

# Inflammatory Oxidative Aging: A New Theory of Aging

## Abstract

Oxidative stress leads to deregulation in key physiologic systems for the maintenance of homeostasis, like immune system and others. The immune system produces deregulation to chronic low grade inflammatory state in the aging process. That is the basis of a new theory named oxy-inflamm-aging. The article describing the basis of this theory and the current researches to support it, in Addition to STI links with the pathogenesis of the age related diseases. The author summarizes the interventions to modulate theoxi-inflamm-aging as a practical application of this theory.

**Keywords:** Aging; Oxidation; Inflammation

## Short Communication

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## Introduction

Aging, such as demographic problem in the world due to conditions well recognized as declining fertility rates, the significant reduction in mortality in the early stages of life and decreased mortality of adult people [1]. When we focus our attention to the aging of the individual and the species causes not seem to be well defined and appear to be multiple and interrelated. At the level biological aging is associated with the accumulation of molecular and cellular damage that, over time, cause the decrease, gradually (although with great variability from one individual to another) reserves physiological and functional capacity, increasing the risk of disease and death [2,3].

As they appear different definitions of biological aging process, over time, we have presented many theories to explain its causes (more than 300) that include their content describing hundreds of cellular and molecular mechanisms that contribute to the specific biology intrinsic aging and, in a more synthetic, can be organized upon a small number of major theories [4,5]. At present, many studies have emphasized the importance of the association between chronic inflammation and aging, and its causal role in many diseases associated with aging such as cancer, arteriosclerosis and osteoarthritis. The source of this chronic inflammation is often attributed to the activation of immune cells over time [6].

The theory or mechanism of aging oxidative inflammatory (oxy-inflamm-aging) has emerged in recent years as hypothesized causal many changes that occur during aging per se, as well as the various diseases associated with aging. This article aims to describe the theoretical elements that set forth the theory of aging oxidative inflammatory (EOI) and their implications for clinical practice, taking into account its links with the major diseases associated with aging.

## Immunosenescence and Flash

In the immune system appear significant changes associated with aging called immune senescence (IS). Currently discussing whether the IS is a process intrinsic aging (particularly thymic

involution) that leads to dysregulation of the immune response is adaptive to the individual's continuous exposure to pathogens (in particular viral infections prolonged as cytomegalovirus) or antigen exposure throughout life [7-9].

The commitment of the immune function with aging affects both the innate immunity as adaptive, and in the latter, particularly the sharing of T cells [10,11]. Another finding distinctive IS is the deviation of the cytokine response of TH1 CD4 helper to a TH2 response leading to increased levels of pro inflammatory cytokine, which all contribute to the deregulation of the answer immune predominantly inflammation chronic low-grade [12].

People long life (ie., The centenarians) appear to face the subclinical inflammation through an inflammatory response. Cytokines are the expression of a network of compounds required genes, polymorphisms and environment and are involved in both inflammation and anti-inflammation (Table 1). The inflammation could be the key to understanding aging and anti-inflammatory one of secrets of longevity [13].

**Table 1:** Profile of cytokines in aging.

Proinflammatory	FNT- $\alpha$ , IL-1, IL-2, IL-6, IL-12, IL-15, IL-18, IL-22, IL-23, IFNAS
Anti-Inflammatory	IL-1RA, IL-4, IL-10, TGF-1
Cytokine Mediators	Lipoxin A4, heat shock protein

Studies show a correlation between aging and significant swelling. Freund, et al. [6] indicate that there is an increase of 2-4 times in serum levels of pro-inflammatory in individuals older than 50 years compared with younger subjects. In addition, healthy centenarians have a lower profile inflammatory that centenarian fragile [14]. It has also demonstrated a high inflammatory state in older adults fragile, marked by high levels of IL-6 and C reactive protein and increasing the number of leukocytes current [15]. Considering many of these issues have proposed a new theory of aging integrator that combines elements of the theory of free radicals proposed by Hartman [16], the mitochondrial theory

of Michael, et al. [17] and the inflammatory theory set which is called oxy-inflamm-aging and that was proposed in 2008 by De la Fuente [18].

Basically, the theories of free radicals and mitochondrial postulate that aging is the result of the accumulation of oxidative damage in biomolecules caused by the high reactivity of free radicals and reactive oxygen species (ROS) produced in all cells, especially mitochondria, organelles which is necessarily used oxygen in the oxidative metabolism [18]. Mitochondria are the site's largest producer and at the same time the main target of ROS as this damage the mitochondrial DNA (mtDNA) and their functions, which in turn causes a vicious cycle of increased production of ROS. The formation of mtDNA mutations can be accelerated by this vicious circle, which could cause accelerated aging [19,20]. High levels of oxidative damage causes cellular changes that include a key reduction of NAD (+) is available, an essential molecule required for a number of vital cellular processes, including DNA repair, immune signaling and epigenetic processes [21].

To protect themselves from oxygen toxicity cells have several mechanisms antioxidants that prevent the formation of ROS or neutralizing after its generation systems (superoxide dismutase, catalase and glutathione reductase) [22,23]. These defensive systems are not perfect and when the concentration of ROS overwhelms the capacity of these systems appears to clarify a situation of oxidative stress which damages the biomolecules (lipids, proteins and DNA) and cellular structures (membranes, mitochondria and nuclear material) [24]. In this way, the functions of the cell and organism are based on a perfect balance between the levels of ROS and antioxidants [25].

The oxidative-inflammatory theory of aging [26,27] suggests that this process is linked to chronic oxidative stress, which affects all body cells, but especially those of the regulatory systems (nervous, endocrine, immune). These systems, as a result, reduce its ability to preserve its redox state, with functional loss incompatible with proper maintenance of homeostasis, physiological cardinal fact of aging. This theory is given a primary role of the immune system, since the deregulation of their responses, increased oxidative stress can lead to increased production of proinflammatory cytokines, which causes a chronic inflammatory condition of low grade that contributes the generation of ROS, so it produces a vicious circle oxidation, inflammation, oxidation [28].

The immune system, due to its need to continuously generate oxidative and inflammatory compounds can activate, if not properly regulated, with factors such as nuclear factor- $\kappa$ B (NF- $\kappa$ B), which after reaching a certain level of activation stimulates expression genes that program the production of these compounds, contributing to the vicious circle mentioned above [29]. Thus, both the oxidative stress as inflammatory stress by damaging physiological homeostasis provoke oxy-inflamm-aging.

### Implications for Clinical Practice

It is now accepted that chronic inflammation is the main underlying condition in many diseases associated with aging such

as atherosclerosis, osteoarthritis, cancer, diabetes, osteoporosis, dementia, vascular diseases, obesity and metabolic syndrome [30,31] (Table 2). In populations aged human metabolic dysfunction, particularly insulin resistance and inflammatory disorders are very common and identify the molecular mechanisms underlying the immune-metabolic integration becomes important for understanding the pathogenesis of these diseases and their approach therapeutic. Moreover, the identification of pathways that control inflammation associated with age is also valuable for understanding and treatments focused on modular oxy-inflamm-aging can be beneficial for longevity [32]. In this sense, the studies have led to changes in lifestyle, such as caloric restriction and physical exercise, and the use of antioxidants. It would be very extensive and this article will address all the details of the pathogenesis of chronic diseases associated with aging, so we will refer only to the importance of inflammation mechanism as producer on three of the most prevalent in elderly people: atherosclerosis, cancer and dementia.

**Table 2:** Aging-Related diseases that have a chronic inflammatory component.

Obesity
Metabolic Syndrome
Diabetes Mellitus Type 2
Arterial Hypertension
Atherosclerosis
Heart Failure
Cancer
Dementia
Other neurodegenerative Diseases (Parkinson's disease)
Osteoporosis
Arthritis
Senile Macular Degeneration

### Inflammation and atherosclerosis

The damage of endothelial cells increases ROS production by cells causing vascular inflammatory response and the onset of atherosclerosis [33]. The oxidative stress is involved also in the lipid metabolism in plaque rupture, thrombosis, myocardial damage, apoptosis, fibrosis and heart failure [34]. Recientes studies provide strong evidence that vascular calcification is associated the inflammatory state and increases the inflammatory cytokines [35].

### Inflammation and cancer

Several surveys suggest a direct link between chronic inflammation and cancer [31,33]. The key molecules linking inflammation with cellular genetic alterations in cancer are prostaglandins, cytokines, NF- $\kappa$ B, chemokines and angiogenic factors. The main effectors are chemicals derived ROS inflammatory reactions that may act directly or indirectly damaging transcription factors such as NF- $\kappa$ B. These observations suggest that the oxy-inflamm-aging contributes to the induction and progression of cancer in the signaling pathway of NF- $\kappa$ B.

## Inflammation and dementia

Research suggests that chronic inflammation may be an important contributor to the development of neurodegenerative diseases, including dementia [31,36]. It is suggested that IFN- $\gamma$  and other proinflammatory cytokines interact with the process of production of the amyloid beta peptide, the findinghallmark of Alzheimer's disease [37]. In addition there immunoreactivity cytokines; such as interleukin-6 (IL-6), the tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ) and factor crecimiento transformante b (TGF-b) [38].

## Caloric restriction

Although it has been shown that calorie restriction (CR), a method to reduce ROS production, slows aging and extends the maximum life in various animal species [39-41], their effects on disease resistance and mortality in primates - the mammalian closest to man - not very consistent. An initial study of 20 years of follow-on rhesus monkeys in which CR was used without malnutrition showed a decrease in the incidence of diseases related to age (diabetes, cancer, cardiovascular disease and brain atrophy) [42]. However, another study tracked 23 years of primates youngsters who underwent CR was also a delay in the onset of age-related diseases, but no improvement in the survival curves [43].

CR in humans, which recently published some results, in most cases involves reducing calorie intake by 25-40% compared with income from normal food, so it was considered a severe intervention with results both beneficial and harmful. Recent clinical trials of restriction of 25% of calories in humans have shown improvement in longevity as predictors of decreased resting metabolic Latas, TNF- $\alpha$  and cardiometabolic risk factors [44] but is identified as significant adverse effects decreased of bone mineral density in clinically important sites for osteoporotic fractures like femoral neck and lumbar spine [45].

Some consider today that the effects of CR on aging are not simply the result of reducing the amount of calories consumed, but also on the composition of the diet, and it is more convenient to perform periodic interventions (cycles) RC not as strict (reduction of less than 20% of calories) that prolonged interventions [46]. What does seem clear is that the lower caloric intake and diet-called healthy compared to the so-called Western diet improves parameters of healthy aging, as demonstrated in a recent study [47]. Is currently developing a multi-center study to better design (phase 2 CALERIE) RC with 25% that measure aspects of medical, physical and psychological behavior that will bring more light on this in a future intervention Mediate [48].

## Antioxidants

Antioxidants protect the body from the damaging effects of free radicals and ROS, normally produced in the oxidative metabolism, where oxygen and nutrients are transformed into energy. The discovery of the antioxidants increased the hope of slowing the aging simply by adding them to the diet. However, studies with antioxidant supplements have provided little support for this conclusion and epidemiological studies are needed on a large scale to clarify this question. For the moment there is positive evidence for the health of the consumption of fruits and vegetables, which are foods rich in natural antioxidants [49].

A recent review of clinical trials on the antioxidant (vitamin C, vitamin E, resveratrol, curcumin, hydroxytyrosol and coenzyme Q10) and its influence on diseases related to aging also found conflicting results, which is explained by a incorrect initial screening of patients, not done a quantitative characterization of the redox state of each individual and not take into account the demands individual as genetic background of these [50].

The use of resveratrol, an antioxidant component of grapes, has been a topic of intense research in recent decades. Recent research has suggested that grape products as a whole (which also contains resveratrol, catechins, polyphenols and flavonoids) may help maintain cardiovascular health and provide protection against aging, their illnesses associated neurodegeneration and cancer [51]. A follow-up study for 3, 6, 9 and over (Aging in the Chianti Project) found that elderly people exposed to a usual diet high in resveratrol had lower risk of developing fragile syndrome, but only during the first 3 years, in later [52].

## Exercise and physical activity

The benefits of exercise and physical activity reported health are indisputable. The evidences are multiple, based on experimental and epidemiological studies that both exercise and physical training combat the aftermath of aging, including Fragile. It has been shown that exercise has antioxidant and anti-inflammatory, exercised primarily on adipose tissue, skeletal muscle, the immune system and cardiovascular system modulating cytokine profile anti / pro-inflammatory transcription factors redox-sensitive as the FN-kB the activator protein-1 enzyme pro oxidants and antioxidants and proteins as restorative protein heat shock, the complex proteasome DNA glycosylase oxiguanina, glycosylase DNA uracil and telomerase [53].

A longitudinal study found that older adults with a lifestyle-based moderate or intense exercise showed a lower profile of inflammatory cytokines, less changes in the T cell compartment and its functions, and showed longer telomeres [54]. Today develop well-designed trials on the role of endurance exercise on the immune system and muscle adaptation coupled with nutritional interventions [55].

## Conclusion

Among the many theories and mechanisms described to explain aging, oxy-inflamm-aging has emerged as a comprehensive proposal based on recent research to reveal the intrinsic biology of this process and its relationship with its related diseases. Adopting from an early age a healthy lifestyle that includes a balanced diet, without excess calories and rich in natural antioxidants and exercise appropriate physical, sustained can help ensure a successful aging, limiting the fragility and preserving function as a measure of quality of life.

They continue to research the potential benefits of caloric restriction and supplements of antioxidant products with the aim of curbing the oxy-inflamm-aging in an attempt to achieve greater longevity and lower burden of diseases associated with aging.

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