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Inflamación y multimorbilidad

Relación y Consecuencias

Dr. Mario Almanza Guerrero
Profesor Geriatra
ALMA 2017, La Habana.

CONTENIDOS

- *Inmunosenescencia e inflamación: ¿están conectados?*
- *Inflammaging and "Garb-aging"*
- *Relación entre inflamación crónica y enfermedades asociadas al envejecimiento.*
- *¿Existen Intervenciones clínicas para la reducción de la inflamación crónica de bajo grado en personas mayores?*

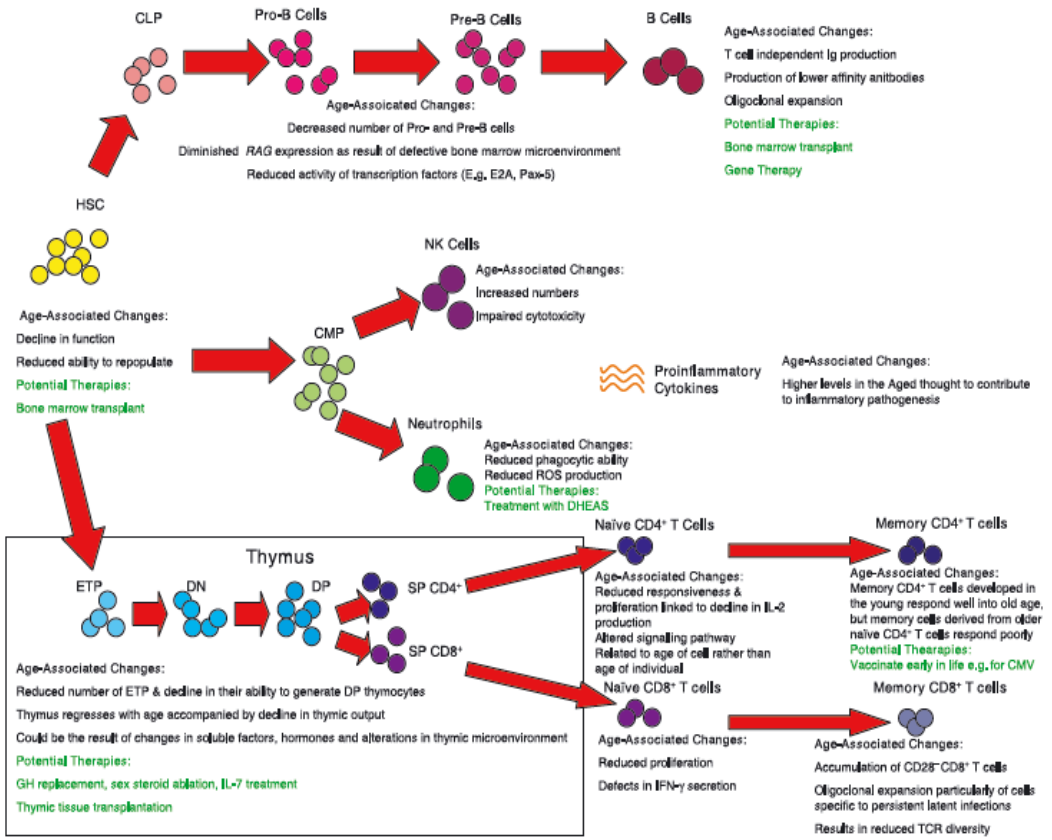


Figure 1. The effect of age on the different components of the innate and adaptive immune systems. Stem cells from the bone marrow give rise to the haematopoietic progenitors under signals from the different microenvironments. Age-associated defects are highlighted in the different haematopoietic stages of development. In addition, potential therapies are described. CLP, common lymphoid precursor; CMP, common lymphoid progenitor; DHEAS, dehydroepiandrosterone sulphate; DN, double-negative; ETP, early thymic precursors; HSC, haematopoietic stem cell; Ig, immunoglobulin; IFN-γ, interferon-γ; NK, natural killer cell; *RAG*, recombination activating gene; ROS, reactive oxygen species; SP, single-positive; TCR, T-cell receptor.

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Review on immunosenescence

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Immunosenescence of ageing

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Immunity & Ageing
BioMed Central

Short report
Open Access

Mechanisms of immunosenescence

Calogero Caruso*[1], Silvio Buffa[1], Giuseppina Candore[1], Giuseppina Colonna-Romano[1], Deborah Dunn-Walters[2], David Kipling[3] and Graham Pawelec[4]

Aw D et al. Immunosenescence: emerging challenges for an ageing population. Inmunology, 2007. Disponible en: doi:10.1111/j.1365-2567.2007.02555.

Trends in Endocrinology & Metabolism

CellPress

Review

Inflammaging and 'Garb-aging'

Claudio Franceschi,[1] Paolo Garagnani,[2,3] Giovanni Vitale,[4,5] Miriam Capri,[2,3,‡,*] and Stefano Salvioli[2,3,‡]

Inflammaging: a term coined by Claudio Franceschi [3] and is the contraction of 'inflammation + aging' to indicate the low-grade chronic inflammation characterizing the aging process (Box 1, main text).

'Garbage': used here to indicate all the cellular and molecular products usually disposed of by specific enzymes or enzymatic complexes. These products can also be recognized by cleaning receptors and phagocytosed by other cells, activating the inflammatory response. Here, the new term 'garb-aging' is proposed (contraction of 'garbage + aging'). This term indicates the production and eventually accumulation of 'garbage' (i.e., misfolded/misplaced self-molecules) as a cause of inflammation and inflammaging.

Trends

Human aging is characterized by a state of chronic, low-grade, sterile inflammation (inflammaging), the causes of which are poorly understood.

A possible cause of inflammaging is the continuous stimulation of macrophages by molecular garbage whose generation–disposal balance becomes impaired with age.

Misplaced self-molecules can be sensed by macrophage receptors and contribute to inflammaging by activating the inflammasome.

Self-molecules (nuclear and/or mtDNA), and other cellular garbage and signaling molecules (miRNAs) freely circulate in bodily fluids within extracellular vesicles carrying inflammatory signals that can spread to distal cells and tissues.

Age-related mitochondrial dysfunction could be linked to inflammaging (source of oxidative stress) and 'self garbage' (mtDNA, cardiolipin, or formyl peptides) that can be sensed by macrophages.

CellPress

Review

Inflammaging and 'Garb-aging'

Claudio Franceschi,[1] Paolo Garagnani,[2,3] Giovanni Vitale,[4,5] Miriam Capri,[2,3,‡,*] and Stefano Salvioli[2,3,‡]

Box 2. Inflammaging and Changes in the Gut Microbiota: Implications and Perspectives

The changes occurring in the GM of older people can have far-reaching biological consequences owing to the important physiological anti-inflammatory role of SCFA and the complex role of Trp in brain physiology within the gut–brain axis [81]. SCFA (acetate, *n*-propionate and *n*-butyrate) are produced in high amounts by commensal bacteria (e.g., clusters IV and XIV of *Clostridia*) that, in addition to being an important energy source, are strong anti-inflammatory molecules that regulate host metabolism and immunity [86]. Butyrate contributes to intestinal homeostasis because it acts as an energy source for colonic epithelial cells, facilitates the differentiation of CD4+ T cells into Treg cells, induces TGF-β secretion by epithelial cells, and triggers the production of IL-10 and retinoic acid by dendritic cells and macrophages [86]. These actions promote the resolution of intestinal inflammation, thus avoiding the leakage of bacteria and bacterial-derived inflammatory compounds into the blood [86]. Reduced plasma levels of Trp are related to increased immune activation and can contribute to inflammaging [16]. It has been observed that the GM of older people and centenarians is enriched in bacteria that consume Trp, affecting its bioavailability; accordingly, a reduction in Trp in the plasma of centenarians has been observed [12]. Given that the GM heavily impacts the health of its host and is involved in inflammaging [87], the possibility to modify and adapt it towards a personalized prohealth ecological system is attractive. Indeed, both physical exercise and diets such as a Mediterranean diet, can modify GM, and physical exercise can attenuate the dramatic effect of a high-fat diet, reducing inflammation [85,88,89]. Moreover, the administration of pre- and probiotics can also help to modulate GM composition in older people.

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Review

Molecular inflammation: Underpinnings of aging and age-related diseases

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Cancer
Osteoporosis

ABSTRACT

Recent scientific studies have advanced the notion of chronic inflammation as a major risk factor underlying aging and age-related diseases. In this review, intra-cellular, neuroendocrine, molecular inflammation is described as an underlying mechanism of aging and age-related diseases, which may serve as a bridge between normal aging and age-related pathological processes. Accumulated data strongly suggest that continuous (chronic) upregulation of pro-inflammatory mediators (e.g., TNF-α, IL-1β, IL-6, COX-2, iNOS) are induced during the aging process due to an age-related redox imbalance that activates many pro-inflammatory signaling pathways, including the NF-κB signaling pathway. These pro-inflammatory molecular events are discussed in relation to their role as basic mechanisms underlying aging and age-related diseases. Further, the anti-inflammatory actions of aging-retarding caloric restriction and exercise are reviewed. Thus, the purpose of this review is to describe the molecular roles of age-related physiological functional declines and the accompanying chronic diseases associated with aging. This new view on the role of molecular inflammation as a mechanism of aging and age-related pathogenesis can provide insights into potential interventions that may affect the aging process and reduce age-related diseases, thereby promoting healthy longevity.

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1. Introduction

It is now accepted that chronic inflammation is a major underlying condition of many age-related diseases, such as atherosclerosis, arthritis, cancer, diabetes, osteoporosis, dementia, vascular diseases, obesity and metabolic syndrome (Yu and Chung, 2006). However, the involvement of inflammation in the aging process has not been seriously considered. We recently proposed the molecular inflammation hypothesis of aging suggesting that a state of chronic, low-grade inflammation is a possible converging process linking normal aging and the pathogenesis of age-related diseases (Chung et al., 2006). The molecular inflammation hypothesis (Chung et al., 2001, 2002) provides molecular insights into the interactions between age-related physiological changes and the pathogenesis of many age-related diseases during aging, while opening up new avenues for exploring the interrelationships between aging and age-related pathological processes (Chung et al., 2006; Yu and Chung, 2006).

The premise of the age-related inflammatory hypothesis is based on two established findings: (1) a dysregulation of the immune system with age, and (2) altered redox states during aging. Both processes lead to increases in systemic inflammatory states due to the activation of a wide variety of inflammatory mediators through mainly oxidative stress-induced redox imbalance. The age-related redox imbalance is likely caused by the net effect of weakened antioxidative defense systems, and increasingly increasing production of reactive species (RS), such as superoxide ($O_2^{\cdot-}$), hydroxyl radical ($^{\cdot}OH$), and hydrogen peroxide (H_2O_2),

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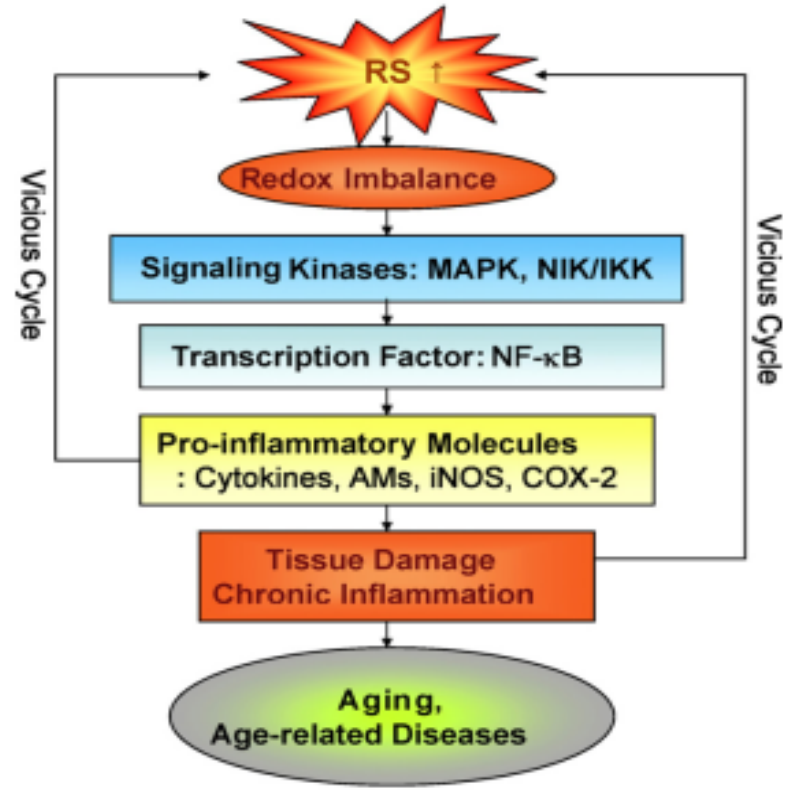


Fig. 1. Major molecular pro-inflammatory pathways involved in aging and age-related diseases. RS, reactive species; MAPK, mitogen-activated protein kinases, NIK, NFκ-B-induced kinase; IKK, IκB kinase; AMs, adhesion molecules; iNOS, inducible NO synthase; COX-2, cyclooxygenase.

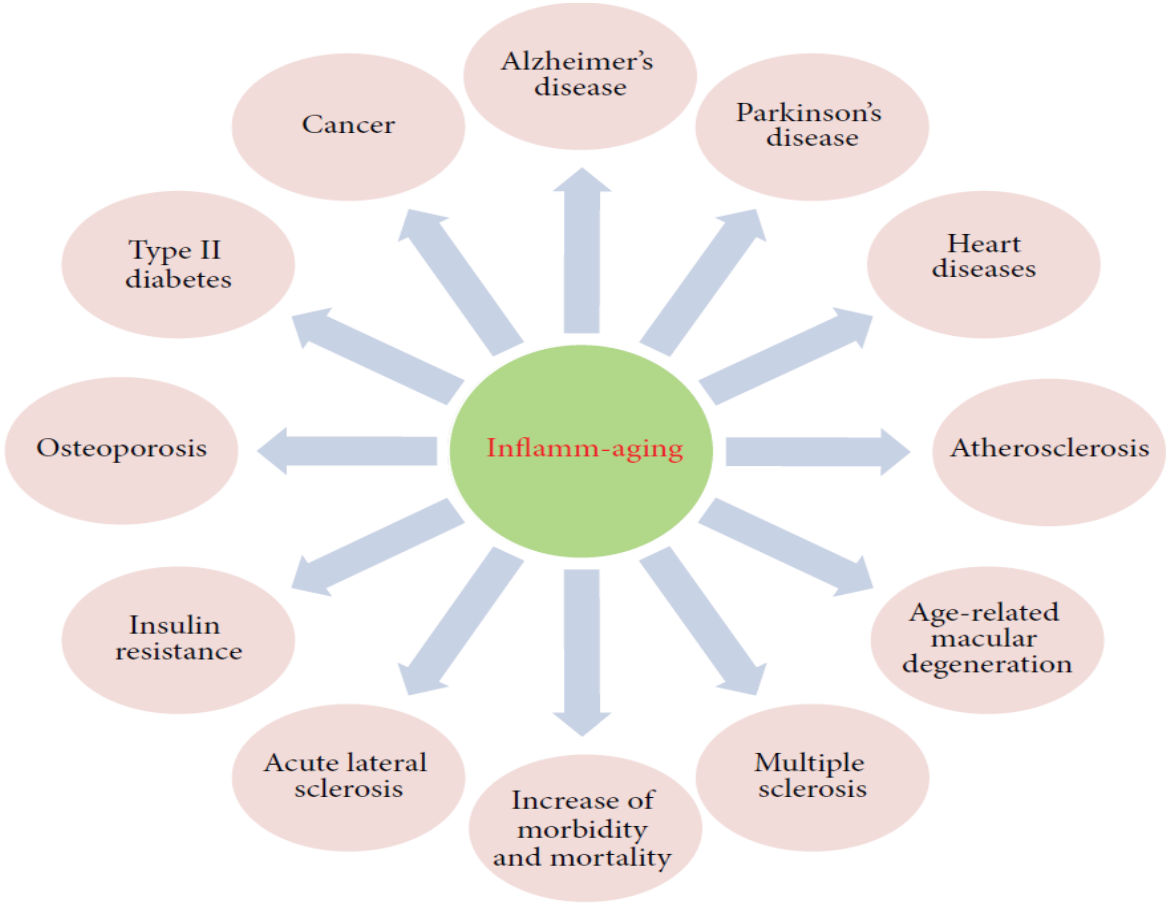


FIGURE 1: The relationship between inflamm-aging and diseases.

Shijin Xia et al. An Update on Inflamm-Aging: Mechanisms, Prevention, and Treatment. Journal of Immunology Research Volume 2016, Article ID 8426874, 12 pages.

AGE (2012) 34:1295–1308
DOI 10.1007/s11357-011-9301-x

The association between systemic inflammation and cognitive performance in the elderly: the Sydney Memory and Ageing Study

Julian N. Trollor · Evelyn Smith · Emmeline Agars · Stacey A. Kuan · Bernhard T. Baune · Lesley Campbell · Katherine Samaras · John Crawford · Ora Lux · Nicole A. Kochan · Henry Brodaty · Perminder Sachdev

Table 7 Regression analyses using each cognitive factor as the dependent variable and all the inflammatory markers as the independent variables

	PAI-1 t(p)	VCAM-1 t(p)	TNF-α t(p)	CRP t(p)	SAA t(p)	IL-1β t(p)	IL-6 t(p)	IL-8 t(p)	IL-10 t(p)	IL-12 t(p)
Model 1 (N=712)										
Language	0.655 (0.512)	−0.398 (0.691)	0.264 (0.792)	−1.62 (0.106)	−2.02 (0.043)	−1.52 (0.129)	1.20 (0.229)	−0.537 (0.592)	1.36 (0.174)	−1.88 (0.060)
Executive/ processing speed	0.545 (0.586)	−0.124 (0.901)	0.773 (0.440)	−2.10 (0.036)	−2.07 (0.039)	−1.06 (0.292)	3.00 (0.003)*	−0.926 (0.355)	−0.500 (0.617)	−3.36 (0.001)*
Memory	0.343 (0.732)	−0.710 (0.478)	−1.27 (0.206)	0.342 (0.733)	−1.24 (0.215)	−0.481 (0.631)	0.873 (0.403)	−0.686 (0.493)	−0.590 (0.556)	-
Learning	0.677 (0.499)	1.95 (0.051)	−0.959 (0.338)	−0.760 (0.448)	−0.615 (0.539)	−1.41 (0.158)	0.346 (0.730)	−0.882 (0.378)	0.242 (0.809)	-

The direction of all significant findings was always negative, with raised systemic inflammation associated with low cognitive performance

All covariates included: sex, age, education, metabolic and cardiovascular factors, depression and *APOE*

PAI-1 plasminogen activator inhibitor-1, *VCAM-1* vascular adhesion molecule-1, *TNF-α* tumour necrosis factor alpha, *CRP* C-reactive protein, *SAA* serum am interleukin-*1β*, *IL-6* interleukin-6, *IL-8* interleukin-8, *IL-10* interleukin-10, *IL-12* interleukin-12

*$p \leq 0.0125$ level of significance after Bonferroni correction of 4× test

Autoimmunity Reviews 11 (2011) 149–153

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Review

Alzheimer's disease, autoimmunity and inflammation. The good, the bad and the ugly

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Frontiers in Neuroendocrinology

journal homepage: www.elsevier.com/locate/yfrne

Review article

Interactions between inflammation, sex steroids, and Alzheimer's disease risk factors

Mariana F. Uchoa [a], V. Alexandra Moser [a], Christian J. Pike [a,b,*]

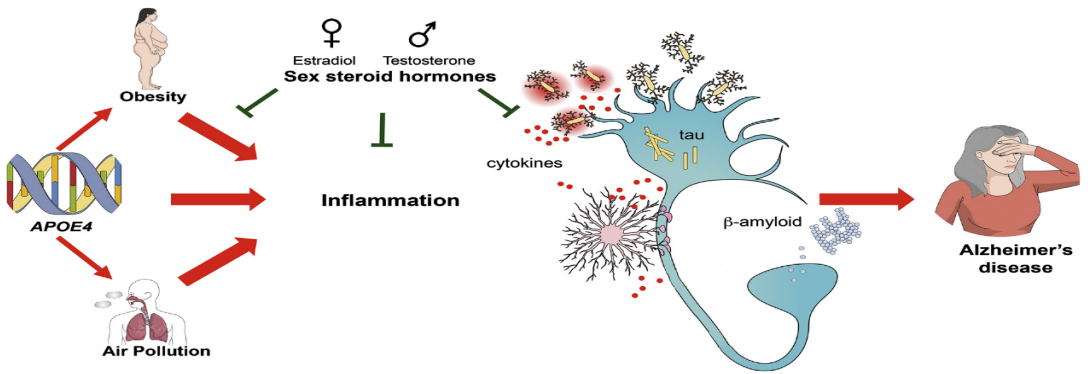


Fig. 1. Inflammation is widely theorized to act as a significant contributor to Alzheimer's disease pathogenesis. Neuroinflammation is associated with activation of microglia and astrocytes, which increase expression of pro-inflammatory cytokines that can promote accumulation of the pathological proteins β-amyloid and hyper-phosphorylated tau. Genetic (*APOE4*), environmental (obesity, air pollution) factors that increase Alzheimer's risk are associated with elevated inflammation. Sex steroid hormones may affect Alzheimer's risk in part by inhibiting inflammation, modulating glial cells, and regulating interactions among risk factors. Illustration was generated using images from www.mindthegraph.com.



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ACTUALIZACIÓN BIBLIOGRÁFICA

Actualización en fragilidad

Update on frailty

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INFORMACIÓN DEL ARTÍCULO

Recibido el 24 de febrero de 2010

Afortunadamente para los geriatras, las publicaciones en el campo de la fragilidad son cada día más numerosas y de mejor calidad. De 2008, se recogen 184 artículos en MEDLINE si cruzamos los términos «frailty» y «elderly», pero cuando usamos referencias cruzadas con otros términos o ampliamos la búsqueda a través de «artículos relacionados», la información se multiplica.

Los avances en fragilidad se están produciendo en todos sus ámbitos, desde epidemiología, patogenia, clínica, diagnóstico y en menor medida, por desgracia, en tratamiento. Pero por encima de los avances, cada vez existe un mayor consenso en que la fragilidad es un estado o condición que antecede a la discapacidad, que está intrínsecamente unida al fenómeno biológico del envejecimiento a través de una pérdida de reserva funcional que origina vulnerabilidad a estresores, que en su constructo patogénico predomina un disbalance energeticometabólico, y que es un importante predictor de eventos adversos en ancianos. Sobre esta base, hay algunos artículos que merecen ser analizados en este último año.

Epidemiología

En el aspecto epidemiológico destacan dos trabajos. Santos-Eggimann et al[1] firman un artículo en el que por primera vez se presentan datos sobre la prevalencia de fragilidad en Europa. Los autores, colaboradores en el proyecto SHARE, llevan a cabo una encuesta en 10 países europeos (España, Suecia, Dinamarca, Holanda, Alemania, Austria, Suiza, Francia, Italia y Grecia) para identificar la prevalencia de fragilidad en mayores de 65 años de la comunidad, aplicando criterios de Fried, aunque con modificaciones en la manera de medir los cinco componentes que la caracterizan. Aunque la encuesta tiene problemas metodológicos, como la elevada tasa de negativa a participar (en España, por ejemplo, el 47% de la muestra seleccionada aleatorizadamente no quiso contestar el cuestionario, y la media de los 10 países fue del 38%) o la modificación de las definiciones operativas de los subcomponentes de la fragilidad, es una primera aproximación rigurosa a la importancia de este problema. Los autores encuentran una prevalencia de fragilidad del 17% y de prefragilidad del 42,3% en la muestra global de los 10 países, y es mayor en mujeres y en los países del sur de Europa, destacando España, Italia, Grecia y Francia. Los datos de nuestro país reflejan una prevalencia de fragilidad del 27,3% y de prefragilidad del 50,9% en los mayores de 65 años de la comunidad, y cuando se analizan sólo los mayores independientes de la comunidad, las cifras son del 21 y el 53,7%, respectivamente. Es llamativa la gran dispersión de los datos entre países, puesto que las prevalencias de fragilidad oscilan entre el 5,8% de Suiza y el 27,3% de España. Esta disparidad puede deberse a los propios problemas metodológicos de la encuesta (aunque a los autores les parece poco probable), a factores socioculturales o ambientales, a factores genéticos o incluso a una manera diferente de entender las preguntas del cuestionario. Los hallazgos del estudio plantean varios interrogantes: ¿Son universales los criterios Fried de fragilidad o deben ser adaptados a las diferentes poblaciones del planeta? ¿Es la fragilidad una condición más prevalente de lo que hasta ahora se pensaba con datos en Estados Unidos de alrededor del 10%? ¿Es la fragilidad en Europa tan buena predictora de eventos adversos como en Estados Unidos?

En contraste con este trabajo, Ávila-Funes et al[2] publican los primeros resultados del Three-City Study, un ambicioso proyecto longitudinal sobre una cohorte de 9.294 mayores de 65 años de Burdeos, Dijon y Montpellier, en Francia. Con una subcohorte de 6.078 personas de la comunidad, no institucionalizados ni dementes, de Burdeos y Dijon exclusivamente y aplicando criterios de Fried ligeramente modificados, los autores encuentran una prevalencia de fragilidad del 7% y de prefragilidad del 47,6%. Los sujetos frágiles fueron más frecuentemente mujeres, de mayor edad, con mayor comorbilidad y menor nivel educacional. La cohorte fue seguida durante 4 años y se comprobó que las personas frágiles tuvieron un riesgo aumentado de discapacidad incidente en

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producen como respuesta. Por *inflamm-aging* se conoce la regulación al alza de determinadas citoquinas proinflamatorias que ocurre en la edad adulta y durante las enfermedades crónicas asociadas al envejecimiento, destacando la IL-6, IL-1, TNF-α, IL-2 y el IFN-α. Esta activación de citoquinas produce como efectos deletéreos inflamación crónica, liberación de reactantes de fase aguda hepáticos, insulinorresistencia y actividad osteoclástica. Para contrarrestar este estado inflamatorio, el organismo actúa a través de las citoquinas antiinflamatorias IL-4, IL-10 e IL-13 produciendo activación del eje hipotalamohipofisosuprarrenal, y originando una elevación del cortisol que causará secundariamente, y como efectos no deseados, resorción ósea, lipólisis, catabolismo proteico, gluconeogénesis y disfunción inmune según el sistema sobre el que actúe, produciendo en último término fragilidad y enfermedad crónica. La coexistencia de fenómenos inflamatorios y antiinflamatorios en el anciano va a tener un efecto negativo sobre el metabolismo, la densidad ósea, la fuerza, la tolerancia al ejercicio, el sistema vascular, la cognición y el afecto, colaborando en última instancia a desencadenar el fenotipo de fragilidad.

Otro aspecto que recientemente ha recibido gran atención es la relación entre el estado de resistencia insulínica y el síndrome de fragilidad. Abbatecola y Paolisso publican una revisión en la que desgranan los mecanismos mediante los cuales la insulinorresistencia puede participar en la patogénesis de la fragilidad[9]. Se conoce que la insulinorresistencia produce pérdida de fibras musculares, aumento de las citoquinas mediadoras de la inflamación (IL-6, TNF-α, PCR y NF-κβ), disfunción endotelial y disminución del flujo sanguíneo muscular, favoreciendo la reducción del metabolismo muscular y produciendo, por consiguiente, sarcopenia, aspecto central de la fragilidad. La insulinorresistencia produce a nivel cerebral una disminución de la acción del receptor de insulina, un aumento de las placas de amiloide y un aumento de los ovillos neurofibrilares[10], favoreciendo el deterioro cognitivo que se ha visto asociado a fragilidad.

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Inflammatory markers in population studies of aging

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Abstract

Purpose—To review findings from major epidemiologic studies regarding risk factors and consequences of elevated markers of inflammation in older adults.

Results—Most of the large, current epidemiologic studies of older adults have included serum interleukin-6 (IL-6), C-reactive protein (CRP) and tumor necrosis factor alpha (TNF-alpha), and some more extensive batteries of measures including soluble receptors. Few risk factors for the modest elevations seen with aging have been defined, including, visceral adiposity, lower sex steroid hormones, smoking, and depression. Of the markers assessed, IL-6 is most robustly associated with disease, disability and mortality.

Conclusion—IL-6 is a non-specific marker of adverse outcomes in older adults.

Keywords

Inflammatory markers; aging; disability; mortality

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Possible interventions—The strong associations of inflammatory markers with adverse health outcomes in older adults suggest the potential for targeting inflammation to reduce disability and mortality in old age. Advances have been made in targeting TNF and more recently IL-6 in rheumatic conditions, but whether these are relevant in old age is not yet known. Proteasome inhibitors, IL-6 and IL-6 receptor antibodies are in their initial stages of testing. Indirect evidence for benefit in reducing inflammatory markers in old age comes from statin trials for cardiovascular disease prevention. Studies of physical activity and hormone replacement also suggest that their potential benefits may be achieved in part via an anti-inflammatory pathway.. Treatment trials for dementia with non-steroidal anti-inflammatory drugs have not been completed due to adverse cardiovascular events on active treatment.

Statins—Reduction of primary and secondary CVD risk because of the lipid-lowering effect of statins has been documented a number of times in the past. Apart from this, recent studies suggest the effect of statins on lowering the levels of inflammatory markers, especially IL-6 and CRP, which may be a promising approach in the use of these drugs for other chronic inflammatory conditions (Niswasi, Osman et al. 2000; Montecucco and Mach 2009; Ridker, Danielson et al. 2009; Quist-Paulsen 2010). Results from Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) demonstrated that statin treatment in apparently healthy subjects with elevated CRP and non-elevated LDL cholesterol resulted in significant reduction in both these markers and CVD (Ridker, Danielson et al. 2009; Mora, Glynn et al. 2010). However, the results of this trial have been controversial as it is not clear whether statins actually reduce the levels of CRP and if a decline in CRP explains the benefit by reduction in CVD (de Lorgeril, Salen et al. 2010; Kaul, Mannisoy et al. 2010).

Physical activity/ exercise—There is promising evidence suggesting a role of physical activity in reducing the levels of inflammatory markers. Even though several theories have been hypothesized, the exact mechanism for this reduction is not clear. A possible mechanism for this reduction may be related to a preferential decrease in visceral fat with physical activity interventions. Numerous cross-sectional and longitudinal studies have now shown the association of physical activity with a decrease in the levels of these markers especially in the elderly. Reuben et al. reported a beneficial association of high levels of recreational activity on IL-6 and CRP with adjusted odds ratio for highest levels of IL-6 = 0.65 and CRP = 0.70 in the MacArthur Studies of Successful Aging (Reuben, Judd-Hamilton et al. 2003). Similar associations between inflammatory markers and physical activity have been found in other large cohort studies like the CHS and the InCHIANTI study (Geffken, Cushman et al. 2001; Reuben, Judd-Hamilton et al. 2003; Illouna, Bartali et al. 2005; Nicklas, Hsu et al. 2008). One clinical trial specifically showed a lowering of these markers related to participation in a physical activity program in the Lifestyle Interventions for Independence for Elders Pilot (LIFE-P).

Hormones—As observational data shows elevation of pro-inflammatory markers with declining levels of sex hormones, a number of clinical trials have been conducted to look at the beneficial effects of hormone therapy to counter this effect. Testosterone administration was shown to be followed by a marked reduction of inflammatory markers in hypogonadal men in a testosterone replacement crossover trial (Malkin, Pugh et al. 2004). But there is still no consensus on this approach as some studies show contradictory results and hormone supplementation has been linked to a number of severe adverse effects. Another study found a significant inverse correlation between testosterone and inflammatory markers (IL-6, CRP), but did not observe any significant effect of testosterone therapy on these markers (Kapoor, Clarke et al. 2007). A recent trial, Testosterone in Older Men with Mobility

Intervenciones

Ejercicio Físico	Anti-Oxidantes	Estatina	Antiinflamatorio

Cadore EL, Casas-Herrero A, Zambom-Ferraresi F, et al. Multicomponent exercises including muscle power training enhance muscle mass, power output, and functional outcomes in institutionalized frail nonagenarians. Age (Dordr) 2014;36:773-85.