular risk factors. FASEB J 1998; 12:433-437.
44. Majno G, Joris I. Cells, Tissues and Disease. Oxford University Press. New York, USA, 2004.
45. Medzhitov R. Origin and physiological roles of inflammation. Nature 2008; 454:428-435.
46. Bouskra D, Brezillon C, Berard M, Werts C, Varona R, Boneca IG, Rberl G. Lymphoid tissue genesis induced by commensals through NOD1 regulates intestinal homeostasis. Nature 2008; 456:507-510.
47. Franceschi C. Continuous remodeling as a key to aging and survival. Biogerontology 2003; 4:329-334.
48. Libby P. Inflammatory and immune mechanisms in atherogeneis. Atherosclerosis Rev 1990; 21:79-89.
49. Ridker PM, Cushman M, Stampfer MJ, Tracy RP, Hennekens CH. Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. N Eng J Med 1997; 336:973-979.
50. Ginaldi L, Di Benedetto MC, De Martinis M. Osteoporosis, inflammation, ageing. Immunity Ageing 2005; 2:14-18.
51. Vlad SC, Miller DR, Neil KW, Felson DT. Protective effects of NSAIDs on the development of Alzheimer's disease. Neurology 2008; 70:1672-1677.
52. Greten FR, Eckmann L, Greten TF, Park JM, Li ZW, Egan LJ, Kagnoff MF, Karin M. IKKβ links inflammation and tumorigenesis in a mouse model of colitis-associated cancer. Cell 2004; 118:285-296.
53. Franceschi C, Bonafe M, Valensin S, Olivieri F, De Luca M, Ottaviani E, De Benedictis G. Inflamm-aging. An evolutionary perspective on immunosenescence. Ann N Y Acad Sci 2000; 908:244-254.
54. Giunta S. Is inflammaging an auto(innate)immunity subclinical syndrome? Immunity Ageing 2006; 3:2-3.
55. Chung HY, Kim HJ, Jung JJ, Yoon JS, Yoo MA, Kim KW, Yu BP. The inflammatory process in aging. Rev Clin Gerontol 2000; 10:207-222.
56. Chung HY, Sung BY, Jung KJ, Zou Y, Yu BP. The molecular inflammatory process in aging. Antioxid Redox Signal 2006; 8:572-581.
57. Dinarello CA. Interleukin 1 and interleukin 18 as mediators of inflammation and the aging process. Am J Clin Nutr 2006; 83:447S-455S.
58. Rawlings DJ. The biology and biochemistry of inflammatory signalosomes. EMBO Reports 2006; 7:25-30.
59. Handschin C, Spiegelman BM. The role of exercise and PGC1α in inflammation and chronic disease. Nature 2008; 454:463-469.
60. Kloner RA, Giacomelli F, Alker KJ, Hale JB, Matthews R, Bellows S. Index of neutrophils into the walls of large epicardial coronary arteries in response to ischemia/reperfusion. Circulation 1991; 84:1758-1772.
61. Cybulsky MI, Gimbrone MA. Endothelial expression of a mononuclear leukocyte adhesion molecule during atherogenesis. Science 1991; 251:788-791.
62. Saikku P, Mattila K, Nieminen MS, Huttunen JK, Leinonen M, Ekman MR, Makela PH, Valtonen V. Serological evidence of an association of a novel Chlamydia, TWAR, with chronic coronary heart disease and acute myocardial infarction. Lancet 1988; 2:983-986.
63. Benditt EP, Barrett T, McDougall JK. Viruses in the etiology of atherosclerosis. Proc Natl Acad Sci U S A 1983; 80:6386-6389.
64. Beck BC, Weintraub WS, Alexander RW. Elevation of C-reactive protein in "active" coronary artery disease. Am J Cardiol 1990; 65:168-172.
65. Thompson SG, Kienast J, Pyke SD, Haverkate F, van de Loo JC. Hemostatic factors and the risk of myocardial infarction or sudden death in patients with angina pectoris. European Concerted Action on Thrombosis and Disabilities Angina Pectoris Study Group. N Eng J Med 1995; 332:635-641.
66. Gupta RA, DuBois RN. Colorectal cancer prevention and treatment by inhibition of cyclooxygenase-2. Nature Rev Cancer 2001; 1:11-21.
67. McGeer PL, Schulzer M, McGeer EG. Arthritis and anti-inflammatory agents as possible protective factors for Alzheimer's disease: A review of 17 epidemiologic studies. Neurology 1996; 47:425-432.
68. ADAPT Research Group. Cognitive function over time in the Alzheimer's disease anti-inflammatory prevention trial (ADAPT). Results of a randomized, controlled trial of naproxen and celecoxib. Arch Neurol 2008; 65:896-905.
69. Hotamisligil GS. Inflammation and metabolic disorders. Nature 2006; 444:860-867.
70. Hundal RS, Petersen KF, Mayerson AB, Randhawa PS, Izucchi S, Shoelson SE, Shulman GI. Mechanism by which high-dose aspirin improves glucose metabolism in type 2 diabetes. J Clin Invest 2002; 109:1321-1326.
71. Wellen KE, Hotamisligil GS. Inflammation, stress, and diabetes. J Clin Invest 2005; 115:1111-1119.
72. Ridker PM. Inflammation, infection, and cardiovascular risk. Circulation 1998; 97:1671-1674.
73. Van Den Biggelaar AH, De Craen AJ, Gussekloo J, Huizinga TW, Heijmans BT, Frölich M, Kirkwood TB, Westendorp RG. Inflammation underlying cardiovascular mortality is a late consequence of evolutionary programming. FASEB J 2004; 18:1022-1024.
74. Ferrucci L, Corsi A, Lauretani F, Bandinelli S, Bartali B, Taub DD, Guralinik JM. The origins of age-related proinflammatory state. Blood 2005; 105:2294-2299.
75. Coussens LM, Werb Z. Inflammation and cancer. Nature 2002; 420:860-867.
76. Mantovani A, Allavena P, Sica A, Balkwill F. Cancer-related inflammation. Nature 2008; 454:436-444.
77. Kuo CC, Shor A, Campbell L, Fukushi H, Patton DL, Grayston JT. Demonstration of *Chlamydia pneumoniae* in atherosclerotic lesions of coronary arteries. J Infect Dis 1993; 167:841-849.
78. Wu TC, Hruban RH, Ambinder RF, Pizzorno M, Cameron DE, Baumgartner WA, Reitz BA, Hayward GS, Hutchins

GM. Demonstration of cytomegalovirus nucleic acids in the coronary arteries of transplanted hearts. Am J Pathol 1992; 140:739-747.
79. Cook PJ, Lip GY. Infectious agents and atherosclerotic vascular disease. QJM 1996; 89:727-747.
80. Lemstrom K, Koskinen P, Krogerus L, Daemen M, Braggerman C, Hayry P. Cytomegalovirus antigen expression, endothelial cell proliferation, and intimal thickening in rat cardiac allografts after cytomegalovirus infection. Circulation 1995; 92:2594-2604.
81. Libby P, Egan D, Skarlatos S. Roles of infectious agents in atherosclerosis and restenosis: an assessment of the evidence and need for future research. Circulation 1997; 96:4095-4103.
82. Balkwill F, Mantovani A. Inflammation and cancer: back to Virchow. Lancet 2001; 357:539-545.
83. Karin M, Lawrence T, Nizet V. Innate immunity gone awry: linking microbial infections to chronic inflammation and cancer. Cell 2006; 124:823-835.
84. Kuper H, Adami HO, Trichopoulos D. Infections as a major preventable cause of human cancer. J Inter Med 2000; 248:171-183.
85. Williams CS, Mann M, DuBois RN. The role of cyclooxygenases in inflammation, cancer, and development. Oncogene 1999; 18:7908-7916.
86. Krabbe KS, Pedersen M, Bruunsgaard H. Inflammatory mediators in the elderly. Exp Gerontol 2004; 39:687-699.
87. Takeda K, Kaisho T, Akira S. Toll-like receptors. Annu Rev Immunol 2003; 21:335-376.
88. Bianchi ME. DAMPs, PAMOs and alarmins: all we need to know about danger. J Leuk Biol 2007; 81:1-5.
89. Miyake K. Innate immune sensing of pathogens and danger signals by cell surface Toll-like receptors. Semin Immunol 2007; 19:3-10.
90. Swann JB, Vesely MD, Silva A, Dharkey J, Akira S, Schreiber RD, Smyth MJ. Demonstration of inflammation-induced cancer and cancer immunoediting during primary tumorigenesis. Proc Natl Acad Sci U S A 2008; 105:652-656.
91. Kumar V, Abbas AK, Fausto N, Mitchell M. Robbins Basic Pathology. W.B. Saunders, Philadephia, USA, 2007.
92. Uchiyama E, Kodaira T, Kurosawa K, Watanabe N, Kobayashi Y. Interaction of phagocytes with apoptotic cells leads to production of pro-inflammatory cytokines. Biochem Biophys Res Commun 1997; 239:799-803.
93. Shibata T, Nagata K, Kobayashi Y. A critical role of nitric oxide in preenting inflammation upon apoptotic cell clearance. J Immunol 2007; 179:3407-3411.
94. Chen CJ, Kono H, Golenbock D, Reed G, Akira S, Rock KL. Identification of a key pathway required for the sterile inflammatory response triggered by dying cells. Nat Med 2007; 13:851-856.
95. Troen BR. The biology of aging. Mt Sinai J Med 2003; 70:3-22.
96. Licastro F, Candore G, Lio D, Porcellini E, Colonna-Romano G, Franceschi C, Caruso C. Innate immunity in aging: a key for understanding age-related disease. Immun Aging 2005; 18:2-8.
97. Barton GM. A calculated response: control of inflammation by the innate immune system. J Clin Invest 2008; 118:413-420.
98. Teder P, Vandivier RW, Jiang D, Liang J, Cohen L, Pure E, Henson PM, Noble PW. Resolution of lung inflammation by CD44. Science 2002; 296:155-158.
99. Campo GM, Avenoso A, Campo S, D'Ascola A, Traina P, Samà D, Calatroni A. Purified human plasma glycosaminoglycans reduced NF-kappaB activation, pro-inflammatory cytokine production and apoptosis in LPS-treated chondrocytes. Innate immunity 2008; 14:233-246.
100. Jiang D, Liang J, Noble PW. Hyaluronan in tissue injury and repair. Annu Rev Cell Dev Biol 2007; 23:435-461.
101. Johnson TE, Brundsgaard H. Implications of hormesis for biomedical aging research. Hum Exp Toxicol 1998; 17:263-265.
102. Calabrese EJ, Baldwin LA. The marginalization of hormesis. Toxicol Pathol 1999; 27:197-194.
103. West DC, Hampson IN, Arnold F, Kumar S. Angiogenesis induced by degradation products of hyaluronic acid. Science 1985; 228:1324-1326.
104. Scaefer L, Babelova A, Kiss E, Hausser HJ, Baliova M, Krzyzankova M, Marsche G, Young MF, Mihalik D, Gotte M, Malle E, Schaefer RM, Grone HJ. The matrix component biglycan is proinflammatory and signals through Toll-like receptors 4 and 2 in macrophages. J Clin Invest 2005; 115:2223-2233.
105. Green RS, Stone EL, Tenno M, Lehtonen E, Farquhar MG, Marth JD. Mammalian *N*-glycan branching protects against innate immune self-recognition and inflammation in autoimmune disease pathogenesis. Immunity 2007; 27:308-320.
106. Van Dyken SJ, Locksly RM. Altered self-*N*-glycans trigger innate-mediated autoimmunity. Immunol Cell Biol 2007; 85:572-574.
107. Shagan BP. Is diabetes a model for aging? Med Clin North Am 1976; 60:1209-1211.
108. Cerami A. Hypothesis Glucose as a mediator of aging. J Am Geriatr Soc 1985; 33:626-634.
109. Mooradian AD. Tissue specificity of premature aging in diabetes mellitus. J Am Geriatr Soc 1988; 36:831-839.
110. Laaksonen DE, Niskanen L, Punnonen K, Nyyssonen K, Tuomainen T, Valkonen V, Salonen JT. The metabolic syndrome and smoking in relation to hypogonadism in middle-aged men: A prospective cohort study. J Clin Endocrinol Metab 2005; 90:712-719.
111. Makhsida N, Shah J, Yan G, Fisch H, Shabsigh R. Hypogonadism and metabolic syndrome: Implications for testosterone therapy. J Urol 2006; 174:827-834.
112. Yassin AA, Saad F, Gooren LJ. Metabolic syndrome, testosterone deficiency and erectile dysfunction never come alone. Andrologia 2008; 40:259-264.
113. Utsinger PD, Zvaifler NJ, Ehrlich GE. Rheumatoid arthritis. Etiology, diagnosis, management. Lippincott, Philadelphia, USA, 1985.
114. Sattar N, McCarey DW, Capell H, McInnes IB. Explaining how "high-grade" systemic inflammation accelerates vascular risk in rheumatoid arthritis. Circulation 2003; 108:2957-2963.
115. del Rincon I, Freeman GL, Haas RW, O'Leary DH, Escalante A. Relative contribution of cardiovascular risk factors and rheumatoid arthritis clinical manifestations to atherosclerosis. Arthritis Rheum 2005; 52:3413-3423.
116. Morand EF, Leech M, Bernhagen J. MIF: a new cytokine link between rheumatoid arthritis and atherosclerosis. Nature Rev Drug Disc 2006; 5:399-410.
117. Simard JF, Mittleman MA. Prevalent rheumatoid arthritis and diabetes among NHANES III participants aged over 60 and older. J Rheumatol 2007; 34:469-473.
118. Pincus T, Sokka T, Wolfe F. Premature mortality in patients with rheumatoid arthritis: Evolving concepts.

Arthritis Rhum 2001; 44:1234-1236.
119. Navarro-Cano G, del Rincon I, Pogosian S, Roldan JF, Escalante A. Association of mortality with disease severity in rheumatoid arthritis, independent of comorbidity. Arthritis Rheum 2003; 48:2425-2433.
120. Sokka T, Abelson B, Pincus T. Mortality in rheumatoid arthritis: 2008 update. Clin Exp Rheumatol 2008; 26(5 Suppl 5):S35-61.
121. Gonzalez A, Kremers HM, Crowson CS, Nicola PJ, Davis JM, Therneau TM, Roger VL, Gabriel SE. The widening mortality gap between rheumatoid arthritis patients and the general population. Arthritis Rheum 2007; 56:3583-3587.
122. Smolen JS, Kalden JR, Maini RN. Rheumatoid arthritis. Springer-Verlag, Berlin, Germany, 1992.
123. Goto M, Sasano M, Yamanaka H, Miyasaka N, Kamatani N, Inoue K, Nishioka K, Miyamoto T. Spontaneous production of an interleukin 1-like factor by cloned rheumatoid synovial cells in long-term culture. J Clin Invest 1987; 80:786-796.
124. Goto M, Tanimoto K, Chihara T. Natural cell mediated cytotoxicity in rheumatoid arthritis and Sjogren's syndrome. Arthritis Rheum 1981; 24:1377-1382.
125. American College of Rheumatology Ad Hoc Group on Use of Selective and Nonselective Nonsteroidal Antiinflammatory Drugs. Recommendation for use of selective and nonselective anti-inflammatory drugs: an American College of Rheumatology white paper. Arthritis Rheum 2008; 59:1058-1073.
126. Saag KG, Teng GG, Patkar NM, *et al*. American College of Rheumatology 2008 recommendations for the use of nonbiologic and biologic disease-modifying antirheumatic drugs in rheumatoid arthritis. Arthritis Rheum 2008; 59:762-784.
127. Gonzalez-Gay MA, De Matias JM, Gonzalez-Juanatey C, Garcia-Porrua C, Sanchez-Andrade A, Martin J, Llorca J. Anti-tumor necrosis factor-alpha blockade improves insulin resistance in patients with rheumatoid arthritis. Clin Exp Rheumatol 2006; 24:83-86.
128. Dessein PH, Joffe BI. Insulin resistance and impaired beta cell function in rheumatoid arthritis. Arthritis Rheum 2006; 54:2765-2775.
129. Hameed B, Panayi GS. Impaired glycemic control with disease remission in rheumatoid arthritis and hypoglycaemic effect of sulphasalazine. Int J Rheum Dis 2008; 11:318-319.
130. Wasko MCM, Hubert HB, Lingala VB, Elliott JR, Luggen ME, Fries JF, Ward MM. Hydroxychloroquine and risk of diabetes in patients with rheumatoid arthritis. JAMA 2007; 298:187-193.
131. Goto M, Miller RW. From premature gray hair to helicase. Werner syndrome: Implications for aging and cancer. Japan Scientific Societies Press, Karger, Tokyo, Japan, 2001.
132. Goto M. Hierarchical deterioration of body systems in Werner's syndrome: Implications for normal ageing. Mech Age Dev 1997; 98:239-254.
133. Goto M, Miller RW, Ishikawa Y, Sugano H. Excess of rare cancers in Werner syndrome (adult progeria). Cancer Epidemiol Biomarker Prevention 1996; 5:239-246.
134. Salk D, Fujiwara Y, Martin GM. Werner's syndrome and human aging. Advances in experimental medicine and biology. Vol 190. Plenum Press, New York, USA, 1985.
135. Goto M, Rubenstein M, Weber J, Woods K, Drayna D. Genetic linkage of Werner's syndrome to five markers on chromosome 8. Nature 1992; 355:735-738.
136. Yu CE, Oshima J, Fu YH, Wijsman EM, Hisama F, Alisch R, Matthews S, Nakura J, Miki T, Ouais S, Martin GM, Mulligan J, Schellenberg GD. Positional cloning of the Werner syndrome gene. Science 1996; 272:258-262.
137. Goto M, Imamura O, Kuromitsu J, Matsumoto T, Yamabe Y, Tokutake Y, Suzuki N, Mason B, Drayna D, Sugawara M, Sugimoto M, Furuichi Y. Analysis of helicase gene mutations in Japanese Werner's syndrome patients. Hum Gent 1997; 99:191-193.
138. Goto M, Kato Y. Hypercoagulable state indicates an additional risk factor for atherosclerosis in Werner's syndrome. Thromb Haemos 1995; 73:576-578.
139. Yokote K, Hara K, Mori S, Kadowaki T, Saito Y, Goto M. Dysadiponectinemia in Werner syndrome and its recovery by treatment with pioglitazone. Diabetes Care 2004; 27:2562-2563.
140. Yokote K, Honjo S, Kobayashi K, Kawamura H, Mori S, Saito Y. Metabolic improvement and abdominal fat redistribution in Werner syndrome by pioglitazone. J Am geriatr Soc 2004; 52:1582-1583.
141. Goto M, Murata K. Urinary excretion of macromolecular acidic glycosamino-glycans in Werner's syndrome. Clin Chim Acta 1978; 85:101-106.
142. Tanabe M, Goto M. Elevation of serum hyaluronan level in Werner's syndrome. Gerontology 2001; 47:77-81.
143. Goto M, Horiuch Y, Okumura K, Tada T, Kawata M, Ohmori K. Immunological abnormalities of aging. An analysis of T lymphocyte subpopulations of Werner's syndrome. J Clin Invest 1979; 64:695-699.
144. Goto M, Tanimoto K, Aotsuka S, Okawa M, Yokohari R. Age-related changes in auto- and natural antibody in the Werner's syndrome. Am J Med 1982; 72:607-614.
145. Goto M, Tanimoto K, Horiuchi Y, Kuwata T. Reduced natural killer cell activity of lymphocytes from patients with Werner's syndrome and recovery of its activity by purified human leukocyte interferon. Scand J Immunol 1982; 15:389- 397.
146. Goto M. Immunosenescent features of human segmental progeroid syndrome: Werner's syndrome. Aging Immunol Infect Dis 1992; 3:203-215.
147. Goto M. What can we learn from Werner syndrome? A biased view from a rheumatologist. Mod Rheumatol 2002; 12:294-299.
148. Goto M. Elevation of soluble Fas (APO-1,CD95) ligand in natural aging and Werner syndrome. BioScience Trends 2008; 2:124-127.
149. Osborne TB, Mendel LB, Ferry EL. The effect of retardation of growth upon the breeding period and duration of life in rats. Science 1917; 45:294-295.
150. Bauer JA, Pearson KJ, Price NL, *et al*. Resveratrol improves health and survival of mice on a high-calorie diet. Nature 2006; 444:21-26.
151. Kaeberlein M, McDonagh T, Heltweg B, Hixon J, Westman EA, Caldwell SD, Napper A, Curtis R, DiStefano PS, Fields S, Bedalov A, Kennedy BK. Substrate-specific activation of sirtuins by resveratrol. J Biol Chem 2005; 280:17038-17045.
152. Haigis MC, Guarante LP. Mammalian sirtuins-emerging roles in physiology, aging and calorie restriction. Genes Dev 2006; 20:2913-2921.
153. Wood JG, Rogina B, Lavu S, Howitz K, Helfand SL, Tatar M, Sinclair D. Sirtuin activators mimic caloric restriction and delay ageing in metazoans. Nature 2004; 430:686-689.

154. Prentice AM, Rayco-Solon P, Moore SE. Insights from the developing world: thrifty genotypes and thrifty phenotypes. Proc Nutr Soc 2005; 64:153-161.
155. Fulco M, Schiltz RL, Lezzi S, King MT, Zhao P, Kashiwaya Y, Hoffman E, Veech RL, Sartorelli V. Sir2 regulates skeletal muscle differentiation as a potential sensor of the redox state. Mol Cell 2003; 12:51-62.
156. Milne JC, Lambert PD, Schenk S, *et al*. Small molecule activators of SIRT1 as therapeutics for the treatment of type 2 diabetes. Nature 2007; 450:712-716.
157. Saklatvala J. The MAP kinase pathway as a therapeutic target in inflammatory disease. Curr Opin Pharmacol 2004; 4:372-377.
158. Davis T, Baird DM, Haughton MF, Jones CJ, Kipling D. Prevention of accelerated cell aging in Werner syndrome using a p38 mitogen-activated protein kinase inhibitor. J Gerontol 2005; 60A:1386-1393.
159. Zhang J. Resveratrol inhibits insulin response in a SirT1-independent pathway. Biochem J 2006; 397:519-527.
160. Ota H, Tokunaga E, Chang K, Hikasa N, Iijima K, Eto M, Kozaki K, Akishita M, Ouchi Y, Kaneki M. Sirt1 inhibitor, sirtinol, induces senescence-like growth arrest with attenuated ras-MAPK signaling in human cancer cells. Oncogene 2006; 25:176-175.
161. Fabeizio P, Gattazzo C, Battistella L, Wei M, Cheng C, McGrew K, Longp VD. Sir2 blocks extreme life-span extension. Cell 2005; 123:655-667.
162. Kaeberlein M, McVey M, Guarente L. The sir2/3/4 complex and sir2 alone promote longevity in saccharomyces cervisiae by two different mechanisms. Genes Dev 1999; 13:2570-2580.

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