Chapter 6

On the Way to Longevity: How to Combat Neuro-Degenerative Disease

Patrizia d'Alessio, Rita Ostan, Miriam Capri and Claudio Franceschi

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/54914

1. Introduction

1.1. Aging and inflammaging

Aging can be defined as the accumulation of unrepaired, deleterious changes occurring in the molecules, cells, tissues and organs of the body over time generated by internal and external sources. An integral part of the aging process is represented by the adaptive mechanisms that the body sets up to compensate and neutralize the adverse effects of such damage that lead to a progressive change of the body composition and its microenvironments. Among others, the multifaceted dynamic process, known as immunosenescence, encompasses all the complex changes occurring in the immune system during aging. It results from the adaptation process of the body to the continuous challenge of infections and is the basis of the age-associated decrease in immune competence that renders individuals more susceptible to diseases. Immunosenescence is associated with an increase of morbidity and mortality [27, 35, 46]. One of the typical aspects of immunosenescence is the profound modification within the cytokine network leading to the development of a low-grade inflammatory status, known as "inflammaging" [28]. This phenomenon is characterized by a general increase in plasmatic levels and cell capability to produce pro-inflammatory cytokines (Interleukin-6, IL-6, Interleukin-1, IL-1 and Tumour Necrosis Factor-α, TNF-α) and by a subsequent increase of the main inflammatory markers, such as C-reactive protein (CRP) and serum amyloid A (A-SAA) [29, 31, 32]. This generalized pro-inflammatory status, interacting with the genetic background and environmental factors, potentially triggers the onset of the most important age-related diseases, such as cardiovascular diseases, atherosclerosis, metabolic syndrome, type 2 diabetes and obesity, neurodegeneration, arthrosis and arthritis, osteoporosis and osteoarthritis, sarcopenia, major

depression and frailty [46]. The first evidence of the age-associated modification in the balance of cytokine network was described by [24] who found an increase of IL-6 plasma levels and a corresponding decrease of IL-2 production in healthy elderly subjects [24, 26].

We have provided several contributions on the relevance of the inflammatory reaction at the vascular site for cell senescence in terms of the reversibility of its inflammatory phenotype [16, 17]. These data could be confirmed by *ex vivo* data of Franceschi's laboratory. A significant increase of IL-6, TNF-α and IL-1β levels were described in mitogen-stimulated cultures from aged donors. Indeed, cells from aged people seem able to up-regulate the production of these cytokines in response to appropriate stimuli indicating that the cellular machinery for the production of these molecules remains active and efficient during aging [24]. It has been hypothesized that inflammaging could be due to the antigenic load and its persistence for the entire lifespan. Antigens of common viruses such as human cytomegalovirus (HCMV) or Epstein-Barr virus (EBV) represent a major driving force for the activation of macrophages and expansion of specific T cell clones (megaclones) producing a large amount of inflammatory cytokines [54, 55]. The increase with age of IL-6 plasma levels appears to be unexpectedly present in both those who underwent successful aging and those who suffered pathological aging. Thus, we must question the factors responsible for successful aging. Data obtained on centenarians by the Franceschi laboratory showed that centenarians also are inflamed [3, 4, 26]. Thus, inflammaging *per se* is not incompatible with longevity. But it is likely that many protective factors, such as the genetic background, epigenetic markers [33] and anti-inflammatory molecules can play a pivotal role in counteracting unfavourable pro-inflammatory signalling [32].

At present it is not understood whether the alteration in the regulation of inflammatory reactions could be a cause or rather an effect (or both in a vicious cycle) of the aging process as a whole. A wide range of elements has been claimed to contribute to the development of low-grade inflammation. In particular, in addition to the main impact of the immune system, a variety of tissues (adipose tissue and muscle in particular), organs (liver and brain) and ecosystems (skin, mouth, vagina and gut microbiota) differently contribute to inflammaging onset, progression and persistence having specific organ-restricted and/or systemic effects [13].

Gut microbiota and the gastrointestinal-associated immune system coexist in a balanced microenvironment where cytokines and lymphocytes have to cope with the antigenic load, in order to control the enormous variety of bacterial species within the intestinal microflora. During aging, subtle changes in intestinal microbial structure may contribute to the age-related inflammatory status. A reduction of some populations of *Clostridia* in favour of enrichment in facultative anaerobes in centenarians has been described. In addition, the remodelling of centenarians' microbiota was associated with an increased inflammatory state, determined by a series of peripheral inflammatory markers (IL-6, IL-8) [7]. The dysbiosis observed in these extremely long-lived subjects represents an important source of continuous antigenic stimulation (immune/inflammatory/toxic/metabolic) to other organs and systems, such as the immune system and the liver, contributing to the development and maintenance of inflammaging. So why are healthy centenarians the best example of successful ageing, even if they

http://dx.doi.org/10.5772/54914

are characterized by inflammaging? Our hypothesis is that their reduced capacity to mount strong inflammatory responses is due to a remarkable genetic pattern (based on anti-inflammatory gene variants) and is able to limit the inflammatory process. A protective genetic component towards the development of age-related pathologies with a strong inflammatory pathogenesis would thus be exerted [32].

Inflammaging can, in turn, undermine the balance between gut microbiota and the gastrointestinal-associated immune system, contributing to the establishment of a vicious inflammatory cycle [8]. Importantly, recent literature suggests the impact of microbiota inflammatory stimuli on the brain [6]. Several studies even suggest an inflammatory pathogenesis at the basis of activation of microglia in response to injury, illness and aging, as described in the following section.

2. Neuro-inflammation

The term neuro-inflammation designates chronic, CNS-specific, inflammation-like glial responses that do not reproduce the classic characteristics of inflammation in the periphery but that may provoke neuro-degenerative events, including plaque formation, dystrophic neurite growth and unwarranted tau phosphorylation, among other signs. Aetiology of neuro-inflammation is not yet clarified even if many strides forward have been made in this field. In fact, during the last decades important discoveries have been made, particularly on risk factors, genetic-associated variants, pro-inflammatory molecules, cellular and sub-cellular modified processes and, ultimately, the gene expression pathways shared in many neuro-degenerative diseases, such as AD. A recent review summarizes microarray human studies in neuro-degenerative diseases showing gene expression profiles shared in these age-associated diseases [15], highlighting the inflammatory component. In addition, RNA splicing and protein turnover are found to be disrupted and mitochondrial dysfunction has been reported.

Franceschi's team is heavily involved in the study of age-related diseases and in particular AD, either in terms of nuclear and mitochondrial genetic variants and pro-inflammatory environments [21, 22, 36-39, 45, 49]. It is well known that AD is a fast growing worldwide pathology: it is a slowly progressive and, after early stage reversible phases, irreversible neuro-degenerative disease. Patients undergo decades of symptomatic progression; multiple interacting molecular mechanisms contribute to the development of the early clinical prodromal stages characterized by episodic memory deficits and decline, as well as impairment of general cognitive functioning, particularly during the final syndromal dementia stage (reviewed in [34]). In the context of AD research, the team studied the role of genetic cytokines variants, such as IL-1, IL-6, TNF-α and interferon-gamma (IFN-γ), in AD patients. The data showed the association between the plasmatic and brain level of IL-6 and IL-6 polymorphisms at 174 position in the promoter region, suggesting a relationship between specific gene variants and circulating levels of a specific inflammatory cytokine; furthermore, cytokine blood level mirrors the quantity of its level in the brain [38]. Similarly, increased levels of IL-1, another pro-inflammatory cytokine, are observed

in association with specific IL-1 gene variants [21]. We think that these findings can be integrated into the more general vision of the inflammaging process, i.e. the chronic age-related pro-inflammatory status together with unfavourable genetic variants can contribute to neuro-inflammation pathogenesis and the onset of AD or neuro-degenerative diseases [30, 11]. Many inflammatory mediators have been detected in regions of the brain of patients with AD [45] according to the hypothesis that inflammation might contribute to the neuro-degeneration characterizing this pathology [42].

The activation of the microglia may be due either to local and/or systemic inflammation. In fact, a strong local inflammatory stimulus, such as a previous head trauma, is a risk factor for AD onset and several epidemiological studies clearly show that blood elevations of acute phase proteins, markers of systemic inflammatory stimuli, may be risk factors for cognitive decline and dementia [21, 52]. Moreover, in AD, astrocytes are involved in the production of neurotoxic substances, such as reactive oxygen and nitrogen species, pro-inflammatory cytokines, complement proteins, and other inflammatory mediators that bring about important neuro-degenerative changes [53].

However, the scenario is much more complex than previously thought. The Franceschi group also identified key molecular actors, such as proteasome and immune-proteasome (the molecular complex induced by INFs), as possible motors of protein turnover alteration [43]. The immune-proteasome has been associated with neuro-degenerative and autoimmune diseases as a marker and regulator of inflammatory mechanisms. Its expression in the brain may occur upon neuro-inflammation in different cell types and affect a variety of homeostatic and inflammatory pathways including the oxidized protein clearance and the self-antigen presentation. Recently, its role in epilepsy has been established. In fact the pathology-specific pattern of immune-proteasome expression could provide insight into the complex neuro-inflammatory pathogenic components of this disease [44]. The same group is currently working on the circulating proteasome/immuneproteasome, in order to establish its role as a possible early-biomarker in neuro-degenerative and inflammatory diseases. In this regard, the circulating mitochondrial DNA, another systemic biomarker of inflammation and disease, is also being investigated [57]. This type of research could be strategic for the improvement of therapeutic intervention, one of the priorities of the current European and US research. The possibility, as well as the difficulty, of identifying a pro-inflammatory prodromal phenotype which will develop the syndromic stage, is crucial for the prevention, diagnosis and therapy of AD and other age-related neuro-degenerative pathologies [56].

The study of post-operative delirium (POD) in elderly patients [1, 2] has been promoted by the same approach. Recent literature suggests the presence of an inflammatory component in the POD onset, showing again the close relationship between systemic inflammation and CNS, particularly when a stressful event such as surgery (or anaesthesia) or infectious diseases may provoke an acute exacerbation (delirium) interacting with pre-intra and post-operative parameters. One of the main hypotheses related to the delirium onset is that peripherally produced pro-inflammatory cytokines enter the brain and activate microglia. Activated microglia may produce inflammatory mediators affecting neuronal functioning, that may be implicated in the symptomatology of delirium.

http://dx.doi.org/10.5772/54914

What are the physiological mechanisms to counteract the pro-inflammatory activation of neuro-inflammation? One of the best characterized is the cholinergic inhibition that controls microglia activation and thereby limits the severity and duration of delirium. If cholinergic inhibition fails, either because of pre-existing neuro-degeneration or use of drugs with anticholinergic effects, neuro-inflammation could spin out of control, leading to severe prolonged delirium that can become associated with dementia [51]. Thus, the first event, i.e., POD, is often a prodromal event for the development of dementia or AD, i.e., a long-term cognitive decline and also an increased mortality. On this last point limited literature is currently available. It is noteworthy that the inflammatory markers are already abundantly present before the post-operative delirium episode (in particular IL-6, IL-8 and CRP) [5] and sometimes this pro-inflammatory status is accompanied by the decrease of anti-inflammatory molecules such as Acetylcholinesterase enzyme (AchE), inducing an imbalance between pro- and anti-inflammatory responses [12].

In progress data from the Franceschi laboratory suggest that the assessing of the level of specific plasmatic pro-inflammatory cytokines, together with other parameters [2], before surgery could be the best strategy for early identification of patients who could develop POD and not only for the best management of patients on the ward. This could lead to fast tracking of elderly patients who could develop neuro-degenerative diseases in the future.

Another model studied by the same laboratory is Down Syndrome (DS), a progeroid syndrome characterized by an accelerated neuro-degenerative process [25, 40]. Ongoing analyses on a cross sectional cohort by means of an ad hoc test battery for cognitive and functional assessments could be essential in gathering evidence on brain areas that first undergo neuro-degeneration.

The strategy for counteracting these different age-related neuro-degenerative clinical pictures and diseases is of primary importance and represents one of most fascinating areas in the field of aging and age-related disease research. In order to slow down and counteract the "destiny" of early identified risk factors in an elderly patient candidate for surgical treatment, what could be the most eligible non-invasive and non-toxic therapeutic intervention? Our driving hypothesis is that we can restrain the onset and the progression of the age-related neuro-degenerative diseases counteracting immunosenescence [10] and inflammaging by diet intervention, moderate and daily physical exercise and the possible use of natural compounds, whose formulation allows specifically reducing inflammatory markers in tissues, cells and blood.

3. Anti-inflammaging/anti-stress intervention

Chronic inflammation is an underlying cause of many apparently unrelated, age-related diseases. This fact is often overlooked, yet persuasive scientific evidence exists that correcting a chronic inflammatory disorder will enable many of the infirmities of aging to be prevented or reversed. When we envisage a link between aging and recurrent or chronic inflammation,

we refer to the pathological consequences of inflammation in well-documented medical literature. Regrettably, the origins as well as the consequences of systemic inflammation continue to be an unsolved problem. By following specific prevention protocols (such as weight loss), the inflammatory stimulation could be significantly reduced. An important role in preventing the onset of a chronic inflammatory condition has been attributed either to the practice of a physical activity or to the prescription of a personalized diet, or both.

Terpens are a large and varied class of organic components classified as secondary metabolites. They are produced by a wide variety of plants, particularly conifers, though also by some insects, such as swallowtail butterflies, which emit terpens from their osmeterium. They are the major components of resin and of turpentine produced from resin. The name terpen is derived from the word "turpentine". The smaller and more volatile terpenoids (C10 and C15) are generally the main constituents of the essential oils obtained from many types of plants and flowers, widely used as natural flavourings for food, as fragrances in perfumes in aromatherapy and in traditional and alternative medicines. Terpenoids possess a common structural feature: they contain an integral number of C5 units (isoprene-like) giving a basic molecular formula (C5H8)n for the hydrocarbons series. They are derived from the metabolism of acetate by the mevalonic acid branch biosynthetic pathways of plants.

Examples of monoterpens (C10) are geraniol and limonene. In particular, *d*-limonene has a pronounced chemotherapeutic activity and minimal toxicity in pre-clinical studies. A phase I clinical trial performed to assess toxicity, maximum tolerated dose (MTD) and pharmacokinetics in patients with advanced cancer was followed by a limited phase II evaluation in breast cancer. We have previously published some *in vitro* results on a tri-terpen [58], implicating a NF-κB dependent anti-inflammatory mechanism of action of the extract of *Trytergium Wolfordii* hoek, used in traditional Chinese medicine for the prevention of arthritis, rheumatoid arthritis and arthrosis.

In performing the experiments for the assessment of the doses to be administered in an *in vivo* rodent model, an anti-stress effect of the terpen AISA 5203-L was unexpectedly revealed by a functional observation battery (FOB). A plethora of parameters addressing behavioural, physiological and neurological parameters in female rats submitted to several stressful conditions were measured. Results showed important effects leading to the capacity of the animals to tolerate stress and even pain when compared to vehicle-treated animals [9].

To these preliminary pre-clinical data we were recently able to add some clinical data showing the coherence of our anti-inflammatory/anti-stress approach [18, 19]. The European Capacity study "Ristomed" enrolled 125 healthy individuals from three different countries (Italy, France and Germany). They all received an 'optimal diet for the elderly' with the supplementation of some nutraceutic compounds for a period of 56 days. The diet was developed on the basis of the current recommendations for elderly people and personalized individual dietary requirements, with particular attention given to food compounds that can affect inflammation, oxidative stress and gut microbiota, such as polyunsaturated fatty acids (PUFAs), antioxidant vitamins, polyphenols, flavonoids and fibres. The diet was adapted to the dietary habits for each country. AISA Therapeutics treatment (here referred to as OPE, i.e., Orange Peel Extract)

http://dx.doi.org/10.5772/54914

associated as dietary supplementation in addition to the Ristomed diet was validated as an anti-inflammatory food complement.

In this article, we will report the results concerning the inflammatory markers and the (concomitant) alterations of the mood, comparing the group receiving the diet without supplementation (14 males, mean age 69.6 ± 4.1 years; 17 females, 71.3 ± 3.8 years) to that receiving a diet supplemented with daily soft gel capsules containing the terpen extract AISA 5203-L (14 males, mean age 70.6 ± 4.4 years; 16 females, 69.6 ± 3.3 years), related to as OPE (Orange Peel Extract).

The laboratory measurements performed included erythrocyte sedimentation rate (ESR), high-sensitivity C-reactive protein (CRP), white blood cell count (WBC) and fibrinogen measurements. Baseline plasma levels of ESR, CRP, WBC, fibrinogen, IL-6 and TNF-α were used to calculate an inflammation score. This enabled the separation of the patients into two groups of respectively low and high inflammation, so that inflammatory status could be evaluated according to the scores of these markers.

Moreover, several self-assessment questionnaires were analysed to investigate quality of life parameters. The SF-36v2 Health Survey was used to evaluate what each subject felt about his/her health using 36 items covering functional status, wellbeing and an overall evaluation of health, that together are referred to as Quality of Life (QoL). Two summary scores — Physical Component Summary (PCS) and Mental Component Summary (MCS) — were calculated to distinguish a possible physical dysfunction and bodily pain from psychological distress and emotional problems. The State-Trait Anxiety Inventory-X (STAI-X) questionnaire was used to assess the anxiety state and trait, and to describe each subject's feelings at a particular point.

The results of this investigation showed that among clinically healthy, aged subjects (i.e., absence of cancer, obesity, metabolic syndrome, diabetes, major cardiovascular complaints, arthritis or dementia), a third of them showed important inflammatory markers' expression. It is precisely these patients that could be at risk of developing delirium in the case of surgical treatment [2]. They would largely be advantaged by a preventive treatment of their inflammatory condition, especially if high levels of IL-6 and TNF-α are measured.

Conclusively, the results confirmed the anti-inflammatory action of the terpen extract in an aged matched (65-85) healthy population (figure 1 and [20], www.ristomed.eu).

Moreover, Ristomed results were conclusive also for the capacity to lower anxiety and thus implicitly for the link between inflammation and anxiety. Interestingly, study results obtained for quality of life assessment (PCS, MCS and GHQ-12), mood (STAI-X) and depression (CES-D) confirmed our findings on mood modulation. We note in particular that OPE treatment was more effective in high-inflamed patients, the anti-depressive effect is more visible in low-inflamed patients (figure 2). These results also confirm previous findings established by our Functional Observation Battery (FOB) in rodents, where AISA 5203-L supplementation was able to substantially contribute to pain tolerance and mood stabilization. However, the most intriguing result was the fact that the stressed animal (non-pathological stress stimulating anxiety), instead of developing a freezing attitude, following oral administration of the food supplement, developed an activity. These data

can be useful to answer the question "Is stress relevant for cell senescence and thus aging?". The important effects on mood in the presence of stress situations has been documented for decades. The mechanism by which a stress is responsible for detrimental organ impairment seems to reside in the complex interconnections between inflammatory and immunosenescence pathways [14, 23, 41, 50].

In conclusion, inflammaging is an age-related process arising from the interaction with the genetic/epigenetic/microbioma–specific background and the environment, as shown in figure 3, and this interaction potentially triggers the onset of the most important age-related diseases. In this regard, lessons from the clinical research teach us that inflammation as well as mood alterations seem relevant for the onset of degenerative diseases. The balancing between pro- and anti-inflammatory agents can be modified by external stimuli both in terms of stress or

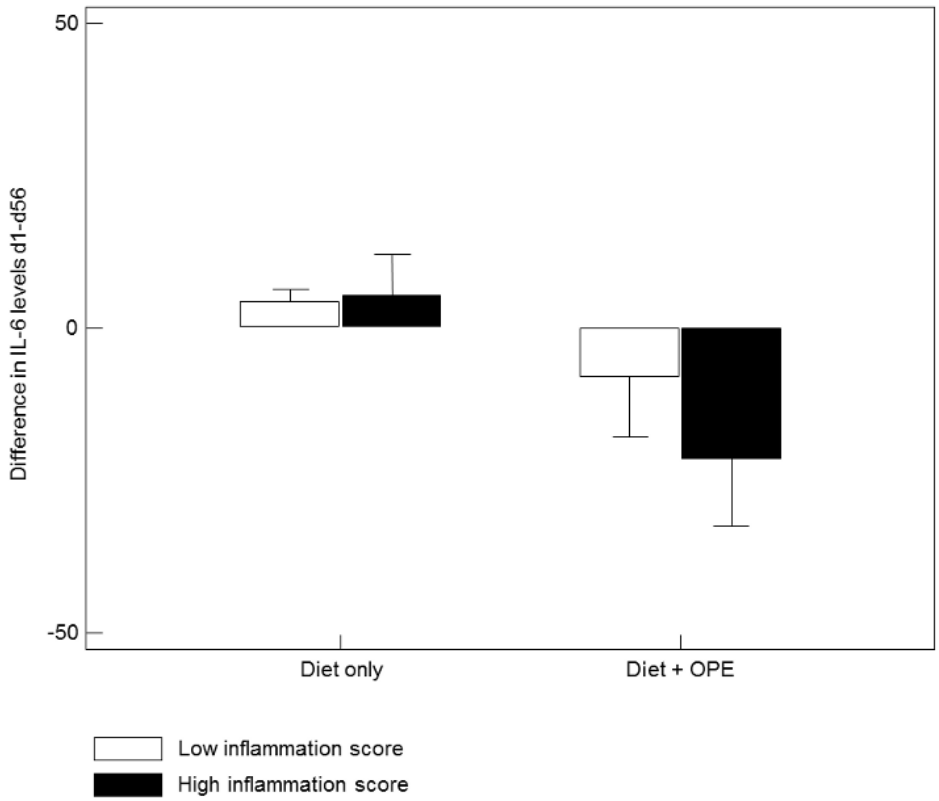

Figure 1. Results of the Ristomed study: inflammation sub-groups and IL-6 variation in diet versus diet plus terpen extract AISA 5203-L, in the figure mentioned as OPE (i.e., Orange Peel Extract).

http://dx.doi.org/10.5772/54914

anti-stress effects. The evidence that post-surgery delirium episodes precipitating dementia are announced by anxiety that in turn is associated to high inflammatory scores, allows us to research efficacious presides to treat these cases. A preventive administration of non-toxic food additives counteracting inflammation and soothing mood alterations could be integrated into the daily diet preceding the surgical intervention. A preventive administration of highly anti-inflammatory specific biocomplements should be included in the recommendations to the healthy aged population by medical institutions and supported by healthy aging guidelines in western countries.

Finally, in order to counteract inflammatory stimuli and to modulate the impact of the environment on inflammaging, we proposed to intervene with diet and food supplementation.

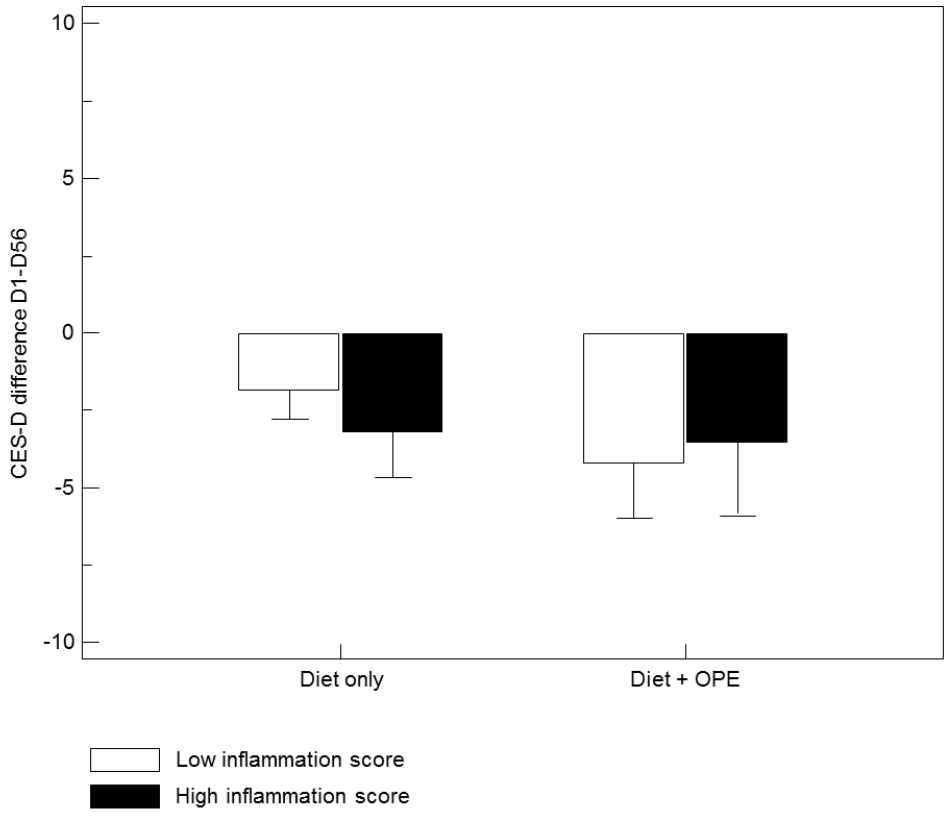

Figure 2. Inflammation subgroups and CES-D variation in diet versus diet plus OPE.

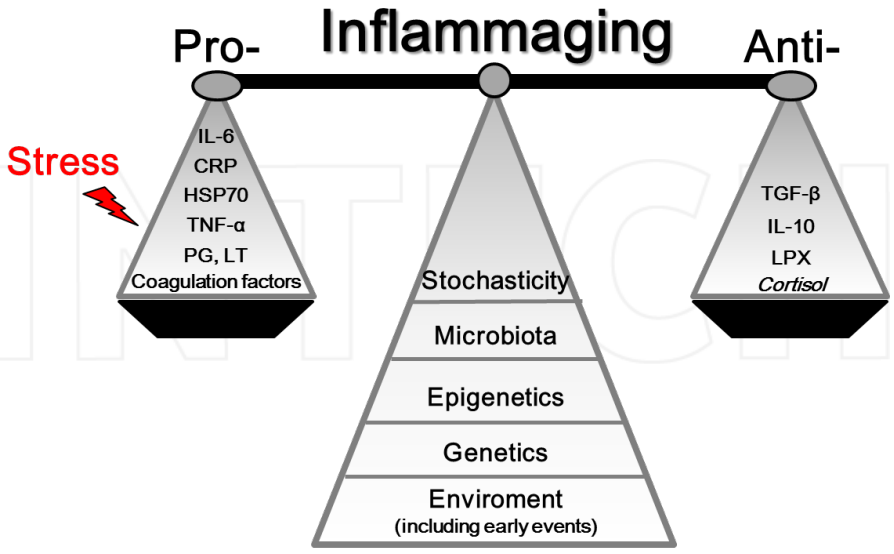

Figure 3. The Inflammaging balance. The low, chronic pro-inflammatory status, characterizing aging interacts with genetic/epigenetic/microbiota background and potentially triggers the onset of the most important age-related diseases. The balancing between pro- and anti-inflammatory agents can be modified by external stimuli, such as stress or anti-stress (diet and anti-inflammatory compounds). PG: prostaglandins; LT: leukotrienes, LPX: lipoxins

Author details

Patrizia d'Alessio[1], Rita Ostan[2], Miriam Capri[2] and Claudio Franceschi[2]

1 University Paris Sud-11 and Biopark Cancer Campus 1, Villejuif, France

2 Department of Experimental, Diagnostic and Specialty Medicine, University of Bologna, Italy

References

[1] Agnoletti V, Ansaloni L, Catena F, Chattat R, De Cataldis A, Di Nino G, Franceschi C, Gagliardi S, Melotti RM, Potalivo A, Taffurelli M. Postoperative Delirium after elective and emergency surgery: analysis and checking of risk factors. A study protocol. BMC Surg. 2005 5:12.

http://dx.doi.org/10.5772/54914

[2] Ansaloni L, Catena F, Chattat R, Fortuna,D, Franceschi C, Mascitti P, Melotti R M. Risk factors and incidence of postoperative delirium in elderly patients after elective and emergency surgery. Br J Surg. 2010 97(2):273-80.

[3] Baggio G, Donazzan S, Monti D, Mari D, Martini S, Gabelli C, Dalla Vestra M, Previato L, Guido M, Pigozzo S, Cortella I, Crepaldi G, Franceschi C. Lipoprotein(a) and lipoprotein profile in healthy centenarians: a reappraisal of vascular risk factors. FASEB J (1998). 12, 433–437.

[4] Barbieri M, Ferrucci L, Ragno E, Corsi A, Bandinelli S, Bonafè M, Olivieri F, Giovagnetti S, Franceschi C, Guralnik J M, Paolisso G. Chronic inflammation and the effect of IGF-I on muscle strength and power in older persons. Am J Physiol Endocrinol Metab. 2003 284(3):E481-7.

[5] Beloosesky Y, Hendel D, Weiss A, Hershkovitz A, Grinblat J, Pirotsky A, Barak V. Cytokines and C-reactive protein production in hip-fracture-operated elderly patients. J Gerontol A Biol Sci Med Sci. 2007 62(4):420-6.

[6] Berer K, Mues M, Koutrolos M, Rasbi Z A, Boziki M, Johner C, Wekerle H, Krishnamoorthy G. Commensal microbiota and myelin autoantigen cooperate to trigger autoimmune demyelination. Nature. 2011 479(7374):538-41.

[7] Biagi E, Nylund L, Candela M, Ostan R, Bucci L, Pini E, Nikkilä J, Monti D, Satokari R, Franceschi, C, Brigidi, P, & De Vos, W. Through ageing, and beyond: gut microbiota and inflammatory status in seniors and centenarians. PLoS One. (2010) 5(5):e10667. Erratum in: PLoS One. 2010;5(6).

[8] Biagi E, Candela M, Fairweather-tait S, Franceschi C, Brigidi P. Aging of the human metaorganism: the microbial counterpart. Age (Dordr). 2012 34(1):247-67.

[9] Bisson JF, Menut C, d'Alessio P. New pharmaceutical interventions in aging. Rejuvenation Research. 2008; Vol. 11, No. 2: 399-407.

[10] Capri M, Monti D, Salvioli S, Lescai F, Pierini M, Altilia S, Sevini F, Valensin S, Ostan R, Bucci L, Franceschi C. Complexity of anti-immunosenescence strategies in humans. Artif Organs. (2006).;30(10):730-42.

[11] Caruso C, Franceschi C, Licastro F. Genetics of neurodegenerative disorders. N Engl J Med. (2003).;349(2):193-4.

[12] Cerejeira J, Nogueira V, Luís P, Vaz-serra A, Mukaetova-ladinska E B. The cholinergic system and inflammation: common pathways in delirium pathophysiology. J Am Geriatr Soc. (2012).; 60(4):669-75.

[13] Cevenini E, Caruso C, Candore G, Capri M, Nuzzo D, Duro G, Rizzo C, Colonna-Romano G, Lio D, Di Carlo D, Palmas MG, Scurti M, Pini E, Franceschi C, Vasto S. Age-related inflammation: the contribution of different organs, tissues and systems. How to face it for therapeutic approaches. Curr Pharm Des. (2010). 16(6), 609-618(10)

[14] Chandola T, Britton A, Brunner E, Hemingway H, Malik M, Kumari M, Badrick E, Kivimaki M, Marmot M. Work stress and coronary heart disease: what are the mechanisms? Eur Heart J. (2008).

[15] Cooper-Knock J, Kirby J, Ferraiuolo L, Heath P R, Rattray M, Shaw P J. Gene expression profiling in human neurodegenerative disease. Nat Rev Neurol. 2012 8(9), 518-30.

[16] d'Alessio P, Endothelium as pharmacological target. Curr Op Invest Drugs. 2002; Vol 2, No. 12:1720-1724.

[17] d'Alessio P. Aging and the endothelium. Exp Gerontol. 2004; 39(2):165-171.

[18] d'Alessio P. New Anti-Inflammatory Molecule AISA 5203-L promotes adaptive strategies in cell aging. in: Adaptation Biology and Medicine, Cell Adaptations and Challenges, eds. Wang P, Kuo CH, Takeda N, Singal PK. Narosa Publishing House Ltd. 2011 Vol 6: 369-378.

[19] d'Alessio P, Bennaceur-Griscelli A, Ostan R and Franceschi C. New Targets for the Identification of an Anti-Inflammatory Anti-Senescence Activity. in: Senescence, ISBN 978-953-308-28-6 In-Tech open access. 2012 chap.2: 647-666.

[20] d'Alessio P, Ostan R, Valentini L, Bourdel-Marchasson I, Pinto A, Buccolini F, Franceschi C, Bené MC. Gender differences in response to dietary supplementation by Orange Peel Extract in elderly people in the RISTOMED study: impact on Quality of Life and inflammation. PRIME. 2012 July/August:30-37.

[21] Di Bona Di Plaia A, Vasto S, Cavallone L, Lescai F, Franceschi C, Licastro F, Colonna-Romano G, Lio D, Candore G, Caruso C. Association between the interleukin-1β polymorphisms and Alzheimer's disease: a systematic review and meta-analysis. Brain Res Rev. (2008). 59(1), 155-63.

[22] Di Bona D, Candore G, Franceschi C, Licastro F, Colonna-Romano G, Cammà C, Lio D, Caruso C. Systematic review by meta-analyses on the possible role of TNF-α polymorphisms in association with Alzheimer's disease. Brain Res Rev. (2009). 61(2), 60-8.

[23] Esler M, Eikelis N, Schlaich M, Lambert G, Alvarenga M, Kaye D, Osta A, Guo L, Barton D, Pier C, Brenchley C, Dawood T, Jennings G, Lambert E. Human sympathetic nerve biology: parallel influences of stress and epigenetics in essential hypertension and panic disorder. Ann NY Acad Sci. (2008). 1148, 338-48.

[24] Fagiolo U, Cossarizza A, Scala E, Fanales-Belasio E, Ortolani C, Cozz, E, Monti D, Franceschi C, Paganelli R. Increased cytokine production in mononuclear cells of healthy elderly people. Eur J Immunol (1993). 23(9), 2315-2378.

[25] Franceschi C, Monti D, Scarfí M R, Zeni O, Temperani P, Emilia G, Sansoni P, Lioi M B, Troiano L, Agnesini C et al. Genomic instability and aging. Studies in centenarians (successful aging) and in patients with Down Syndrome (accelerated aging). Ann N Y Acad Sci. (1992). 663, 4-16.

http://dx.doi.org/10.5772/54914

[26] Franceschi C, Monti D, Sansoni P, Cossarizza A. The immunology of exceptional individuals: the lesson of centenarians. Immunol Today (1995). 16(1), 12-16.

[27] Franceschi C, Passeri M, De Benedictis G, Motta L. Immunosenescence. Aging (Milano) 1998 10: 153–154.

[28] Franceschi C, Bonafè M, Valensin S, Olivieri F, De Luca M, Ottaviani E, De Benedictis G. Inflammaging. An evolutionary perspective on immunosenescence. Ann N Y Acad Sci. 2000 Jun;908:244-54.

[29] Franceschi C, Valensin S, Bonafè M, Paolisso G, Yashin A. I, Monti D, De Benedictis G. The network and the remodeling theories of aging: historical background and new perspectives. Exp Gerontol. 2000; 35: 879–896.

[30] Franceschi C, Valensin S, Lescai F, Olivieri F, Licastro F, Grimaldi L. M, Monti D, De Benedictis G, Bonafè M. Neuroinflammation and the genetics of Alzheimer's disease: the search for a pro-inflammatory phenotype. Aging (Milano). (2001).;13(3):163-70.

[31] Franceschi C, Capri M, Monti D, Giunta S, Olivieri F, Sevini F, Panourgia M P, Invidia L, Celani L, Scurti M, Cevenini E, Castellani G C, Salvioli S. Inflammaging and anti-inflammaging: a systemic perspective on aging and longevity emerged from studies in humans. Mech Ageing Dev. (2007). 128(1), 92-105.

[32] Franceschi C. Inflammaging as a major characteristic of old people: can it be prevented or cured? Nutr Rev. 2007 65: S173-6.

[33] Gentilini D, Mari D, Castaldi D, Remondini D, Ogliari G, Ostan R, Bucci L, Sirchia S M, Tabano S, Cavagnini F, Monti D, Franceschi C, Di Blasio A M, Vitale G. Role of epigenetics in human aging and longevity: genome-wide DNA methylation profile in centenarians and centenarians' offspring. Age (August 2012).

[34] Hampel H, Prvulovic D, Teipel S, Jessen F, Luckhaus,C, Frölich L, Riepe M W, Dodel R, Leyhe T, Bertram L, Hoffmann W, Faltraco F. German Task Force on Alzheimer's Disease (GTF-AD). The future of Alzheimer's disease: the next 10 years. Prog Neurobiol. (2011). 95(4), 718-28.

[35] Larbi A, Franceschi C, Mazzatti D, Solana R, Wikby A, Pawelec G. Aging of the immune system as a prognostic factor for human longevity. Physiology (Bethesda). (2008). 23, 64-74.

[36] Lescai F, Pirazzini C, Agostino D, Santoro G, Ghidoni A, Benussi R, Galimberti L, Federica D, Marchegiani E, Cardelli F, Olivieri M, Nacmias F, Sorbi B, Bagnoli S, Tagliavini S, Albani F, Martinelli D, Boneschi,F, Binetti G, Forloni G, Quadri P, Scarpini E, Franceschi C. Failure to replicate an association of rs5984894 SNP in the PCDH11X gene in a collection of 1,222 Alzheimer's disease affected patients. J Alzheimer's Dis. (2010). 385-8.

[37] Lescai F, Chiamenti A M, Codemo A, Pirazzini C, Agostino D, Ruaro G, Ghidoni C, Benussi R, Galimberti L, Esposito D, Marchegiani F, Cardelli F, Olivieri M, Nacmias F,

Sorbi B, Tagliavini S, Albani F, Martinelli D, Boneschi F, Binetti G, Santoro A, Forloni G, Scarpini E, Crepaldi G, Gabelli C, Franceschi C. An APOE haplotype associated with decreased ε4 expression increases the risk of late onset Alzheimer's disease. J Alzheimers Dis. (2011). 24(2), 235-45.

[38] Licastro F, Grimaldi L M, Bonafè M, Martina C, Olivieri F, Cavallone L, Giovanietti S, Masliah E, Franceschi C Interleukin-6 gene alleles affect the risk of Alzheimer's disease and levels of the cytokine in blood and brain. Neurobiol Aging. (2003).24(7):921-6.

[39] Listì F, Candore G, Balistreri C R, Grimaldi M P, Orlando V, Vasto S, Colonna-Romano G, Lio D, Licastro F, Franceschi C, Caruso,C. Association between the HLA-A2 allele and Alzheimer disease. Rejuvenation Res. (2006). 9(1), 99-101.

[40] Lockrow JP, Fortress AM, Granholm AC. Age-related neurodegeneration and memory loss in Down Syndrome. Curr Gerontol Geriatr Res. 2012 463909.

[41] McGeer EG, McGeer PL. The importance of inflammatory mechanisms in Alzheimer disease. Exp Gerontol. 1998 Aug;33(5):371-8.

[42] May L, van den Biggelaar A H, van Bodegom D, Meij H J, de Craen A J, Amankwa J, Frölich M, Kuningas M, Westendorp R G. Adverse environmental conditions influence age-related innate immune responsiveness. Immun Ageing. 2009 30:6-7.

[43] Mishto, M, Bellavista, E, Santoro, A, Stolzing, A, Ligorio, C, Nacmias, B, Spazzafumo, L, Chiappelli M, Licastro F, Sorbi S, Pession A, Ohm T, Grune T, Franceschi C. Immunoproteasome and LMP2 polymorphism in aged and Alzheimer's disease brains. Neurobiol Aging. (2006). Jan;, 27(1), 54-66.

[44] Mishto M, Ligorio C, Bellavista E, Martucci M, Santoro A, Giulioni M, Marucci G, Franceschi C. Immunoproteasome expression is induced in mesial temporal lobe epilepsy. Biochem Biophys Res Commun. (2011). 408(1), 65-70.

[45] Mrak R E, Sheng J G, Griffin W S. Glial cytokines in Alzheimer's disease: review and pathogenic implications. Hum Pathol. (1995). 26(8), 816-23.

[46] Ostan R, Bucci L, Capri M, Salvioli S, Scurti M, Pini E, Monti D, Franceschi C. Immunosenescence and immunogenetics of human longevity. Neuroimmunomodulation. (2008). 15(4-6), 224-240.

[47] Passeri G, Pini G, Troiano L, Vescovini R, Sansoni P, Passeri M, Gueresi P, Delsignore R, Pedrazzoni M, Franceschi C. Low vitamin D status, high bone turnover, and bone fractures in centenarians. J Clin Endocrinol Metab. (2003). 88(11),5109-15.

[48] Santoro A, Balbi V, Balducci E, Pirazzini C, Rosini F, Tavano F, Achilli A, Siviero P, Minicuci N, Bellavista E, Mishto M, Salvioli S, Marchegiani F, Cardelli M, Olivieri F, Nacmias B, Chiamenti A M, Benussi L, Ghidoni R, Rose G, Gabelli C, Binetti G, Sorbi S, Crepaldi G, Passarino G, Torroni A, Franceschi C. Evidence for sub-haplogroup h5 of mitochondrial DNA as a risk factor for late onset Alzheimer's disease. PLoS One. (2010). 5(8):e12037.

[49] Scola L, Licastro F, Chiappelli M, Franceschi C, Grimaldi L M, Crivello A, Romano G, Candore,G, Lio D, Caruso C. Allele frequencies of +874T -A single nucleotide polymorphism at the first intron of IFN-gamma gene in Alzheimer's disease patients. Aging Clin Exp Res. (2003). 15(4), 292-5.

[50] Shibeshi W A, Young-Xu,Y, Blatt C M. Anxiety worsens prognosis in patients with coronary artery disease.J Am Coll Cardiol. (2007). 49(20)

[51] Van Gool W A, van de Beek D, Eikelenboom P Systemic infection and delirium: when cytokines and acetylcholine collide. Lancet. (2010). 375(9716), 773-5.

[52] Vasto S, Candore G, Duro G, Lio D, Grimaldi M P, Caruso C. Alzheimer's disease and genetics of inflammation: a pharmacogenomic vision. Pharmacogenomics. 2007; 8: 1735-45.

[53] Vasto S, Candore G, Listì F, Balistreri C R, Colonna-Romano G, Malavolta M, Lio D, Nuzzo D, Mocchegiani E, Di Bona D, Caruso C. Inflammation, genes and zinc in Alzheimer's disease. Brain Res Rev. (2008). 58(1), 96-105.

[54] Vescovini R, Biasini C, Fagnoni F F, Telera A R, Zanlari L, Pedrazzoni M, Bucci L, Monti D, Medici M C, Chezzi C, Franceschi C, Sansoni P. Massive load of functional effector CD4+ and CD8+ T cells against cytomegalovirus in very old subjects. Journal of Immunology (Baltimore, Md: 1950). 2007; 179 (6):4283-4291.

[55] Vescovini R, Biasini C, Telera A R, Basaglia M, Stella A, Magalini F, Bucci L, Monti D, Lazzarotto T, Dal Monte P, Pedrazzoni M, Medici M C, Chezzi C, Franceschi C, Fagnoni FF, Sansoni P. Intense antiextracellular adaptive immune response to human cytomegalovirus in very old subjects with impaired health and cognitive and functional status. Journal of Immunology (Baltimore, Md: 1950) 2010:184 (6):3242-3249.

[56] Weksler M E, Pawelec G, Franceschi C. Immune therapy for age-related diseases.Trends Immunol. (2009). 30(7), 344-50.

[57] Zhang Q, Raoof M, Chen Y, Sumi,Y, Sursal T, Junger W, Brohi K, Itagaki K, Hauser C J. Circulating mitochondrial DAMPs cause inflammatory responses to injury. Nature. 2010 Mar 4;464(7285):104-7.

[58] Zhang DH, Marconi A, Xu LM, Yang CX, Sun GW, Feng XL, Xu SM, Ling CQ, Qin WZ, Uzan G, and d'Alessio P. Tripterine, inhibits the expression of adhesion molecules in activated endothelial cells. Journ Leuko Biol. 2006; vol 80:309-319.

INTECH