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Effects of tumor necrosis factor-alpha and interleukin-6 in elderly populations

Abstract

Aging is associated with low-grade increases in circulating levels of TNF-a and IL-6. A wide range of factors, including smoking, obesity, infections, the decline in sex hormones, and the genotype, induce and modify this age-related inflammatory activity, which on the other hand may cause age-related pathology. Several classical risk factors are indeed controlled by TNF-a and IL-6. TNF-a induces insulin resistance and endothelial dysfunction, IL-6 promotes procoagulant changes and both cytokines cause dyslipidaemia. Moreover,

systemic low-grade elevations in both cytokines have been related to cardiovascular diseases and TNF-a has been associated with Alzheimer's disease and type 2 diabetes mellitus. TNF-a and IL-6 are also differently and independently of each other associated with mortality in elderly populations, indicating points of distinction in the biological effects of the two cytokines. Moreover, the association between cytokines and mortality is independent of co-morbidity, suggesting that low-grade increases in circulating cytokines are strong, independent risk factors of morbidity and mortality in old populations, although life style factors and co-morbidity may modulate levels.

Full text

Introduction

Circulating levels of proinflammatory and anti-inflammatory cytokines are influenced by aging. The purpose of the present summary is to discuss how chronic, low-grade increases in systemic tumour necrosis factor-a (TNF-a) or interleukin-6 (IL-6) levels are related to morbidity and mortality in elderly populations.

Pro- and anti-inflammatory cytokines

TNF-a and IL-6 are both multifunctional cytokines with important regulatory roles in immune processes, the coagulation system, and the metabolism of fat, proteins, carbohydrates, and bones [1, 2]. TNF-a is a proinflammatory cytokine and constitutes a direct and important stimulator of IL-6 production. IL-6 has been categorized as both a pro-inflammatory, as well as an anti-inflammatory cytokine, but the present view is that it has predominantly anti-inflammatory and immunosuppressive roles. Thus, IL-6 inhibits the transcription of the TNF gene, induces the release of glucocorticoids, and stimulates the production of anti-inflammatory cytokines [3]. In epidemiological studies, the strong link between TNF-a and IL-6 often makes it difficult to separate their biological effects from each other, although their roles in inflammatory processes are reversible.

Aging and inflammatory cytokines

Circulating levels of TNF-a, IL-6, natural cytokine antagonists and acute phase proteins increase with aging [4]. TNF-a was correlated with IL-6, circulating TNF receptors, and C reactive protein (CRP) in 126 centenarians [4], indicating an interrelated activation of the entire inflammatory cascade in the very old. The age-related increases in inflammatory markers are only 2-4 fold compared to concentrations observed in young healthy controls. However, although these increases are minute, as compared to levels observed during acute infections, this chronic low-grade inflammatory activity is of clinical importance in elderly populations [5].

Cytokines and morbidity in elderly populations

Inflammation is a characteristic part of the neuropathology in Alzheimer's disease and in atherosclerotic lesions. High plasma levels of TNF-a are independently associated with Alzheimer's disease and atherosclerosis in centenarians [4]. Although a linear relationship was found between TNF-a and IL-6, similar associations were not found for IL-6, indicating that systemic TNF-a had a direct role in the pathogenesis of dementia and cardiovascular diseases (CVD) in the very old. The association between circulating TNF-a and the prevalence of CVD was confirmed in a cohort of 130, 80-year-old people [6] and moreover, TNF-a predicted insulin resistance with advancing age [7]. Most immunogerontological studies have focused on IL-6, which has turned out to be a very strong predictor for the risk of developing CVD and type 2 diabetes mellitus [1]. However, IL-6 may partly act as a bystander phenomenon to TNF-a in some studies, *e.g.* experimental studies suggest that TNF-a, but not IL-6, has a mechanistic role in insulin resistance [8, 9]. Furthermore, it is unclear if increased circulating levels of cytokines cause age-associated diseases or if it reflects the sum of ongoing pathological processes.

Cytokines are associated with mortality independently of co-morbidity

If cytokines cause age-related mortality, it is to be expected that cytokines are predictors of mortality, independently of co-morbidity. In contrast, if cytokines are markers of disease states, it is to be expected that the hazard function will be severely affected when adjusting for the prevalence of co-morbidity in elderly populations. High plasma levels of TNF-a, but not IL-6, were associated with mortality independently of the prevalence of dementia and CVD in a Cox regression analysis of 126 centenarians (Bruunsgaard *et al.*, unpublished data).

In contrast, IL-6 was associated with mortality in a study of 675 healthy older persons with or without CVD, and similar results were found for cardiovascular and non-cardiovascular causes of death [10]. IL-6 levels could have reflected a bystander phenomenon to TNF-a in the latter study, considering the close link between the two cytokines. However, in a study of 333, healthy, 80-year-old people, circulating levels of TNF-a in men and low-grade increases in IL-6, in both sexes, were independently of each other associated with all-cause mortality in the following 7 years, indicating different biological effects of the two cytokines (Bruunsgaard *et al.*, unpublished data). Associations between the two cytokines and mortality were also independent of classical risk markers and co-morbidity in this study. Accordingly, these studies together show that low-grade increases in circulating cytokines are strong, independent risk factors of morbidity and mortality in old populations. Consistent with the assumption that the two cytokines are separately associated with mortality due to points of distinction in their biological effects, several risk factors are indeed affected differently by TNF-a and IL-6 (Figure 1) [1, 2]. Thus, both cytokines induce dyslipidaemia, but only TNF-a affects the function of endothelial cells and increases their expression of adhesion molecules. Furthermore, TNF-a, but not IL-6, inhibits insulin receptor activity, and induces down-regulation of insulin receptors in experimental studies as already stated. IL-6 *per se* promotes procoagulant changes including fibrinogen production and aggregation of platelets. Furthermore, circulating levels of IL-6 may represent a better marker of the sum of ongoing inflammation in the body than systemic levels of TNF-a, because locally produced TNF-a does not escape to the circulation although it induces a strong, systemic IL-6 response. IL-6, together with TNF-a stimulates the production of CRP, which has been associated with thromboembolic events, and with mortality in elderly populations [10]. However, the latter association might simply reflect activities of TNF-a or IL-6 because IL-6 is a better predictor of mortality than CRP [10]. Different biological effects of the two cytokines, together with the different prevalence of co-morbidity could also explain why TNF-a, but not IL-6, is associated with mortality in centenarians, whereas IL-6 is the strongest predictor of mortality in octogenarians. For instance, high circulating levels of IL-6 may represent a bystander phenomenon to the increased systemic levels of TNF-a, to a greater extent in centenarians than in octogenarians, *e.g.* systemic levels of TNF-a explained 20 % of the variability in IL-6 in centenarians but only 8 % in octogenarians (Bruunsgaard *et al.*, unpublished data). Such a scenario could result from a high mortality among octogenarians with a systemic anti-inflammatory profile, due to local inflammatory processes or to a genetic disposition and, thus, a selection of

individuals without this risk profile for longevity. On the other hand, the anti-inflammatory response may be insufficient to counteract the detrimental effects of the systemic proinflammatory activity in centenarians with high circulating levels of TNF-a.

What is the triggering signal for age-related increases in systemic levels of cytokines ?

Considering that low-grade increases in circulating pro- and anti-inflammatory cytokines seem to induce age-related morbidity, it is important to isolate the triggering factors in order to improve health in elderly populations. Actually, a wide range of factors affect and modulate the production of TNF-a and IL-6 including smoking, obesity, infections, the age-related decline in sex hormones, trauma, exercise, and polymorphisms in the promoter genes. To our knowledge, no studies have determined the balance between the contribution of life style factors *versus* genetic programming.

CONCLUSION

Concluding remarks

Aging is associated with chronic, low-grade increases in circulating levels of TNF-a and IL-6, which are both associated with mortality, independently of co-morbidity in different elderly populations. Furthermore, in relatively healthy octogenarians, TNF-a and IL-6 were associated with life style factors but not with chronic diseases (Bruunsgaard *et al.*, unpublished data). This strongly suggests that cytokines cause age-related pathology instead of being a reflection of the diseases present, although co-morbidity may contribute to high levels. The production of TNF-a and IL-6 is very closely linked and, accordingly, it is sometimes difficult to distinguish between their effects in epidemiological studies. Despite this, TNF-a and IL-6 seem to have separate effects on morbidity and mortality in old populations. Thus, low-grade increases in TNF-a and IL-6 represent independent links between life style factors and genetic programming on one hand and age-related risk factors, inflammatory diseases and mortality on the other.

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Figures

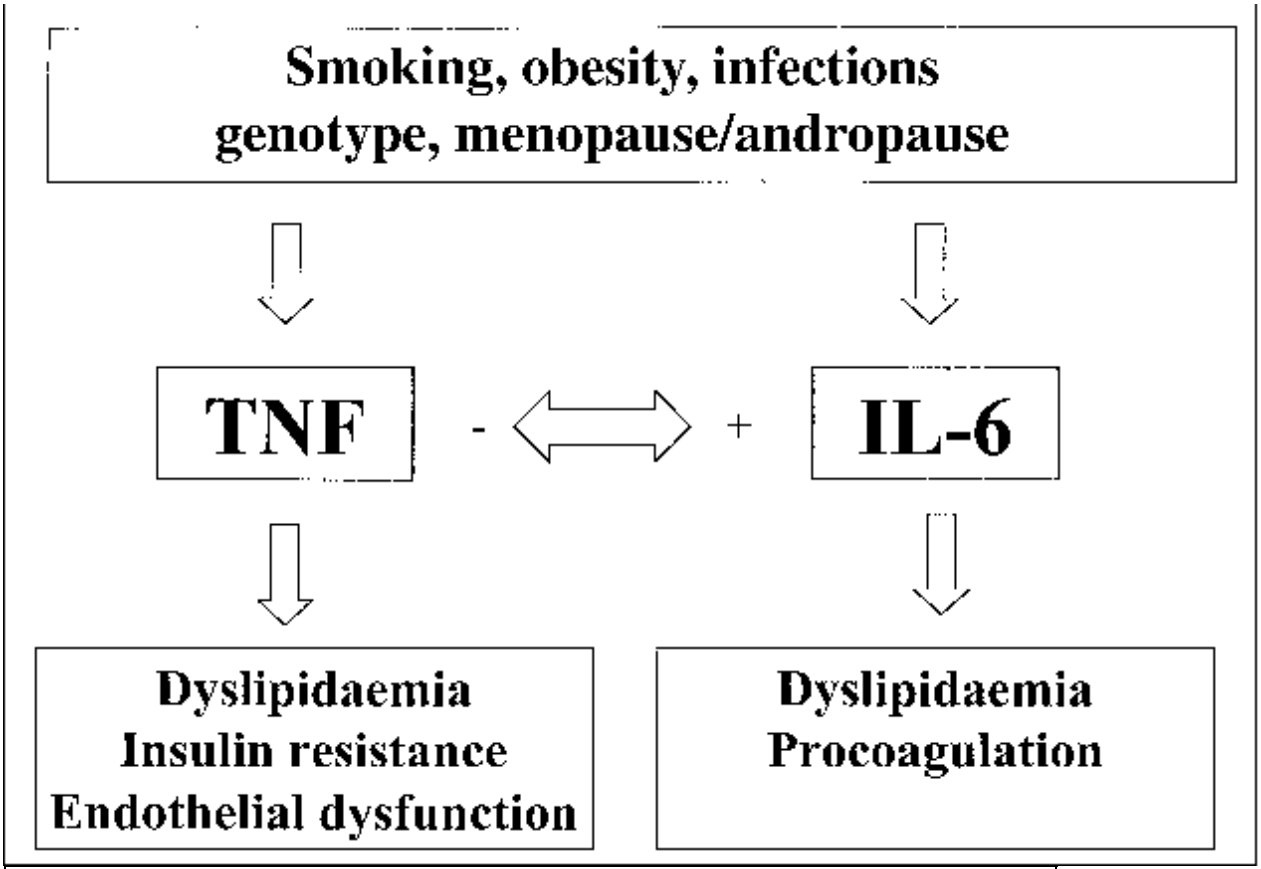

Figure 1 : Cytokines form links between life style factors and age-related risk factors

Authors

Helle Bruunsgaard

Department of Infectious Diseases M7641, Rigshospitalet, Blegdamsvej 9, 2100 Copenhagen ø, Denmark.

In this issue

◯ European Cytokine Society president's address

Josef van Damme

Losing balance : cytokine signaling and cell death in the context of hepatocyte injury and hepatic failure

Tom Luedde, Christian Liedtke, Michael P Manns, Christian Trautwein
liver failure, apoptosis, tumor necrosis factor, NF-KB, interleukin-6, Fas

Presented at the 4th symposium on Cytokines and apoptosis in the cardiovascular system, Halle, Germany, June 6-7, 2002

Activated STAT-1 pathway in the myocardium as a novel therapeutic target in ischaemia/reperfusion injury

Anastasis Stephanou
STAT, heart, ischaemia/reperfusion, apoptosis

A subset of caspase substrates functions as the Jekyll and Hyde of apoptosis

Jian-Yan Yang, Christian Widmann
RasGAP, MEKK1, caspase substrates, apoptosis, survival

Compromised IFN-gamma production in the elderly leads to both acute and latent viral antigen stimulation: contribution to the immune risk phenotype?

Qin Ouyang, Wolfgang M Wagner, Anders Wikby, Ed Remarque, Graham Pawelec
Aging, T-cell, IFN-g, CMV, EBV, immune risk phenotype, longitudinal study

Cytokines in chronic heart failure: possible involvement in the neurohormonal and the cytokine systems at the cAMP level?

Claudia Werner, Harald Loppnow, Mathias Rauchhaus, Armin Wessel, Karl Werdan, Reiner Buchhorn
Adult, b-blocker, children, chronic heart failure, cyclic AMP, cytokine, infant, interleukin, soluble TNF receptor, tumor necrosis factor

Effects of tumor necrosis factor-alpha and interleukin-6 in elderly populations

Helle Bruunsgaard
TNF-a, IL-6, aging, mortality, inflammation

Energetic depression caused by mitochondrial dysfunction

Frank Norbert Gellerich, Sonata Trumbeckaite, Ying Chen, Marcus Deschauer, Tobias Müller, Stephan Zierz
Mitochondria, outer membrane, inner membrane, mitochondrial disease, sepsis, phosphorylation potential

Senescence: the cost of being young and healthy?

Graham Pawelec

The regulation of death-associated protein (DAP) kinase in apoptosis

Galit Shohat, Taly Spivak-Kroizman, Miriam Eisenstein, Adi Kimchi
apoptosis, DAPk, autophosphorylation, negative regulation

Neisseria meningitidis can induce pro-inflammatory cytokine production via pathways independent from CD14 and toll-like receptor 4

Tom Sprong, Peter van der Ley, Liana Steeghs, Will J Taw, Trees JW Verver-Janssen, Mihai G Netea, Jos WM van der Meer, Marcel van Deuren
Neisseria meningitidis, lipopolysaccharide, endotoxin, cytokines, CD14, TLR4

Evaluation of tumor necrosis factor alpha production in ex vivo short term culture whole blood from women with polycystic ovary syndrome

A Veronica Araya, Adam Aguirre, Carmen Romero, Cristian Miranda, Maria Carmen Molina, Arturo Ferreira
LPS, polycystic ovary syndrome, TNF-a, whole blood cell culture

Plasma levels of IL-12, IL-18 and TGF-beta in Plasmodium falciparum malaria

Lucia Malaguarnera, Salvatore Pignatelli, Jacques Simporè, Mariano Malaguarnera and Salvatore Musumeco
Il-12, IL-18, TGF-b, Plasmodium falciparum

In vitro analysis of IGN-gamma and IL-12 production and their effects in ileal Crohn's disease

Stefaan Colpaert, Kathleen Vastraelen, Zhanju Liu, Philippe Maerten,Chong Shen, Freddy Penninckx, Karel Geboes, Paul Rutgeerts, Jan L Ceuppens

IL-12, IFN-g, anti-IL-12/ anti-IFN-g, in vitro, Crohn's disease

Differential modulation of IL-2- and IL-4-mediated early activation of normal human B lymphocytes by the caspase inhibitor zVAD-fmk

Shahul Mouhamad, Damien Arnoult, Marie-Thérèse Auffredou, Jérôme Estaquier, Aimé Vazquez
IL-2, IL-4, B lymphocyte, caspase, proliferation, cell cycle entry

Prolactin-cytokine network in the defence against Acanthamoeba castellani in murine microglia

Nunzia Benedetto, Claude Auriault
Prolactin, cytokine, A. castellani, MGC.

CINC-1 mediates the sympathetic component of inflammatory mechanical hypersensitivitiy in rats

Berenice B Lorenzetti, Fabiane H Veiga, Claudio A Canetti, Stephen Poole, Fernando Q Cunha, Sergio H Ferreira
Inflammatory hyperalgesia, CINC-1, tumour necrosis factor alpha, interleukin-1b, interleukin-8, sympathetic mediators, prostaglandin E2

A CXC chemokine sequence isolated from the rainbow trout Oncorhynchus mykiss resembles the closely related interferon-gamma-inducible chemokines CXCL9, CXCL10 and CXCL11

Kerry J Laing, Niels Bols, Christopher J Secombes
Chemokine, rainbow trout, IP10, I-TAC, Mig

Meeting report of the "Club Cytokine" (French Society of Immunology) meeting, in Le Croisic, France

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