Chapter 18
Inflammaging and Its Role in Ageing and Age-Related Diseases

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Abbreviations

IS	Immune system
NES	Neuro-endocrine system
POMC	Pro-opiomelanocortin
BA	Biogenic amines
NOS	Nitric oxide synthase
ACTH	Adrenocorticotrophic hormone
CRH	Corticotrophin-releasing hormone

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Lay Summary The growing number of elderly and the increase in age-related diseases are pressing issues for medicine and public health. Inflammaging (i.e. a chronic, low-grade inflammatory status that occurs during ageing) represents a common mechanism to the vast majority of age-related disorders. Accordingly, inflammaging and inflammation are strategic targets for prevention and treatment of these conditions. Inflammation and stress response are the result of a complex network of interactions between genes and environment. They are ancestrally interconnected and can be considered a most ancient and evolutionary-conserved maintenance/repair mechanism owing to its crucial capability to cope with and neutralize damaging agents. Evolutionary adaptation is thus treated as a "plural model", according to Ingold [1]. In this chapter, we illustrate the evolution of inflammation/stress response, the role of inflammation during ageing, including what we propose to call "immunological biography", which includes all the immune adaptive mechanisms that occur lifelong. We contextualize inflammaging within a human eco-anthropological perspective to better understand the role that changes occurred in the human environment in the last 200 years played in the demographic explosion of the elderly population. This comprehensive view on inflammation and inflammaging can have a far-reaching beneficial impact in the medical field and, in particular, could represent a strong, evolutionary-based conceptual framework to identify the most effective strategies (e.g. dietary interventions) to slow ageing and avoid/postpone age-related pathologies.

18.1 Introduction

Population ageing and age-related diseases are pressing issues for modern healthcare systems. Accumulating evidence suggests that ageing and the major age-related diseases are characterized by a chronic low-grade inflammation, referred to as inflammaging [2] to indicate its central role in the ageing process. High levels of inflammatory markers such as IL-6 and others are the powerful predictors of mortality and morbidity [3]. The major sources of inflammatory stimuli with age and inflammaging and are as follows: (1) endogenous self-derived debris that accumulate during ageing as a consequences of an increased production of and a reduced clearance of dead cells and damaged organelles, (2) *senescent cells* and cells which harbour a DNA damage and are capable of a "*DNA damage response*" that secrete a variety of pro-inflammatory cytokines that alter the microenvironment or tissues and organs, (3) persistent infections that accelerate immunosenescence, (4) products of the gut microbiota that undergo profound changes during ageing and (5) increasing activation of the coagulation system [4]. Thus, we have proposed the new word *garbaging* to indicate the exogenous and endogenous inflammatory stimuli that, as a whole, increase progressively with age and trigger inflammaging.

In the medical field, inflammation is often considered a pathological process that contributes to diseases, but from a biological point of view, inflammation has to be

considered a fundamental process crucial for survival and an adaptive/protective response to damaging agents/stressors. Indeed, as first suggested by Metchnikoff, inflammation is an evolutionary-conserved "positive" phenomenon, enabling the body to react to and neutralize foreign damaging agents. It can be predicted that the capability to mount a strong inflammatory process can contribute to fitness and survival at younger ages (development and reproduction) and that genetic variants that codes for this trait have been positively selected for.

In this chapter, we will first describe the evolution of stress response to understand the evolutionary mechanisms that lead to inflammation. The stress response is at the heart of the matter to understand the physiological phenomena of immunosenescence and inflammaging within an evolutionary context. Then, we will described the pool of molecules involved in inflammatory pathway that are common to different systems (NES and IS). This pool of molecules, that is well conserved during evolution, reduces the semantic boundaries between inflammation, stress response and immune response. The bow tie architecture revealed how the organisms/individuals could mediate between the wide range of signals originating from the environment and the limited pool of effector molecules. The antagonist pleiotropy theory helps us in understanding how certain genetic characteristics and biological responses could exert a beneficial effect at young age and a deleterious effect later in life (and vice versa), and we surmise that this scenario can explain the double and apparently contradictory (beneficial and deleterious) role of inflammation lifelong. The beneficial effects of inflammation early in life and in adulthood become a detrimental/damaging process late in life, in a period where positive selection fades. However, inflammation and inflammaging are likely not the only cause of an unhealthy ageing, and the "two-hits" theory was proposed to explain such a complex outcome. Then, we will describe the link between inflammation and environment, introducing the concept of "immunological biography". We and others [5] suggest that the inflammatory response in humans has been optimized through evolution to cope with an environment that has been largely modified in the last ten thousand years and particularly in the last two hundred years and that in most cases does not exist anymore. Here, the variety of cultural habits of human beings will be discussed, to connect inflammation and inflammaging with cultural and anthropological settings, with particular attention to the effects of transitions.

In conclusion, it is fundamental to posit this intricate scenario in a broader context both at the macro- and micro-evolutionary level. Using the well-defined framework of evolutionary biology could be crucial to explain in depth the phenomena observed by clinicians, such as inflammaging and to identify public health and individual strategies to reduce the progressive age-related increase of inflammatory process that constitute an inherent characteristic of major chronic age-related. We suggest nutrition and dietary interventions as important tools for intervention to slow down ageing rate of several domains (cognitive, cardiovascular, immunological and among others).

18.2 Research Findings

18.2.1 The Evolution of Stress Responses

The stress response is at the heart of the physiological phenomena of immunosenescence and inflammaging in an evolutionary context. A brief outline is needed to understand the meaning and the complexity of stress response. In the past, changes in the immune system (IS) have often been proposed to be the direct consequences of the activation of the neuro-endocrine system (NES) after a stress signal, and the IS has often been suggested to be a target of the stress response itself.

However, about 15 years ago, new hypotheses and data on the influence of the IS on the NES emerged, leading to something of a conceptual revolution in the field. The idea that the IS was not only a target of the stress response but also an active component of this response began spreading. It is now accepted that a stress response can be induced (1) by cognitive stimuli through the five senses and (2) by non-cognitive stimuli that may impact the IS. An example of the latter is illustrated by antigens, which might be considered as stressors from an evolutionary point of view [6]. Several studies showed that antigens, like stressors, are capable of inducing an increase in the blood concentration of ACTH and corticosterone, and a concomitant increase of the overall electrical activity of neurons. Furthermore, antigens and stressors are able to activate a complex network of common responses, which include chemotaxis, phagocytosis, the release of biogenic amines (BA) and others. This is the main reason why antigens can be considered as one particular type of a broader category of stressors. The interaction between the IS and the NES is also supported by various data, including the possibility of neuropeptides and hormones to bind to receptors on immune cells (lymphocytes). It follows that the IS may be considered as a "*sensory organ*" which alerts the organism of those danger signals coming from the inside (i.e. antigens) and cannot be perceived by the classical five senses, as already hypothesized by Blalock [7].

The stress response is an adaptive mechanism that has played a key role for the survival of species, as demonstrated by the fact that it is a highly conserved mechanism from a phylogenetic point of view. Across our evolutionary history, while the structural and hierarchical organization of the immune–neuro-endocrine system has changed, the pool of effector molecules remained largely conserved [8]. From invertebrates to humans, the cellular response to a number of stressors appears to be highly maintained and involves the up-regulation of a variety of evolutionary-conserved mediators, such as oxygen-free radicals, nitric oxide (NO), pro-inflammatory cytokines (IL-1, IL-6, TNFα), propiomelanocortin-derived peptides (ACTH, β-endorphin, α-MSH), steroids (cortisol), BA (noradrenaline, adrenaline, dopamine) and neuropeptides (CRH) [2]. These observations formed the basis for the hypothesis of "*a common origin of the immune and neuro-endocrine systems*" [6, 8]. Macrophages, i.e. the cells with phagocytic activity first described by Metchnikoff and present from invertebrates to man, play a primary role in defence mechanisms and are able to release all the above-mentioned molecules. Thus, we

argued that this cell could be considered the eyewitness of the common evolutionary origin of the immune and neuro-endocrine systems. For this reason, we argued that the macrophage is the best candidate to play a central role in inflammaging, a condition linked to the chronic activation of the macrophage with age ("*macroph-aging*") [2]. We also argued that owing to the capability of the macrophage to secrete such a variety of immune and neuro-endocrine molecules, this cell could be considered a sort of "*mobile immune brain*". The link between macrophages and inflammation is particularly striking in the fat tissue. The visceral fat that increases with age is a source of inflammation as this tissue tends to become infiltrated of macrophages that, in turn, produce large amounts of pro-inflammatory cytokines.

The increasing of complexity observed through evolution, it is likely to be linked to a host–pathogen co-evolution. In this complex system, an anatomical subdivision between the immune and the neuro-endocrine systems as well as a new organization at the level of organs and systems (thymus, hypothalamus, pituitary and adrenal gland) and new uses of the above-mentioned "old" conserved molecules emerged during evolution. In conclusion, a progressive increase in complexity is the main difference between vertebrates and invertebrates, while the immune–neuro-endocrine responses continue to use the same pool of basic molecular mediators such as POMC-products, NOS, CRH and cytokines, which are still fundamental for the maintenance of body homeostasis (Fig. 18.1). Thus, the NES and the IS are deeply

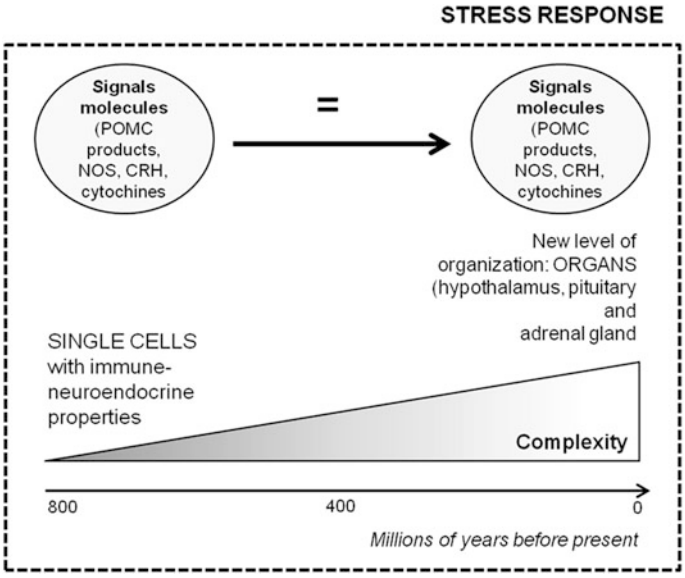

Fig. 18.1 The ancestral response to stress is exerted by a multifunctional cell called "the mobile immune brain" to indicate its immune–neuro-endocrine functions. During the evolution of vertebrates, moving towards a higher level of complexity, the same immune–neuro-endocrine properties have been organized in new interconnected organs (thymus, pituitary adrenal gland, etc.)

interconnected by a bidirectional communication system [7, 9]. Within such a conceptual evolutionary framework, the distinction between "hormone", "neurotransmitter" and "cytokine" is more blurred and less defined than previously assumed.

The pool of molecules shared by the IS and the NES—cytokines, CRH, ACTH, BA, NO and glucocorticoids—plays a major role in inflammation as well as in natural immunity, supporting the view that natural immunity, inflammation and the stress response can be considered as highly linked and connected processes. It is clear that a limited pool of molecules has to react to many input signals. The organism needs to be able to dynamically respond to an enormous amount of ecologically defined environmental stimuli that could potentially constitute a danger for the organism itself (input signals) [10]. Concomitantly, a high variety of fine-tuned responses are required in order to ensure survival (output signals). These complex input and output signals are mediated by the above-mentioned limited pool of molecules (which may be conceived as a kind of "compressed" information network). It has been suggested that these processes could be represented by the bow tie architecture (Fig. 18.2), as originally proposed by Csete and Doyle [11]. The advantage of this architecture is to save on the energy costs associated with the stimulation of the neuro-endocrine and/or the IS, thereby reducing and minimizing the pool of mediators involved. This process is closely dependent on the environment, the context in which the body is living and therefore this type of phenomena is often referred to as ecoimmunology [12].

18.2.2 Inflammaging, Immunosenescence and the Antagonistic Pleiotropy Theory

From an evolutionary perspective, *immunosenescence* could be considered as the progressive impairment of the IS (at the level of cells, organs and system) which

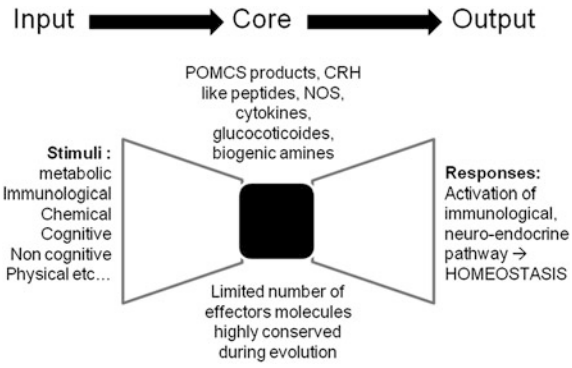

Fig. 18.2 Bow tie architecture. The highly conserved pool of molecules involved in natural immunity, inflammation and the stress response constitutes the core of this architecture. The bow tie architecture ensures that the high number of stimuli is compressed, but at the same time allows a high variety of responses in order to maintain the homeostasis of the organism. Figures adapted from [12]

occurs with age. It is important to note that the ancestral innate immunity is highly preserved, while the recent adaptive immunity (lymphocyte-centred) deeply deteriorates during ageing [13]. T cell reactivity indicates that the body is able to react to antigenic load even at high and extreme age, but at the same time, the response tends to run out with ageing. The evidence is that during ageing an accumulation of clones of memory cells that fill the "immunological space" occurs, while naive T cells are much less represented, contributing to the reduced response to new antigens/stressors, as observed during vaccination towards a variety of bacteria and viruses [13]. If antigens are compared to stressors, immunosenescence could be considered to be the result of the continuous attrition caused by the exposure to biological (bacteria, viruses, parasites and xenobiotic) and non-biological (life events, emotional and socio-economical stress) stressors lifelong.

Age-related diseases and longevity could be conceptualized as the result of the adaptation of the body to continuous stimuli and stressors occurring over time. Age remodelling is a universal physiological process that occur in all individuals and represents the basis of the "*remodelling theory of ageing*" [14, 15] proposed in 1995 to conceptualize the results emerged from studies on human immunosenescence. This hypothesis suggests that immunosenescence is the result of the continuous adaptation of the body to the deteriorative changes occurring over time. The continuous stimulation by antigens/stressors leads to the decline/exhaustion of the adaptive IS and concomitantly to the increased pro-inflammatory status (innate immunity) that we indicated as inflammaging. Healthy old subjects and centenarians could be considered as those individuals with the best ability to adapt to damaging agents and immunological and non-immunological stressors [15] by setting up a variety of anti-inflammatory responses capable of neutralizing, at least in part the detrimental effects of inflammaging [16].

From an evolutionary and ecological perspective, each individual is characterized by an ability to cope with environmental insults, and this ability may move the effect of stress towards *hormesis*. "Hormesis refers to the beneficial effects of a treatment that at a higher intensity is harmful. In one form of hormesis, sublethal exposure to stressors induces a response that results in stress resistance. The principle of stress-response hormesis is increasingly finding application in studies of ageing, where hormetic increases in life span have been seen in several animal models" [17]. Thus, in order to understand the subtle shift from a harmful outcome to a hormetic beneficial effect of a given stimulus, a characterization of the environment where an individual is embedded is mandatory. Environment is expressed by local practices (i.e. "concrete matrixes" for a set of specific skills) and can be understood as a silent and incorporated knowledge within a specific context [18]. The term "dwelling" is used in cultural anthropology in general and by Ingold in particular to illustrate how human beings are always "embedded" in their experience of being with a specific body within a specific environment.

This ability to adapt to the surrounding environment through a pro-inflammatory status and then to deal with the associated stress is presumably a complex trait with a genetic and socio-cultural component. It is also presumed that genotypes that can generate a strong inflammatory response have been positively selected [19]. From

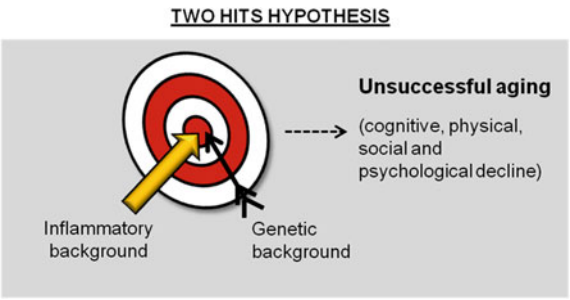

Fig. 18.3 The two-hits hypothesis of inflammaging. A strong inflammatory background and a genetic make-up not apt to counteract external or internal stressors are the two conditions that lead to unhealthy ageing

an evolutionary perceptive, the framework just described can be understood by invoking the antagonistic pleiotropy theory, first suggested by Williams in 1957 [20–23]. This theory suggests that many of the genes that have deleterious effects later in life may be favoured by natural selection because those same genes are associated with beneficial effects at a young age. Ageing is thus thought to have evolved as the result of optimizing fitness early in life. Accordingly, it can be predicted that inflammatory genes have been positively selected because they contributed to the survival of individuals, at least until they attain reproductive age [19]. A two-hits theory was proposed to better explain this phenomenon (Fig. 18.3): the first hit is constituted by the inflammatory background, and a second hit is necessary for the onset of age-related diseases. The second hit can be identified in the absence of robust gene variants and/or the presence of frail gene variants.

18.2.3 Immunological Biography and Socio-Cultural Life Histories: A Case Study

The study of what the body recognizes as "self" or as a stressor is very important. The attempt to understand the immune response in an evolutionary perspective leads to a reappraisal of the concept of the *immunological self*. Indeed, an abstract and well-established dichotomy between self and non-self is simplistic, and to reduce the concept of the immunological self to a fixed entity within a static scenario is misleading. It is better to adopt an integrated dynamic approach (the immunological biography), where the immunological self can undergo continuous changes in a personalized space- and time-dependent manner [24]. All the processes involved in the immune response are and have been shaped by, at least, two dimensions: (1) the spatial and ecological dimension constituted by the relations between human beings and their environment, according to the geography and history of the populations to which they belong (nutrition, climate, lifestyle, etc.) and (2) the temporal dimension since each individual is the result of a lifelong process of adaptation to the biological and non-biological (cultural/anthropological) determinants of his/her environment(s) (Fig. 18.4).

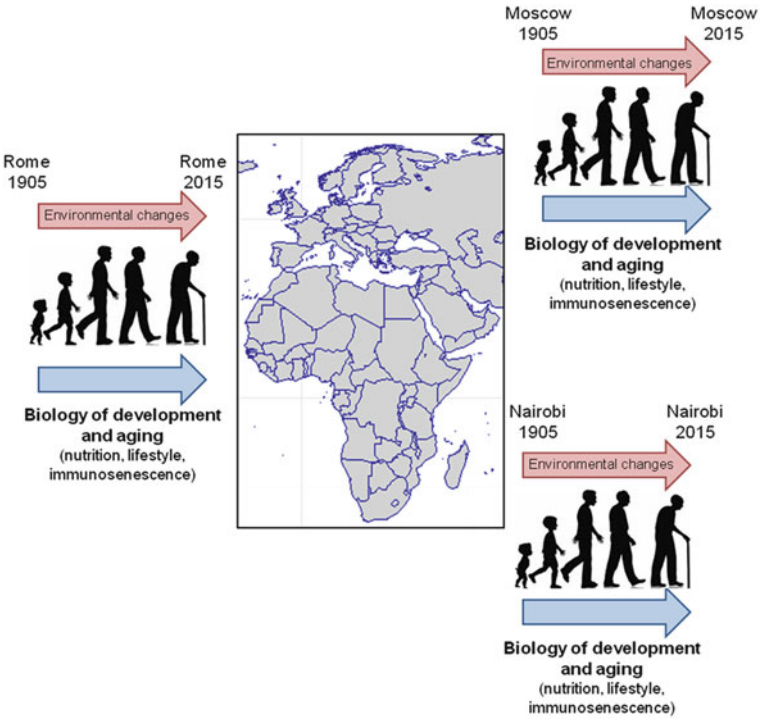

Fig. 18.4 Environmental and individual changes in space and time shape the immunological biography. Inflammation and the stress response are complex processes that must be analysed as a whole: an individual undergoes a lot of changes during development, adulthood and ageing. These changes could include a physiological dimension (nutrition, lifestyle) as well as a pathological one (infection, diseases). Moreover, individuals live in environments that have changed according to past migrations, adaptation and biodemography, and are changing during an individual's lifetime

Indeed, it is true that each individual constantly changes over time according to the different ages and phases of life (nutrition, school, work, housing, marriage(s), diseases, stress stimuli), concomitantly with changes in the surrounding environment. The environment undergoes profound remodelling during an individual's lifetime, but also in a wider timescale, such as the major changes that have occurred during the period spanning from the Palaeolithic to the Neolithic or the changes that have taken place over the last 200 years. Knowing these significant environmental modifications allows us to understand the conditions in which humans have evolved and adapted. Ultimately, this approach enables us to understand how the cultural and anthropological context may have shaped the human genetic and immunological make-up. If we consider the life of an individual, for example a living centenarian, it is likely that during his/her life, a very profound reshaping of the social and cultural scenario occurred.

In more general terms, the industrialization process, which started about 250 years ago in Europe has led to rapid and extreme changes in the social, biotic

and abiotic environments. Epidemiological studies generally identify two main transitions during the history of modern populations. The first concerns the transition from Palaeolithic (200,000 years ago) to Neolithic times (10,000 years ago), from a subsistence mode based mainly on hunting and gathering to a diversification of subsistence modes, including pastoralism, horticultural and agriculture [25, 26]. In populations relying on large-scale agriculture, sedentarism and greater contact with animals have increased the risk of infection via the oro-faecal route. With the organization in small cities (about 3000 years ago), the incidence of communicable diseases (such as influenza and mumps) has significantly increased to become endemic. The second major epidemiological transition took place at the beginning of 1900. This transition indicates a shift from the rural small cities towards a more organized idea of industrialized cities, and hygiene behaviour itself changed dramatically in the West (clean and chlorinated water, soaps, detergents, antibiotics, etc). These changes have greatly reduced the rate of death from infectious diseases, placing the chronic and degenerative diseases at the first place among the leading causes of death in the developed world [27, 28].

The picture is further complicated by population genetics, that is, the result of biodemographic dynamics and adaptations characterizing the different history of human populations. The immunological biographies, as fluid, dynamic and malleable entities, need to be rethought and reconceptualized in relation with socio-cultural and anthropological aspects, and an ethnographic example is proposed below, regarding a population we have direct experience of and we have thoroughly studied from a biological, cultural and anthropological point of view [29, 30].

The population here examined is that of the Wichí in the Argentine Chaco. Traditionally hunters, fishers and gatherers, homogeneous in their social and political subdivision and organized in bands, nowadays they are 50,419 (2010 Census) in the Chaco region, and about 3500 in the Misión Nueva Pompeya village, where a series of ethnographical surveys have been carried out since 2004 [30, 31]. Up to the mid-nineteenth century, the Wichí of the Argentine Chaco engaged in their traditional activities which they carried out following the rhythm of the seasons and consequently practicing a regular semi-nomadic lifestyle. From the mid-nineteenth century, though, salaried jobs on the sugar cane and later cotton plantations, as well as the creation of missions (both Catholic and Anglican) on their territories, slowly but inevitably led them to become sedentary; this sedentary lifestyle was then reinforced by ever increasing schooling. The indigenous populations were to be educated through schools and religion to abandon their ancestral customs (whether religious, economic or political). Indigenous lands have been confiscated by the state, and today, the biggest multinational companies are cultivating soy on these lands (especially in the Salta area) and what is not cultivated has been cleared, falling prey to the animals farmed by the Criollo breeders who have settled in this area together with the Wichí. We are now facing a native population that, although trying to save the integrity of its knowledge (of local flora and fauna, and in general their mythical corpus) lives in an environment that is degraded [32], has changed lifestyle and consequently its nutritional habits [33, 34]. The Wichí no

longer live on the proceeds of hunting and gathering, rather they feed themselves thanks to state-issued pensions, with which they are able to buy most of the food they consume (bread, pasta, flour, corn meal, meat); the balanced, seasonally driven, protein-rich diet has given way to a high-carbohydrate one. Immune responses in this sense are certainly moulded by the environment, by the climate, by local and global policies. Issues relating to identity are also dictated by incidental political and economical convenience. Thus, the ethnic blending between the Wichí and the Criollo often allows them to define as indigenous or Creole according to the needs of the moment [30]. The relationship with one's environment, with one's body (a "rotund" body certainly signals economic wellbeing), with traditional knowledge, the taste of new food and the memory of ancient foods, these are all elements that must be taken into account to understand the answers in cultural and biological terms. What we have very succinctly summarized here has happened very rapidly. The transition undergone by the Wichí has not been neither slow nor gradual, without any of the features of the above-mentioned historical transitions (Palaeolithic/Neolithic). The social and cultural history of the elderly Wichí who have lived the semi-nomadic lifestyle, who experienced the salaried work on the plantations and who today receive state pensions is that of grandparents who today see their children or their grandchildren malnourished and obese: misfits, both from an evolutionary and a cultural and environmental point of view.

This and other examples of social structure (another well-known example is the caste system in India) is of great importance to study inflammation and the stress response because the social structure could easily be linked to the so-called social stress that occurs as a consequence of social confrontation. The importance of social stress for immunology has been clearly demonstrated in studies on fish. Experiments showed that two fish randomly selected from a group sharing the same environment when put into a small aquarium start to combat for establishing hierarchy. After a fighting, one fish emerges as dominant (alpha) and the second as subordinate (beta). The most important observation is that many immunological alterations, due to the stress response, were present only in the beta fish and not in the alpha fish, despite the fact that both fishes experienced the fight. Moreover, only the alpha fish was able to successfully counteract the infection of pathogenic bacteria, while the beta fish succumbed. Thus, every type of intervention to slow down inflammaging and age-related diseases should be planned into a population-context perspective. Strategies that consider the population and the individual dimension can best maximize health benefits, preventing healthcare resources from being wasted.

18.3 Implications for Policy and Practice

Inflammation is a process that is beneficial, and also stress, in a broader sense, can be considered a type of positive/adaptive reaction. What is relevant is the threshold above which an individual is no longer able to cope with inflammatory stimuli and

stressors and inflammaging and its deleterious effects start. This threshold is strictly linked to the concept of immunological biography, depending on social and cultural histories of communities and individuals, and marks the divide between healthy and unhealthy ageing (inflammaging and anti-inflammaging).

Inflammaging must also be contextualized from a population point of view, because the evolutionary history of each population may have shaped the ability to cope with specific stressors (e.g. infectious agents and food) typical of the context and of the specific environment. The study of inflammaging and immunosenescence and the understanding of rearrangements that occur lifelong are often neglected and should be carefully considered to appreciate not only the individual capability to adapt to damaging agents and stressors but also to quantify the whole immunological/stressful load, which is likely critical to explain most of the chronic pathologies which start usually decades before their clinical onset. Therefore, the population genetic structure and evolutionary processes such as selection, drift and migrations should be taken into account in the clinical setting. This is especially true in our century, where globalization and migration are increasing, and people of different ancestry need to cope with environments different from those they were exposed to in early/adult life, and despite a genetic background that might not be the best to cope with the new context. Thus, the concepts of healthy ageing and inflammaging should be analysed as a dynamic and integrated process with the final aim of promoting public health.

Thus, we can argue that a profound link exists between garbaging, inflammaging and the demographic revolution in which humans experienced a more than a doubling of human life expectancy in about 100 years and four generation [35]. During this period, people experienced a decreased rate of inflammaging, due to a decreased production/exposure to external danger signals, such as:

- less microorganisms and "hygienized" environment;
- sanitation;
- better nutrients and better gut microbiota;
- improvement in life conditions of: (1) pregnant women and (2) newborns and children in their first years of life

and to internal/self-generated danger signals such as:

- less cellular and molecular damages as a consequence of (1) less physically and emotionally stressful work, (2) more, comfortable housing, etc.

Thus, the identification of the major sources of inflammaging paves the way for a variety of possible interventions aimed at eliminating and neutralizing the "unnecessary" "excessive" inflammatory stimuli, thus slowing down the rate of inflammaging. This approach has the potential to postpone or even avoid the onset of age-related phenotypes and pathologies altogether instead of one by one. Possible strategies include the following: (1) elimination of senescent cells (2) healthy nutrition (Mediterranean diet) and physical exercise and (3) gut microbiome modulation (Fig. 18.5).

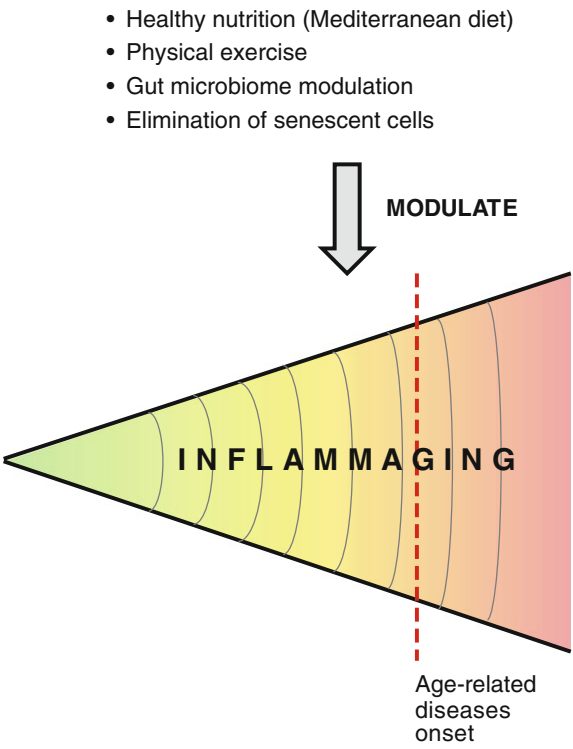

Fig. 18.5 Possible strategies to modulate inflammation and to slow down the rate of inflammaging. This approach has the potential to postpone or avoid the onset of age-related pathologies

Nutritional interventions are expected to give promising results targeted towards some impairments of the aged IS. Such interventions could have a relevant impact on age-related diseases such as diabetes, brain disorders and heart diseases as dietary interventions hit the process of inflammation that is central for many systems. An example of nutritional intervention capable of neutralizing genetic risk factors regards the role of the Mediterranean diet in preventing a specific age-associated disease. A recent study observed that individuals having the TT genotype of the TCF7L2 gene (rs790316), a top ranking gene for type 2 diabetes risk in all the genome-wide association studies (GWAS) reported to date, have also a higher risk of cardio- and cerebrovascular diseases. However, it has been reported that TCF7L2 TT subjects that consumed and where strictly adherent to a Mediterranean diet neutralized completely the risk of stroke, in comparison with TCF7L2 TT who followed a controlled diet [36], suggesting that a healthy diet can counteract a strong genetic risk for an important age-related disease. Evidence that nuts by themselves or as part of a cholesterol-lowering diet may significantly reduce markers of inflammation has also been reported [37–39]. Fibre consumption was inversely associated with inflammatory markers (such as C-reactive protein and interleukin-6) [40] and molecular mechanisms to explain this phenomenon have

been proposed [41]. Curcumin is also a widely studied phytochemical which has a variety of anti-inflammatory activities [42].

Dietary interventions have also the potential to modulate the gut microbiota composition, and targeting the gut microbiota biodiversity could constitute a new therapy for the modulation of inflammation during ageing. Indeed, we showed that a decrease of gut microbiota diversity and of "good" bacteria capable of producing short chain fatty acids (SCFA) and an increase of "bad" bacteria (pathobionts) is a characteristic of the gut microbiota of the elderly, highly correlated with the increase of pro-inflammatory cytokines in the blood [43, 44]. The IS in fact has evolved not only in response to external pathogens but also in response to the gut microbiota, which is also highly connected with many organs including the brain (gut–brain axis). The co-evolution of the gut microbiota with their host has been strongly influenced by the specific diet of the different populations during human evolution since modern humans had to face different environmental challenges (such as food availability, climate changes and pathogen loads) after they moved out of Africa [45]. The diet could be a target for new therapy that aims to modulate the composition of the microbiota to reduce inflammaging.

Glossary

Antagonistic pleiotropy theory of ageing	This hypothesis was first proposed by Williams in 1957 who suggested that a certain gene variant can be beneficial in early life (fitness), while it can become detrimental later in life
Biodemographic dynamics	The analysis of demography within an evolutionary biology context, with particular attention on events that impact on human population structure, such as colonization, migrations and expansion
Ecoimmunology	Discipline that integrates the analysis of the immune system function within animal biology and that considers the interaction between an organism and their ecological environment during evolution
Garbaging	The exogenous and endogenous inflammatory stimuli that, as a whole, increase progressively with age and trigger inflammaging
Heterochronic parabiosis	Parabiosis is an experimental model where two animals, here mice, are joined together surgically to create shared blood circulation. Heterochronic parabiosis indicates that the two animals joined together are of different ages (one old and one young)

Hormesis	Literally from Greek it means "to stimulate", and it indicates the ability of respond positively to low amounts of substances (or stressors) that would otherwise be highly toxic at higher concentrations
IL-6	Interleukin 6 (IL-6) is a cytokine with various biological functions, among which a role in the acute phase response. It is secreted by T cells and macrophages to stimulate the immune response and acts as both a pro-inflammatory and an anti-inflammatory cytokine. It is also a myokine discharged into the bloodstream after muscle contraction and acts to increase the breakdown of fats and to improve insulin resistance
Immunological space	is a metaphor to conceptualize the IS as a whole from a spatial (volume) point of view. During immunosenescence, a progressive accumulation of clones of memory cells tends to fill the "immunological space", reducing the number of other immune cells, such as naïve T cells, and the possibility to respond to new antigens
Inflammaging	Human ageing is characterized by a chronic, low-grade inflammation (high levels of inflammatory cytokines and other inflammatory markers such as C-reactive protein), and this phenomenon has been termed "inflammaging". Inflammaging is a highly significant risk factor for both morbidity and mortality in the elderly, as the vast majority of age-related diseases share an inflammatory pathogenesis

References

1. Cartledge B (1998) Mind, brain, and the environment. Oxford University Press, Oxford/New York
2. Franceschi C, Bonafè M, Valensin S et al (2000) Inflamm-aging. An evolutionary perspective on immunosenescence. Ann NY Acad Sci 908:244–254
3. Morrisette-Thomas V, Cohen AA, Fülöp T et al (2014) Inflamm-aging does not simply reflect increases in pro-inflammatory markers. Mech Ageing Dev 139:49–57. doi:10.1016/j.mad.2014.06.005
4. Franceschi C, Campisi J (2014) Chronic inflammation (inflammaging) and its potential contribution to age-associated diseases. J Gerontol A Biol Sci Med Sci 69:S4–S9. doi:10.1093/gerona/glu057

5. Okin D, Medzhitov R (2012) Evolution of inflammatory diseases. Curr Biol CB 22: R733–R740. doi:10.1016/j.cub.2012.07.029
6. Ottaviani E, Franceschi C (1996) The neuroimmunology of stress from invertebrates to man. Prog Neurobiol 48:421–440
7. Blalock JE (1989) A molecular basis for bidirectional communication between the immune and neuroendocrine systems. Physiol Rev 69:1–32
8. Ottaviani E, Malagoli D, Franceschi C (2007) Common evolutionary origin of the immune and neuroendocrine systems: from morphological and functional evidence to in silico approaches. Trends Immunol 28:497–502. doi:10.1016/j.it.2007.08.007
9. Holzer P, Farzi A (2014) Neuropeptides and the microbiota-gut-brain axis. Adv Exp Med Biol 817:195–219. doi:10.1007/978-1-4939-0897-4_9
10. Kitano H (2007) Towards a theory of biological robustness. Mol Syst Biol 3:137. doi:10.1038/msb4100179
11. Csete M, Doyle J (2004) Bow ties, metabolism and disease. Trends Biotechnol 22:446–450. doi:10.1016/j.tibtech.2004.07.007
12. Ottaviani E, Malagoli D, Capri M, Franceschi C (2008) Ecoimmunology: is there any room for the neuroendocrine system? BioEssays 30:868–874. doi:10.1002/bies.20801
13. Franceschi C, Bonafè M, Valensin S (2000) Human immunosenescence: the prevailing of innate immunity, the failing of clonotypic immunity, and the filling of immunological space. Vaccine 18:1717–1720
14. Franceschi C, Monti D, Barbieri D et al (1995) Immunosenescence in humans: deterioration or remodelling? Int Rev Immunol 12:57–74. doi:10.3109/08830189509056702
15. Franceschi C, Valensin S, Bonafè M et al (2000) The network and the remodeling theories of aging: historical background and new perspectives. Exp Gerontol 35:879–896
16. Franceschi C, Capri M, Monti D et al (2007) Inflammaging and anti-inflammaging: a systemic perspective on aging and longevity emerged from studies in humans. Mech Ageing Dev 128:92–105. doi:10.1016/j.mad.2006.11.016
17. Gems D, Partridge L (2008) Stress-response hormesis and aging: "that which does not kill us makes us stronger". Cell Metab 7:200–203. doi:10.1016/j.cmet.2008.01.001
18. Ingold T (2000) The perception of the environment: essays on livelihood, dwelling and skill. Routledge, London/New York
19. Raj T, Kuchroo M, Replogle JM et al (2013) Common risk alleles for inflammatory diseases are targets of recent positive selection. Am J Hum Genet 92:517–529. doi:10.1016/j.ajhg.2013.03.001
20. Rose M, Charlesworth B (1980) A test of evolutionary theories of senescence. Nature 287:141–142
21. Hughes KA, Alipaz JA, Drnevich JM, Reynolds RM (2002) A test of evolutionary theories of aging. Proc Natl Acad Sci USA 99:14286–14291. doi:10.1073/pnas.222326199
22. Parsons PA (2007) Antagonistic pleiotropy and the stress theory of aging. Biogerontology 8:613–617. doi:10.1007/s10522-007-9101-y
23. Capri M, Salvioli S, Monti D et al (2008) Human longevity within an evolutionary perspective: the peculiar paradigm of a post-reproductive genetics. Exp Gerontol 43:53–60. doi:10.1016/j.exger.2007.06.004
24. Grignolio A, Mishto M, Faria AMC et al (2014) Towards a liquid self: how time, geography, and life experiences reshape the biological identity. Front Immunol 5:153. doi:10.3389/fimmu.2014.00153
25. Ulijaszek SJ (1995) Human energetics in biological anthropology. Cambridge University Press, Cambridge/New York
26. Ulijaszek SJ, Mann N, Elton S (2012) Evolving human nutrition: implications for public health. Cambridge University Press, New York
27. Trevathan W, Smith EO, McKenna JJ (2008) Evolutionary medicine and health: new perspectives. Oxford University Press, New York
28. Banwell C, Ulijaszek S, Dixon J (2013) When culture impacts health—global lessons for effective health research. Elsevier, Amsterdam

29. Moretti E, Castro I, Franceschi C, Basso B (2010) Chagas disease: serological and electrocardiographic studies in Wichì and Creole communities of Misión Nueva Pompeya, Chaco, Argentina. Mem Inst Oswaldo Cruz 105:621–627
30. Sevini F, Yao DY, Lomartire L et al (2013) Analysis of population substructure in two sympatric populations of Gran Chaco. PLoS ONE, Argentina. doi:10.1371/journal.pone.0064054
31. Franceschi ZA, Dasso MC (2010) Etno-grafías: la escritura como testimonio entre los wichí. Corregidor, Buenos Aires
32. Morello JH, Rodriguez AF (2009) El Chaco sin bosques: La Pampa o el desierto del futuro, 1a ed. Orientación Gráfica Editora, Buenos Aires
33. Torres GF, Santoni ME, Romero LN (2007) Los Wichi del Chaco Salteño: ayer y hoy: alimentación y nutrición. Crisol, Salta
34. Franceschi ZA, Peveri V (2014) Raccontare di gusto - Arti del cibo e della memoria in America latina e Africa, ETS
35. Burger O, Baudisch A, Vaupel JW (2012) Human mortality improvement in evolutionary context. Proc Natl Acad Sci USA 109:18210–18214. doi:10.1073/pnas.1215627109
36. Corella D, Carrasco P, Sorlí JV et al (2013) Mediterranean diet reduces the adverse effect of the TCF7L2-rs7903146 polymorphism on cardiovascular risk factors and stroke incidence: a randomized controlled trial in a high-cardiovascular-risk population. Diab Care 36:3803–3811. doi:10.2337/dc13-0955
37. Jenkins DA, Kendall CC, Marchie A et al (2003) EFfects of a dietary portfolio of cholesterol-lowering foods vs lovastatin on serum lipids and c-reactive protein. JAMA 290:502–510. doi:10.1001/jama.290.4.502
38. Ros E (2009) Nuts and novel biomarkers of cardiovascular disease. Am J Clin Nutr 89:1649S–1656S. doi:10.3945/ajcn.2009.26736R
39. Kendall CWC, Josse AR, Esfahani A, Jenkins DJA (2010) Nuts, metabolic syndrome and diabetes. Br J Nutr 104:465–473. doi:10.1017/S0007114510001546
40. Wannamethee SG, Whincup PH, Thomas MC, Sattar N (2009) Associations between dietary fiber and inflammation, hepatic function, and risk of type 2 diabetes in older men: potential mechanisms for the benefits of fiber on diabetes risk. Diab Care 32:1823–1825. doi:10.2337/dc09-0477
41. Ghanim H, Chaudhuri A, Dandona P et al (2010) Associations between dietary fiber and inflammation, hepatic function, and risk of type 2 Diabetes in older men: potential mechanisms for the benefits of fiber on diabetes risk response to Wannamethee et al. Diab Care 33:e43–e43. doi:10.2337/dc09-2127
42. Salvioli S, Sikora E, Cooper EL, Franceschi C (2007) Curcumin in cell death processes: a challenge for CAM of age-related pathologies. Evid-Based Complement Altern Med ECAM 4:181–190. doi:10.1093/ecam/nem043
43. Biagi E, Nylund L, Candela M et al (2010) Through ageing, and beyond: gut microbiota and inflammatory status in seniors and centenarians. PLoS ONE 5:e10667. doi:10.1371/journal.pone.0010667
44. Collino S, Montoliu I, Martin F-PJ et al (2013) Metabolic signatures of extreme longevity in northern Italian centenarians reveal a complex remodeling of lipids, amino acids, and gut microbiota metabolism. PLoS ONE 8:e56564. doi:10.1371/journal.pone.0056564
45. Quercia S, Candela M, Giuliani C et al (2014) From lifetime to evolution: timescales of human gut microbiota adaptation. Front Microbiol 5:587. doi:10.3389/fmicb.2014.00587