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Review

Proinflammatory Cytokines, Aging, and Age-Related Diseases

Martin Michaud MD [a,*], Laurent Balardy MD [a], Guillaume Moulis MD [b,c,d], Clement Gaudin MD [a], Caroline Peyrot [e], Bruno Vellas MD, PhD [a], Matteo Cesari MD, PhD [a], Fati Nourhashemi MD, PhD [a]

[a] *Department of Geriatric Medicine, Gérontopôle de Toulouse, Toulouse University Hospital, Toulouse, France*
[b] *Department of Internal Medicine, Toulouse University Hospital, Toulouse, France*
[c] *Toulouse University, UMR1027, Toulouse, France*
[d] *Inserm, UMR1027, Toulouse, France*
[e] *Direction of Research and Innovation, Toulouse University Hospital, Toulouse, France*

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A B S T R A C T

Inflammation is a physiological process that repairs tissues in response to endogenous or exogenous aggressions. Nevertheless, a chronic state of inflammation may have detrimental consequences. Aging is associated with increased levels of circulating cytokines and proinflammatory markers. Aged-related changes in the immune system, known as immunosenescence, and increased secretion of cytokines by adipose tissue, represent the major causes of chronic inflammation. This phenomenon is known as "inflamm-aging." High levels of interleukin (IL)-6, IL-1, tumor necrosis factor-α, and C-reactive protein are associated in the older subject with increased risk of morbidity and mortality. In particular, cohort studies have indicated TNF-α and IL-6 levels as markers of frailty. The low-grade inflammation characterizing the aging process notably concurs at the pathophysiological mechanisms underlying sarcopenia. In addition, proinflammatory cytokines (through a variety of mechanisms, such as platelet activation and endothelial activation) may play a major role in the risk of cardiovascular events. Dysregulation of the inflammatory pathway may also affect the central nervous system and be involved in the pathophysiological mechanisms of neurodegenerative disorders (eg, Alzheimer disease).The aim of the present review was to summarize different targets of the activity of proinflammatory cytokines implicated in the risk of pathological aging.

The improvement of knowledge about the mechanisms of aging represents an important goal of current research. It is estimated that the population aged 65 years and older will present a 3.5-fold increase by 2025 to 2030 compared with other age groups.[1] Among the biological mechanisms more likely to affect the distinction between a successful and pathological aging process, inflammation surely is one of the most studied.

Aging is characterized by quantitative and qualitative modifications of the immune system. This phenomenon, known as "immunosenescence," is accompanied by cytokine dysregulation, which is an increase of proinflammatory cytokines and reduction of anti-inflammatory cytokines, leading to a chronic low-grade inflammatory state.[1] The potential clinical consequences of such condition are relevant, including the increased risk of comorbidities and mortality. In other words, inflammation may constitute a biological foundation of the pathophysiological process of frailty.[1] Bone, nutritional, and muscle metabolisms are all affected by the inflammatory state accompanying aging.[2–5] The pathophysiology of neurodegenerative disorders (such as Alzheimer disease [AD]) also seems to be partly inflammatory and influenced by these changes in cytokine secretions.[6] The well-established relationship between systemic inflammation and cardiovascular events is also noteworthy.[7] On the other hand, the lack of alteration of inflammatory biomarkers appears to be associated with "successful aging."

The aim of the present article was to review the literature on the relationship between proinflammatory cytokines and "pathological aging."

Origin of Low-Grade Inflammation

Immunosenescence

Immunosenescence is a progressive modification of the immune system that leads to greater susceptibility to infections, neoplasias, and autoimmune manifestations. This phenomenon is mainly due to prolonged antigenic stimulation across the life span.[8] The main alteration responsible for immunosenescence concerns the

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* Address correspondence to Martin Michaud, MD, Department of Internal Medicine and Gerontology, 170 Avenue de Casselardit, 31300 Toulouse, France.
E-mail address: martin.michaud85@gmail.com (M. Michaud).

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functioning of T cells.[9] Consequences of the thymic involution occurring with aging are decreases of the regulatory T lymphocytes and naïve T lymphocytes (in favor of memory T lymphocytes).[10] Such reorganization of the immune system contributes to modifying the profile of cytokine secretion, causing "inflamm-aging."[11]

With aging, the level of type 1 and 2 cytokines increases in T lymphocytes.[12,13] T-helper (Th) lymphocytes are cells that are central to the immune response and are strongly involved in cytokine synthesis. After activation, Th lymphocytes differentiate into Th1, Th2, Th9, Th17, follicular helper T (Tfh), or memory T lymphocytes.[14] The age-related dysregulation leads to the abnormal distribution of the subtypes Th1 and Th2 (ie, Th1-Th2 commutation), with a consequent relative increase of the number of Th2 lymphocytes compared with Th1.[15,16] It is noteworthy that the profile of cytokine secretion is different between these 2 subtypes of Th lymphocytes.[17] Plasma levels of proinflammatory Th2 cytokines and their soluble receptors are higher in aged than in young subjects.[16,18–31]

Other Factors

Although immunosenescence appears to be the principal factor at the origin of low-grade inflammation, the following factors may also play a role.

Adipose tissue, through the intermediary of the macrophages that it contains, produces IL-6, tumor necrosis factor (TNF)-α, and adipokines.[32] A large amount of visceral adipose tissue or a high-fat diet is correlated with an increase in plasma levels of C-reactive protein (CRP) and interleukin (IL)-6 in obese individuals, and also in individuals who are not obese.[33,34] Aging is accompanied by a decline in sex hormones in both sexes. The role of androgens and estrogens in low-grade inflammation has been confirmed in vitro by their ability to suppress transcription of the IL-6 gene.[35] Chronic periodontitis, frequent in the elderly, contributes to systemic inflammation.[36] And, finally, chronic exposure to stress, through the intermediary of increased endogenous secretion of glucocorticoids, has a proinflammatory influence on T lymphocyte function.[37]

Impacts of Aging on Low-Grade Inflammation

Cytokines, Morbidity, and Mortality

Elevated levels of TNF-α, IL-6, and CRP are correlated with an increased risk of morbidity and mortality (all causes together), not only in a frail population (defined according to Fried et al's criteria[38]) but also in independent, nonfrail elderly.[39–49] The effects of cytokine dysregulation are independent of the other usual mortality risk factors (tobacco use, diabetes, arterial hypertension, hypercholesterolemia) and comorbid conditions.[40,42,45,46,50]

Cytokines and Frailty

Some studies have shown higher levels of IL-6, TNF-α, and CRP in the elderly frail population (as defined by Fried et al[38]) than in the control population of the same age.[46,51–57] Elevated levels of IL-6 are associated with slower gait velocity and are predictive of gait speed decline in the medium term in community-dwelling older persons.[58] Patients with impaired functioning in the activities of daily living (ADLs)[59] have higher plasma IL-6 levels than patients who are not disabled.[41,47] Various mechanisms could explain this close link between frailty syndrome and increased proinflammatory cytokines. Current and future research will enable us to study the impact of numerous other mechanisms that have not yet been investigated.

Cytokines and Nutritional Status

Involuntary weight loss is an independent factor of morbidity and mortality.[60] Proinflammatory cytokines have a direct influence on the development of malnutrition.[61,62] Increase in levels of TNF-α, IL-1, and IL-6 has metabolic consequences with increased lipolysis, decreased lipid synthesis, decreased lipoprotein lipase activity, decreased protein synthesis, and increased proteolysis.[3,5,63] In addition, TNF-α acts directly on the digestive system by reducing gastric filling capacity and slowing peristaltic activity.[64]

As well as such direct actions, cytokines induce malnutrition through changes in the hormonal secretions involved in satiety (changes in cholecystokinin, glucagon, and adrenocorticotropic hormone secretion).[65–67] The central nervous system also intervenes in the mechanism of malnutrition, in particular the hypothalamic nuclei, which express cytokine receptors that are activated in response to systemic inflammation.[68–70]

Cytokines and Muscle Mass

Physiologically, muscle mass decreases by 1% to 2% yearly after the fifth decade of life.[71] In vitro, exposure of myoblasts to TNF-α results in decreased production of myofilament proteins and in regulation of key transcription factors involved in differentiation of striated muscle cells.[72] The inflammatory syndrome, and TNF-α in particular, in fact causes increased muscle catabolism.[73] In murine models, inhibition of inflammation pathways promotes muscle regeneration.[74] In addition, the decrease in myofibrillar contractility is partly mediated by the increase in oxidative stress and nitric acid production, both of which are promoted by the increase in TNF-α levels.[73,75] By contrast, muscle training promotes the decrease of TNF-α levels.[76,77]

In subjects older than 65 years, elevated plasma levels of IL-6, TNF-α, and/or CRP are associated with lower physical performance, muscle strength, and muscle mass.[2,77–82] Plasma TNF-α level is moreover predictive of a significant decrease in muscle strength at 4 years in subjects aged 85 years[83] and at 5 years in subjects aged 70 to 79 years.[84] In women in good health aged older than 65 years with femoral neck fracture, the lowest levels of IL-6 were significantly correlated with better functional and muscular recovery in the year after fracture.[85,86]

Cytokines and Bone Density

Bone remodeling and resorption are in part modulated by proinflammatory cytokines.[4,87] IL-6 stimulates osteoclastogenesis and osteoclastic activity, while shortening osteoblast survival.[88–93] Elevated levels of CRP, IL-6, and TNF-α are associated with increased risk of osteoporosis.[94–97] These markers of inflammation are also predictive of fracture risk in both sexes.[98–100]

Cytokines and Vascular Risk

Atherosclerosis begins early in the life of an individual with penetration and accumulation of low-density lipoprotein (LDL) cholesterol in the intima. This lipid infiltration is followed by oxidative change of the LDL that is responsible for endothelial dysfunction, causing subendothelial infiltration by inflammatory cells (macrophages, lymphocytes T) attracted by chemotaxis.[101] These cells then release proinflammatory cytokines (mainly IL-1, IL-6, TNF-α, and transforming growth factor-β). The result is overexpression of adhesion molecules and procoagulant agents.[102,103] TNF-α, IL-1, and INF-γ are proapoptotic inducers of smooth muscle cells.[103] Adding to these effects is the local arterial vasoconstriction induced by TNF-α, IL-6, and IL-10, through their impact on the endothelium and through synthesis of nitric acid.[104] Inflammatory cytokines thus participate in both the growth of the plaque and its fragilization.

In addition, IL-1, IL-2, IL-6, and TNF-α directly influence coagulation pathways. They modify endothelial function, leading to a prothrombotic state with inhibition of fibrinolysis, increased production of platelet activation factors, and activation of the intrinsic and extrinsic coagulation pathways.[105,106]

The presence of conventional cardiovascular risk factors (tobacco use, arterial hypertension, dyslipidemia, diabetes, obesity) is accompanied by increased plasma levels of TNF-α and CRP.[107–112]

In the aged population, the relative weight of traditional risk factors in the occurrence of cardiovascular and cerebrovascular events is lower than in the nonelderly population.[7]

The inflammatory syndrome thus seems to have a major influence. In the elderly population, high levels of CRP, fibrinogen, TNF-α, and IL-6 are independent risk factors for cerebrovascular and cardiovascular events.[42,45,108,110,113–116]

Cytokines and Cognitive Decline

Cytokines are produced within the brain, and in addition, peripheral cytokines have a direct influence on the central nervous system, as reviewed by Rosano et al.[117] Peripheral cytokines are capable of inducing central neurological disturbances, as in the course of sickness behavior.[118] The endothelial cells of the blood-brain barrier are able to produce cytokines or inflammatory molecules (prostaglandin and nitric acid) in response to an increase in the level of peripheral cytokines.[119] Cytokines are also produced within the brain, principally by activated microglia that are capable of synthesizing more than 20 cytokines.[120]

In populations free of cognitive disturbance, high levels of IL-6, CRP, or TNF-α have been found to be markers of decline in cognitive performance in the medium term.[121–128] Other studies, however, found no significant link.[129,130]

Cytokines and AD

Inflammation is part of the pathophysiology of AD.[131] Postmortem histopathological examination of the brains of patients with AD showed high levels of proinflammatory cytokines, CRP, and complement proteins in senile plaques and neurofibrillary tangles.[132,133]

Peripheral cytokines can influence the onset or the cognitive decline of AD.[6,134] The influence of proinflammatory cytokines has been well argued on the basis of study of genetic polymorphisms. Certain polymorphisms of the TNF-α, IL-1, and IL-6 genes increase the risk of developing AD.[135,136] High levels of IL-1 and TNF-α have been found to be potential predictive markers of development of AD at 7 years.[134]

In patients with mild or moderate AD, plasma levels of IL1, IL-6, or TNF-α have been found to be higher than in healthy individuals.[27,137–141] However, other studies did not confirm this relationship.[142–145]

Higher intrathecal levels of IL-6 have been observed in patients with AD.[146,147] In addition, hippocampal volume may be inversely correlated with plasma IL-6 level in healthy middle-aged adults.[148] Cognitive decline may be more rapid in patients with high levels of TNF-α.[149]

Cytokines and Cognitive Decline of Vascular Origin

Cytokines also play a damaging role in the pathophysiology of vascular dementia. They are atherogenic and prothrombotic factors and can thus directly influence the occurrence of ischemic cerebrovascular events.[150] In addition, an exaggerated cytokine response to ischemia worsens cell damage. Some studies found a correlation between elevated levels of CRP and IL-6 and vascular dementia.[126,127,142] However, this correlation was not found in all studies.[151]

Table 1
Proinflammatory Cytokines, Aging, and Age-related Diseases: Principal Cytokines Involved and Pathophysiology

Principal Cytokines Involved	Pathophysiology
Cytokines and Cognitive Decline	
TNF-α, IL-6, IL-1	Genetic polymorphism and AD risk[135,136] Decrease in hippocampal volume[148] Microglial activation[120] Complement activation[132,133] Oxidative stress[119]
Cytokines and Vascular Aging	
CRP, TNF-α, IL-6	Endothelial activation[105,106] Inhibition of fibrinolysis[105,106] Prothrombotic activity[105,106] Platelet activation[105,106] Activation of coagulation[106] Atherosclerosis[101–103]
Cytokines and Nutritional Status	
TNF-α, IL-1, IL-6, INF-γ	↑ lipolysis, ↓ lipid synthesis[3,5,63] ↓ lipoprotein lipase activity[3,5,63] ↓ protein synthesis, ↑ proteolysis[3,5,63] ↑ anorexigenic hormones[65–67] ↓ gastric filling capacity[64] ↓ peristaltic activity[64]
Cytokines and Bone Metabolism	
TNF-α, IL-6	↑ bone remodelling[4,87] ↑ bone resorption[4,87] ↑ osteoclastogenesis[4,87] ↓ osteoblast survival[88–93]
Cytokines and Muscle Metabolism	
TNF-α, IL-6	↓ myofibrillar protein synthesis[72] ↑ oxidative stress[73,75] ↑ muscle catabolism[73]

AD, Alzheimer disease; CRP, C-reactive protein; IL, interleukin; INF, interferon; TNF, tumor necrosis factor.

Conclusion

Aging is accompanied by immune, hormonal, and adipose changes leading to a chronic inflammatory state. Levels of proinflammatory cytokines, principally TNF-α and IL-6, have damaging effects on aging (Table 1). They influence the onset of frailty, cognitive decline, and cardiological, neurological, and vascular events. They are also closely linked to the genesis of cancers, with cardiac remodeling in heart failure, and so forth. The limitations of this review arise from the numerous methodological factors of confusion. In fact, studies are not comparable, as measurement methods and threshold values differ and populations are not homogeneous from one study to another. Also, much work is still required, in particular with regard to the influence of multimodal management on levels of proinflammatory cytokines and on the progressive course of these diseases. Simple measures, such as physical activity and a moderate-fat diet, have always been recognized as having a beneficial effect on aging by reducing, in particular, the degree of low-grade inflammation.

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