Active Ageing and Healthy Living
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Lifestyles and Ageing: Targeting Key Mechanisms to Shift the Balance from Unhealthy to Healthy Ageing

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Abstract. The increase in life expectancy has dramatically enhanced the prevalence of age-related chronic diseases resulting in growing costs for both society and individuals. Identification of strategies contributing to healthy ageing is thus one of the major challenges of the coming years. Lifestyle has a primary role among non-genetic factors affecting health and lifespan. In particular, nutrition, mental and physical activity impact the molecular and functional mechanisms whose alterations cause the major age-related diseases. A better understanding of mechanisms underlying the beneficial action of correct lifestyles is useful to develop interventions aimed at preventing and/or delaying the onset of chronic degenerative diseases, to identify high-risk populations who could be targeted in intervention trials as well as to identify novel biomarkers of healthy ageing. A multidisciplinary team of basic scientists and clinicians operating at the Catholic University Medical School in Rome is actively working on this topic to determine the ability of healthy lifestyles to promote active ageing and counteract the major age-related diseases affecting brain health, musculoskeletal function and gut microenvironment. This chapter summarizes our strategic approaches, the major results we obtained so far and the main experimental and translational perspectives.

Keywords. Sarcopenia, Cognitive Decline, Dysbiosis, Insulin Resistance, Inflammageing

Introduction

Over the past decades advances in diagnostic and therapeutic strategies have contributed to an increase in life expectancy that has progressively led to a growth of the older population. Individuals nowadays live longer, the life expectancy at birth for the 53 countries in the World Health Organization (WHO) European Region being over 72 years for men and around 80 for women [1]. The increase in life expectancy has been paralleled by an increase in the prevalence of non-communicable, chronic diseases such as cardiovascular, metabolic, respiratory and neurodegenerative diseases, as well as cancer. These represent a social and economic problem that is steadily

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growing, imposing a large burden on European societies and individuals. As such, it is pivotal to implement strategies aimed at improving not only the "quantity", but also the quality of life and health status of elderly individuals. Active ageing, defined by the WHO as "the process of optimizing opportunities for health, participation and security in order to enhance quality of life as people age [...]", allowing people to "[...] realize their potential for physical, social and mental well-being throughout the life course" [2], has therefore become a key priority for the future sustainability of health and social policies in Europe.

It is widely known that "healthy" lifestyle (e.g. diet, cognitive training and physical activity) may lead to a postponement of initial disability and decreased lifetime disability [3, 4], ultimately resulting in a healthier ageing process. It is the responsibility of the Governments to implement large-scale healthy ageing policies aimed at increasing the awareness of the benefits brought about by a healthy lifestyle. In this chapter we will describe how, using a translational, multidisciplinary approach, a number of basic and clinical research groups of our Faculty of Medicine are characterizing in detail the pathophysiological mechanisms underlying "unhealthy" ageing and the complex interactions among them to identify the mechanisms to target in order to ameliorate the physical, mental and social well-being of elderly people.

1. The Relevance of the Research Topic for Active Ageing and Healthy Living

Ageing may be seen as a chronic condition characterized by progressive functional decline in organs and systems of the body. As we grow older, the functional capacity of the body to maintain homeostasis and to respond adequately to physiological needs deteriorates. Ageing results in a progressive loss of muscle mass and strength (sarcopenia) that is closely related to increased morbidity and mortality in healthy individuals and patients, and has been identified as an important risk factor for injurious falls and hip fractures in the elderly. Age-related conditions affecting the brain such as mild cognitive impairment (MCI), i.e., a cognitive decline greater than expected for an individual's age and education level but that does not interfere notably with activities of daily life, are also associated with variable clinical outcomes including dementia, depression, cardiovascular diseases, and respiratory disorders. Sarcopenia and cognitive impairment should be considered as hallmarks of unhealthy ageing, since these two conditions deeply affect the functional capacity of the individual and are risk factors for the development of chronic diseases.

Shared pathophysiological mechanisms may underlie both sarcopenia and cognitive impairment: mitochondrial dysfunction and oxidative stress, insulin resistance and a number of epigenetic changes all appear to contribute to these hallmarks of ageing. Interestingly, most of these mechanisms can be influenced by lifestyle.

Ageing is associated with a progressive mitochondrial dysfunction, which leads to an overproduction of reactive oxygen species (ROS) that sustains and further deteriorates mitochondrial dysfunction, thereby inducing global cellular damage [5]. At a systemic level, the cascade of events secondary to oxidative stress triggers an inflammatory response, thus contributing to additional oxidative stress and eventually to the functional and structural modifications associated with advancing age such as cognitive decline and sarcopenia [6]. Additionally, alterations in mitochondrial dynamics could be involved in the development of sarcopenia, and are known to play a

critical role in nutrient-induced pancreatic β-cell apoptosis and possibly in the pathophysiology of type 2 diabetes mellitus (T2DM) [7]. In turn, glucose intolerance and T2DM have been associated with deficits in cognitive functions and with an increased risk of developing dementia [8]. This is in agreement with the notion that age-related cognitive decline does not depend only on neuronal mechanisms and intrinsic factors within the brain, but is also influenced by important hormones and neuromodulators that are released from peripheral organs and endocrine glands.

Interestingly, it has even been suggested that Alzheimer's disease (AD) may be a form of type 3 diabetes, based on the evidence for insulin resistance and impaired insulin response pathways in the Alzheimer's brain [9]. On the other hand, loss of skeletal muscle, i.e., the largest insulin-responsive target tissue, produces insulin resistance, which may eventually contribute to the development of the metabolic syndrome and T2DM [10]. It has also been proposed that common pathways may underlie both muscle insulin resistance and sarcopenia. As an example, serum magnesium status is an independent correlate of muscle performance in the elderly, and alterations of magnesium metabolism associated with ageing could contribute to the pathophysiology of insulin resistance and cardiometabolic syndrome in the elderly [11, 12]. Finally, it should also be underscored that metabolic regulation, genome maintenance mechanisms as well as genetic and epigenetic factors (i.e., the "mark" of the environment on our genes) all cooperate to drive the ageing process.

Lifestyle represents a central factor able to influence several of the common players involved in the ageing process. As such, lifestyle factors appear very relevant not so much to determine how long we will live, but rather because they can influence how healthily we will age. A growing body of evidence supports the role of healthy diet, cognitive training and physical activity in slowing the progression of cognitive impairment and sarcopenia associated with ageing [13-16]. Given the pivotal role of nutrition in health, it is also important to understand how nutrients "interact" with the body. In this light, gut microbiota - a complex ecosystem consisting of trillions of microorganisms and thousands of bacterial species - has emerged as a key factor that may play an important role in the development of several chronic diseases via modulation of the host metabolism and inflammatory/immune pathways [17]. Diverse forms of neuro-immune and neuro-psychiatric disorders appear to be correlated with or modulated by variations of microbiota, microbiota-derived products and exogenous antibiotics and probiotics [18]. A role for gut microbiota in the onset and progression of sarcopenia and T2DM has also been proposed [17, 19].

Based on these premises, we aim to characterize the close relationship among lifestyle, microbiota, brain and muscle health through an integrated approach encompassing experimental, clinical and translational studies, in order to identify common mechanisms that could be the target for interventions specifically designed to shift the balance from unhealthy to healthy ageing (Figure 1).

2. Our Actual Research Activity

2.1 Impact of Diet and Microbiota on Ageing

The gut microbiota is involved in the regulation of multiple host metabolic pathways and, through the gut-brain axis, interacts with brain health and mood, thus playing a pivotal role in the process of ageing [20].

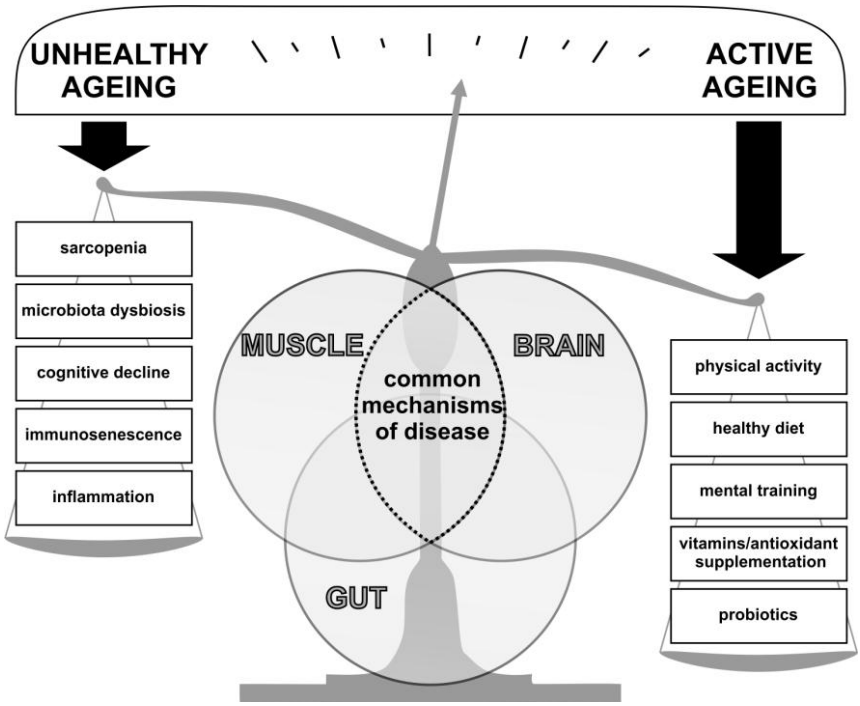

Figure 1. Overview of the common mechanisms that, by acting in key target organs such as muscle, brain and gut, may shift the balance from unhealthy to healthy ageing.

The gut microbiota shows a relevant degree of plasticity in response to environmental changes resulting in modification of its phylogenetic and functional profile, which allows the host to rapidly optimize metabolic and immunological performances to preserve health and homeostasis. In this context, the preservation of a correct and balanced gut microbiota-host mutualistic interaction is a key for healthy ageing. Clinical and experimental studies are unravelling the main features of the gut microbiota in the elderly and the pathophysiological consequences associated with age-related changes in its composition. Although the gut microbiota exhibits a high degree of inter-individual variability, during ageing it appears to be associated with a trend toward reduced biodiversity and compromised stability, with a decrease in the prevalence of certain relevant anaerobes and a bloom of facultative anaerobes such as Streptococci, Staphylococci, Enterococci and Enterobacteria. These bacterial species, also termed “pathobionts”, can prosper and accumulate in the inflamed gut, overtaking mutualistic commensals and further boosting inflammation. Changes in nutrition, diet and lifestyle, together with the physiological process of immunosenescence, are among the most relevant causes underlying the changes in gut microbiota composition that lead to dysbiosis.

In this context, our multidisciplinary research group aims to gain insights on the impact of diet and microbiota on ageing by addressing different points.

Among the well-documented consequences of age-related alterations of gut microbiota is the reduced intestinal level of short chain fatty acids (SCFAs), which are microbial metabolites known to play a pivotal role in several aspects of human

physiology. In the elderly, a decline in SCFAs can be detrimental for wellbeing as it can compromise nutrition, immune function, signalling, appetite and behaviour and more in general the nervous system, as suggested by recent findings showing that certain age-related gut microbiota dysbioses can be involved in cognitive decline and depression that are typical of the frail elderly. Moreover, an altered production of SCFAs from bacterial fermentation could be responsible for a reduction in the secretion of glucagon-like peptide 1 (GLP-1), a gastrointestinal hormone involved in the regulation of glucose-stimulated insulin secretion. Researchers from the Institutes of Clinical Biochemistry, Human Physiology and Neurology, and the Endocrinology and Metabolic Diseases Unit, are actively working to clarify the underlying mechanisms and to identify novel biomarkers of diet-induced ageing and metabolic diseases. Their research questions stem from the fact that the abnormal dietary patterns (e.g., high glycaemic index, saturated fat content and caloric intake) affecting the main mechanisms regulating glucose metabolism (i.e., insulin sensitivity and insulin secretion), cause functional alterations that are reminiscent of ageing. Indeed, nutrient excess induces cellular metabolic stress, and altered cellular metabolism observed in diabetes is associated with accelerated ageing of almost all tissues and organs. Dietary habits and their impact on cognitive, muscular and metabolic functions are being assessed in a large cohort of subjects at risk for T2DM. The diet-induced functional alterations found in humans are further characterized by reproducing the nutritional/metabolic environments associated with human unhealthy diets in cellular models (blood, skeletal muscle cells) and mice models of metabolic derangement (insulin-resistance, T2DM, high glucose variability). Finally, the molecular data obtained from cellular and animal models are being validated in a selected and accurately characterized subgroup from the original cohort of subjects at risk for T2DM, in order to identify novel biomarkers of age- and diet-related early target organ damage to be routinely used in clinical practice.

The investigators from the Endocrinology and Metabolic Diseases Unit have also undertaken a clinical trial on *Lactobacillus acidophilus* and *Bifidobacterium lactis* supplementation to study the effects of these probiotics on glycaemic control, gastrointestinal hormones such as GLP-1, inflammatory markers and quality of life in elderly patients with T2DM. Specifically, haemoglobin A1c (HbA1c), fasting blood glucose levels, insulin sensitivity, plasma levels of GLP-1, inflammatory cytokines (TNF-α, IL-6) and self-perceived health status are being evaluated at baseline and after three months of probiotic supplementation.

An interventional study to assess whether faecal microbiota transplantation in conjunction with lifestyle changes may lead to a greater reduction in insulin resistance as compared to that achievable with lifestyle modifications alone is also being implemented by the same group.

Hypomagnesaemia is another pro-inflammatory condition that exacerbates inflammation-driven diseases and as such may play a role during the ageing process. Intestinal mucosa and kidneys are the natural access routes for magnesium into the blood stream. Magnesium absorption and re-absorption through these two epithelia regulate whole body magnesium. Two distinct mechanisms are involved: passive paracellular absorption, which relies on tight junction permeability, and active transcellular transport, which involves cation channels and transporters among which transient receptor potential melastatin (TRPM) channels 6 and 7. In particular, the TRPM6 channel is expressed at high levels in the distal small intestine and colon, where Mg^{2+} absorption mainly takes place, and in the renal distal convoluted tubule,

where the "fine-tuning" of Mg^{2+} re-absorption occurs. TRPM6 has been defined as the gatekeeper of systemic magnesium homeostasis, since mutations in the TRPM6 gene or in genes regulating TRPM6 cause rare genetic diseases characterized by severe hypomagnesaemia and related symptoms.

Researchers at the Institute of General Pathology aim to assess whether magnesium absorption through the colonic mucosa, associated with other stimuli, has a role in determining chronic inflammation and carcinogenesis in the gut, i.e., two disease conditions frequently found in ageing [21]. They are measuring TRPM6/7 expression in epithelial cells in *in vitro* and *in vivo* systems under experimental conditions that mimic inflammation. Another membrane transporter, the organic cation transporter 1 (OCTN1), which is expressed by epithelial and inflammatory cells, may play a role in the absorption of diet-derived anti-inflammatory and antioxidant compounds. Importantly, a common variant of OCTN1 has been found to be associated with inflammatory bowel disease (IBD) in humans, and researchers from the Institute of General Pathology have shown that such association particularly applies to IBD patients progressing to intestinal malignancy [22]. Studies are ongoing to investigate the impact of OCTN1 on the inflammatory processes and autophagy following exposure of epithelial cells to faecal bacteria. These investigations will shed light on the inflammatory processes favouring cancerogenesis in colitis-associated cancers.

2.2 Impact of Lifestyle on Muscle Function

The pathophysiology of muscle loss during the ageing process is complex, involving muscle and associated neural and hormonal regulation [23]. With normal ageing, the quality of muscle fibres slowly deteriorates and peak power, shortening speed and elasticity decline slowly. The weakness of muscle fibres can be explained by the interaction of several age-related changes, including loss of anabolic stimuli due to both a decline in the concentration of anabolic hormones and age-associated subclinical inflammation. Reductions in the number and activation of satellite cells, especially those associated with type IIA fibres, also occur in older people, which may reduce the regenerative capacity of muscle fibres and compensatory capacity. Myostatin levels also increase with age. As myostatin is a negative regulator of muscle mass, an increase in its circulating levels may lead to muscle atrophy. Changes in regulation of the myostatin gene may also contribute to age-related changes in the protein profile of muscle [23].

Nutrition and physical exercise are the cornerstones of management in sarcopenia. Resistance exercise training increases muscle strength and mass and improves protein accretion in skeletal muscle. Aerobic exercise training may also benefit ageing skeletal muscle and improve insulin sensitivity. Exercise has to be prescribed, and is most probably beneficial when properly supervised and sustained over time [15].

Correction of nutritional deficits is also needed. Caloric intake should be increased to cover increased demands posed by exercise. Protein requirements are also increased, therefore the recommended protein intake in sarcopenic patients is >1.2 g of protein per kilogram of body weight per day, except in patients with significant renal failure. Leucine, β-hydroxy β-methylbutyrate, creatine and some milk-based proteins may have beneficial effects on protein balance in skeletal muscle. Correction of vitamin D deficiencies is needed for proper muscle function, but the role of vitamin D in the presence of normal blood levels is yet to be determined [24].

In this regard, researchers from the Institute of Internal Medicine and Geriatrics and from the Institute of Histology and General Embriology highlighted the importance of sarcopenia as a common, complex and costly syndrome impairing health in older individuals and resulting from incompletely understood interactions of disease and age on multiple systems producing a constellation of signs and symptoms.

Epidemiological studies demonstrated that sarcopenia is highly prevalent among older subjects and it is correlated with highest risk of death, regardless of age, gender, and other confounding factors. Malnutrition, poor diet and sedentary lifestyle are the most common risk factors for the onset and progression of sarcopenia [25, 26].

The age-dependent loss in muscle mass and function, namely sarcopenia, has been identified as an important risk factor for injurious falls and hip fractures. Noticeably, a significant amount of muscle mass is lost following a hip fracture due to immobilization, surgical stress and poor nutrition. Recently, a great emphasis has been placed on alterations in myocyte quality control (MQC) processes as possible factors involved in the pathogenesis of sarcopenia and acute muscle atrophy. Evidence suggests that dysfunctional autophagy may be the result of derangements in mitochondrial dynamics (i.e., fission/fusion) upstream of the autophagic/lysosomal pathway. The study currently ongoing in the Geriatrics Unit aims to investigate for the first time relevant MQC pathways in the skeletal muscle of hip fracture patients and to determine the relationship between MQC and functional recovery in this patient population. The specific aim is to investigate MQC signalling pathways (autophagy, fusion and fission) in hip fractured patients in comparison to elderly subjects undergoing total hip replacement for osteoarthritis. This study will reveal whether specific alterations in cellular housekeeping processes are linked to the disabling process in older subjects [27, 28]. Novel therapeutic strategies (i.e., specific nutritional interventions) are being developed to counteract physical function impairment that will be tested in future interventional studies.

Similarly, the studies (human and animal) that are being conducted in the Gastroenterology Unit aim to assess whether and how sarcopenia occurs in IBD and how and whether it could be counteracted by specific therapeutic interventions. Ulcerative colitis and Crohn's disease are characterized by clear alterations in bowel physiology, involving absorption, bowel habit, food intake and also microbiota composition and function. Weight loss and malnutrition are a common finding in IBD, particularly in the active phases of the disease. Researchers from the Gastroenterology Unit are investigating the presence of sarcopenia in a cohort of IBD patients stratified by other risk factors (including age, state of disease, disability, etc.) and are seeking to correlate sarcopenia with intestinal or serological markers. Furthermore, a mouse model of dextran sulphate sodium (DSS) colitis is being used for experimental studies. Animals are exposed to 2.5% DSS in drinking water for either 7 days or three 5-day cycles separated by a 2-week exposure to regular water, in order to induce acute or chronic colitis, respectively. During the induction of colitis and during the recovery phase, muscular strength of each animal is assessed with special treadmills that allow measuring time to “fatigue” for each animal. Specific modulation of cytokines, microbiota composition and inflammatory markers are being tested to verify whether they directly affected muscle homeostasis.

Using animal models, investigators from the Institute of Histology and General Embriology are determining whether specific nutritional strategies may counteract the loss of muscle mass and function in senescent muscle. Interestingly, injured tibialis anterior (TA) muscle of mice which received intra-peritoneal injection of taurine show

enhanced regeneration response as demonstrated by the presence of central nucleated fibres, less amount of inflammatory cells and fibrosis, if compared to control muscles.

To better analyse the inflammatory status of TA muscles from control and taurine-treated mice, the expression level of the transcription factor NF-kB, one of the most important players in inflammation, is being examined. Preliminary results indicate that NF-kB expression is strongly up-regulated in injured muscle of control mice, while its expression is only slightly increased in injured muscle of taurine-injected mice. These results suggest a role of taurine in the down-regulation of inflammation and the enhancement of regeneration in skeletal muscle.

2.3 Impact of Lifestyle on Brain Functional Decline

Human studies have provided intriguing evidence for positive effects of proper lifestyle on neurocognitive function in older adults. In particular, healthy diet, cognitive and physical training are able to slow down brain ageing, at least in part by counteracting mitochondrial dysfunction and insulin resistance. Conversely, physical inactivity, poor diet and even more metabolic diseases (i.e., obesity and diabetes) accelerate the ageing process. Although the mechanisms underlying the pathological cognitive decline in the elderly are not yet fully known, it is recognized that changes in metabolism and redox state may influence the onset and progression of age-related neurodegenerative diseases. In this regard, researchers from the Institute of Neurology highlighted a close relationship between an altered copper metabolism and the progression of AD [29, 30].

Alterations of copper homeostasis lead to ROS production, either directly or via inhibition of antioxidant activities [31]. In particular, patients with adequate copper plasma concentrations showed better performance when evaluated with memory tests.

Changes in the availability of oligoelements such as copper can determine an increase in inflammatory cytokines and impact on oxidative stress and cellular metabolism. Researchers from the Institute of Pharmacology have developed enzymatic assays to measure markers of oxidative stress (e.g. 8-isoPGF2α) that they have already validated in atherothrombotic disease [32]. The above mentioned research groups are working in synergy on this project, in order to identify novel biomarkers of age-dependent cognitive decline and to validate their diagnostic and/or prognostic role in a large cohort of patients with MCI or early to advanced AD. In particular, this study is comparing the redox state measured in cerebrospinal fluid with systemic oxidative stress, with the aim of using these tests as predictive tools to identify patients at increased risk for progression from MCI to AD. The same researchers are also prospectively studying, by means of clinical and laboratory tests, a group of patients with MCI in whom they are evaluating the impact of an antioxidant-enriched and copper-deficient diet on the progression of disease. The concept that common mechanisms associated with lifestyle-dependent ageing may affect different organs and tissues is also at the root of another project involving researchers from the Institutes of Clinical Biochemistry, Human Physiology and Neurology, and the Endocrinology and Metabolic Diseases Unit. As already mentioned, they hypothesized that abnormal dietary patterns affecting the main mechanisms regulating glucose metabolism may cause functional alterations that are reminiscent and predictive of unhealthy ageing. Correlations between unhealthy dietary habits (e.g., high glycaemic index, high fat, high caloric intake, low fibre) related to and predictive of glucose metabolism alterations, markers of oxidative stress and functional alterations in target organs such as the brain are being investigated in a large cohort of subjects at risk for T2DM.

To characterize the molecular mechanisms underlying diet-induced functional alterations, researchers from the Institute of Human Physiology reproduced the nutritional/metabolic environments associated with human unhealthy diets in cellular (neural stem cells and neurons) and mice models of metabolic derangement (insulin-resistance, T2DM). The ability of exercise and novel enriched environment (NEE, a paradigm of mental and physical training) to counteract the damage caused by metabolic unbalance is also being assessed. Evaluating the effects of diet and exercise in animal models has the advantage of reducing some of the inherent confounding variables that often complicate human studies. The animal studies mentioned below are being used to evaluate the potential of lifestyle to affect neurocognitive plasticity by analysing: i) behavioural performance on learning and memory paradigms; ii) neural activity and long-term potentiation (LTP), a cellular model of memory; iii) the growth and differentiation of newborn neurons; iv) expression of molecular factors associated with brain plasticity. The researchers from the Institute of Human Physiology used a high fat diet (HFD, 60% fat, for 8 weeks) alone or in combination with chronic hyperglycaemia induced by intraperitoneal injection of streptozotocin (STZ) as models of altered lipid and carbohydrate metabolism, respectively. Their findings suggest that overnutrition and dysmetabolism alter the physiological cell signalling in the brain and affect central nervous system plasticity by influencing neuronal activity and synaptic transmission, as well as adult neurogenesis. Mice exposed to HFD ± STZ showed alterations of learning and memory recognition ability, but the simultaneous exposure of animals to NEE prevented the impairment of cognitive functions. Moreover, in mice fed with HFD a significant reduction in adult neurogenesis and decreased expression of key neuronal genes (HES-1, nNOS, PGC-1α, SIRT1) in their hippocampi were observed.

These data are consistent with the results generated by the researchers of the Institutes of Anatomy and Cell Biology and General Pathology, who showed that HFD reduced hippocampal neurogenesis by a neuroinflammatory mechanism that might involve the transcription factor CREB. One attractive possibility is that fat-induced inflammation and insulin resistance also occur in cognitive areas of the brain, thus promoting neurodegeneration. Recently, researchers of the Institutes of Human Physiology and General Pathology identified the CREB-SIRT1 axis as a critical player that mediates the response to nutritional signals in the brain [33]. They discovered a novel role of CREB as a metabolic sensor in the brain, and brought to light one of the molecular mechanisms by which the nutrients modulate behavioural, functional and gene expression responses in both neural stem cells and differentiated neurons. In conclusion, nutrient excess seems to act in the brain on both the stem cell compartment and differentiated neurons by interfering with CREB, a key factor for the development and function of the nervous system, and the transcriptional machinery attached to it.

3. Our Future Research Activity

The network of studies set out by our multidisciplinary group delves into a topic of great relevance to healthcare through a highly integrated approach encompassing basic, clinical and translational research. Our project is characterized by a strong intra-faculty integration that will allow to develop an increasing number of multidisciplinary lines of investigation, and to understand the impact of lifestyles on ageing from the molecular, cellular and functional point of view. Our preliminary findings, along with extensive

evidence from the literature, emphasize how changes in the composition of the gut microbiota influence normal physiology and contribute to the development of inflammatory and metabolic diseases. Pre-clinical and clinical studies are also being carried out to assess the impact of interventional strategies on the gut microbiota that may prevent or subvert inflammatory processes. A therapeutic intervention aimed at counteracting intestinal inflammation in a cohort of IBD patients will be implemented, and its effect will be assessed by characterizing the gut microbiota and by measuring relevant inflammatory markers at baseline and at study end.

It has recently become evident that microbiota, especially microbiota within the gut, can greatly influence all aspects of physiology, including gut–brain communication, brain function and even behaviour [34]. Our future research will focus on delineating the relative contributions of immune, neural and endocrine pathways through which the gut microbiota communicates with the brain. Further work is also needed to reveal the key factors and molecular mechanisms involved in this complex network. We will investigate whether different microbial strains or metabolites released by gut bacteria (such as nitric oxide or GABA) are able to influence learning and memory or to affect the mood in animal models. We will also analyse the relationship between microbiota alterations and neurological diseases in selected cohorts of patients from the Institutes of Neurology and Psychiatry and Clinical Psychology. One of our future research projects aims to identify the mechanisms and mediators underlying the obesity-related cognitive decline and the improvement in memory function related to bariatric surgery. It is well known that gut hormones (in particular GLP-1 and ghrelin), adipokines and proinflammatory mediators are influenced by bariatric surgery. GLP-1 and ghrelin may play an important role in synaptic plasticity and are involved in memory formation.

The "Sarcopenia and Physical fRailty IN older people: multi-componenT Treatment strategies" (SPRINTT) project – coordinated by the Department of Geriatrics and recently funded by the European Community (IMI- Innovative Medicine Initiative) - is geared to produce significant advancements in the management of frail elders by promoting a consensus among academia, regulators, industry, and patients' representatives over i) clear operationalization of the presently vague concept of frailty and sarcopenia; ii) identification of a precise target population with unmet medical needs; iii) evaluation and validation of a new methodology to implement preventive and therapeutic strategies among frail elders at risk of disability in Europe; iv) definition of an experimental setting serving as template for regulatory purposes and pharmaceutical investigations; v) identification of biomarkers and health technology solutions to be implemented in clinical practice. In this respect, the SPRINTT project represents the first attempt to identify a precise subset of frail elderlies with unmet medical needs and to implement a multi-component intervention (based on physical activity, nutritional intervention and ICT implementation) aimed at preventing incident disability and major negative health-related events.

Finally, in recent years early life stress and environmental exposure have become one of the major topics of research in biology. The idea that not only the lifestyle that we adopt during adulthood, but also the environment to which we are exposed in the early stages of life or even our parents' experiences can definitely affect our wellbeing and susceptibility to the diseases in the later stages of life is fascinating. We aim to study the epigenetics of ageing to discover how early-life experience influences the age-related decline and the susceptibility to diseases. It is hypothesized that the degree of vulnerability to changes in epigenetic patterns is high during early embryonic

development, a period of life in which epigenetic patterns are established and cell differentiation is intense. An upcoming project aims to reveal the impact of parents' dietary habits or that of the environment to which an organism is exposed in the early stages of life (stress, microbiota alterations, mental training) on its cognitive, muscular and metabolic function in the adulthood.

4. The Practical Value of this Research Activity for Active Ageing and Healthy Living and Conclusions

To summarise, science has the potential to identify the most rational and cost-effective approaches to enhance healthy ageing, in an effort to improve the efficacy of strategies implemented by governmental organisations to promote healthy lifestyles in the overall population. In this direction, the main endeavour of research is to determine the most useful and sensitive biomarkers of healthy and unhealthy living, with the aim of identifying populations at higher risk for unhealthy ageing, and of developing appropriate therapeutic tools and intervention plans (Figure 2).

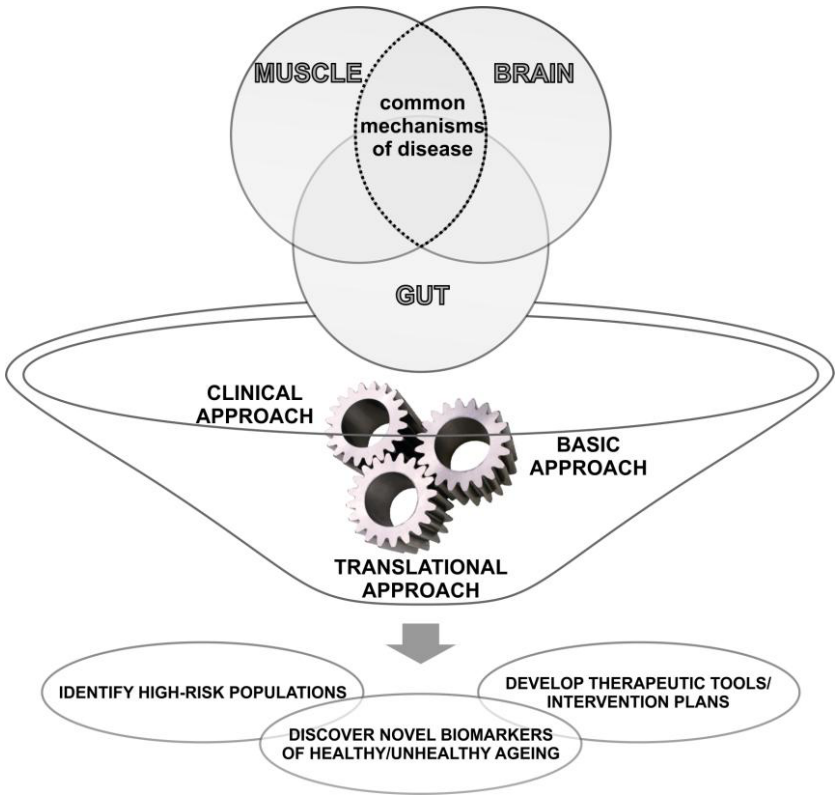

Figure 2. Schematic representation of our multidisciplinary network that, by using basic, clinical and translational approaches, is characterising the common mechanisms underlying unhealthy ageing in key target organs such as muscle, brain and gut in order to identify high-risk populations, develop novel therapeutic tools/intervention plans and discover novel biomarkers of healthy/unhealthy ageing.

While most scientists adopt individual and competitive approaches, our unique group harmoniously blends basic, clinical and translational scientists who work in concert, combining several diverse experiences with the shared aim of promoting healthy ageing. Several original research projects have been undertaken in which an innovative strategy, i.e., the characterisation of the common mechanisms underlying unhealthy ageing in brain, muscle and gut, has been implemented. Our preliminary results have already laid the foundations for a significant progress of science and public health.

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