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Nutrigenomics, Inflammaging, and Osteoarthritis: A Review

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7.1 Introduction

The global incidence of age-related diseases of the bone, joint, and muscle is steadily rising, seriously affecting the health of millions of people across the world. According to the United Nations (UN) (www.un.org) and the World Health Organization (WHO) (www.who.int) musculoskeletal and arthritic conditions are leading causes of morbidity and disability throughout the world, giving rise to enormous healthcare expenditures and loss of work (sources: The Arthritis Foundation (AF) and WHO: Ehrlich, 2003; Salminen *et al.*, 2012a; Symmons *et al.*, 2000; Woolf *et al.*, 2003;[1, 2, 3]). Many types of rheumatic diseases and arthritic conditions are essentially "inflammatory" disorders wherein that inflammation promotes disease progression. The term "arthritis" characterizes a group of conditions involving inflammatory damage to synovial joints (Di Paola *et al.*, 2008). Arthritis literally means inflammation (*itis*) of the joints (*arthr*). It involves pain, redness, heat, swelling, and other harmful effects of inflammation within the joint. There are over 200 different forms of arthritis.

[1] www.arthritis.org
[2] www.who.int/healthinfo/statistics/bod_osteoarthritis.pdf
[3] http://www.who.int/bulletin/volumes/81/9/Ehrlich.pdf

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However, the most common and economically important form of arthritis is osteoarthritis (OA), also known as osteoarthrosis or degenerative joint disease (DJD) although it must be noted that osteoarthrosis and DJD are now considered to be inappropriate and incorrect terms for describing OA. OA is the major cause of pain and disability affecting the elderly (Aigner *et al.*, 2004). Other forms of arthritis include psoriatic arthritis and rheumatoid arthritis (RA), an autoimmune disease in which the body's own immune system attacks synovial joints. The risk factors for arthritis are gender, age, family history, ethnic background, and smoking tobacco (Oliver *et al.*, 2009). It is important to note that OA and RA are both now considered to be systemic disturbances. Although synovial joints are primarily affected in both arthritides, these diseases can also wreak havoc in other organs. For example, in RA the pancreas and the heart also undergo significant changes. Ultimately, the major consequences of all forms of arthritis include disability, chronic pain and significant morbidity. Pain is a constant and daily feature in well-established forms of the disease. A large component of arthritic pain arises from the inflammation that occurs around and within the joint. Disability in patients with arthritis is a consequence of degeneration in the joint and surrounding tissues, and is further enhanced by this inflammation-induced ("inflammatory") pain. Aside from analgesics, there are currently no effective pharmacotherapies capable of restoring the structure and function of the damaged synovial tissues in any form of arthritis. Consequently, there is significant interest from patient groups, rheumatologists, and commercial companies in any nutrients, nutraceuticals, and natural products that may provide complementary therapeutic support for patients with inflammatory diseases of joints. In this chapter we introduce readers to clinical aspects of OA and discuss factors that lead to its development and progression. We then explore the concept of inflammaging and how the emerging field of nutrigenomics may be applied to understanding the effects of nutraceuticals and functional foods on synovial joint tissues, particularly muscle.

7.2 Osteoarthritis (OA)

OA is the most common form of arthritis. A study carried out in the USA estimated that OA is one of the top five causes of disability amongst non-hospitalized adults (source: Centers for Disease Control and Prevention, USA (CDC): Salminen *et al.*, 2012b). According to estimates from the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) more than 20 million Americans currently suffer from OA. In 2006, it was estimated that around 35 million to 40 million Europeans had OA. It is anticipated that by the year 2030, 20% of adults will have developed OA in Western Europe and North America. Furthermore, since our population appears to have ever increasing longevity, OA is expected to place a growing economic burden on health and social care systems, and community services in Europe and the rest of the world.

OA is rare in people under 40 and advancing age is a major risk factor. Perhaps not surprisingly, there is radiographic evidence of OA in at least one joint in the majority of people aged 65 or over. The end stage treatment for OA is surgery, either to modify or replace the joint. With increasing life expectancy, growth in the elderly population and an alarming escalation of chronic, inflammatory and age-related conditions (such as OA), there is increased demand for new treatments and preventative approaches. Although OA is primarily associated with aging, there are other important contributing factors (Figure 7.1) (Lotz *et al.*, 2010). These include genetics, underlying anatomical and orthopedic disorders (i.e., congenital hip dislocation), obesity, underlying inherited or acquired metabolic disease, endocrine disease, various disorders of bone turnover and blood clotting, joint infection, crystal deposition, previous RA or a history of joint trauma, repetitive use, muscle weakness, or joint instability. The mechanical and metabolic alterations that occur in obesity, along with the pro-inflammatory factors produced by white adipose tissue in the chronically overweight, are thought to be major factors in the progression of the disease (Yusuf *et al.*, 2010). The factors that contribute to OA progression are summarized in Figure 7.2.

Symptoms of OA in the most frequently affected joints include pain, stiffness (crepitus), and limited mobility, as well as swelling, and, occasionally, warmth. These manifestations are highly variable, depending on joint location and disease severity. OA can affect any synovial joint but it commonly affects large load-bearing joints such as the hip and knee. The disease was traditionally thought of as being due to daily wear and tear of the joint and, indeed, the accumulation of microtrauma to cartilage and bone contribute to pathogenesis. The most prominent anatomical feature is the progressive destruction of articular cartilage (Buckwalter *et al.*, 2005). However, OA is an inflammatory disease involving not only articular cartilage but also the synovial membrane, subchondral bone and peri-articular soft tissues (Goldring and Goldring, 2007). Inflammation of the synovium occurs in both the early and late phases of OA and is associated with alterations in the adjacent cartilage. This inflammatory synovitis is qualitatively highly similar to that seen in RA. Catabolic and pro-inflammatory mediators such as cytokines, nitric oxide (NO), prostaglandin E_2 (PGE_2), and neuropeptides are produced by the inflamed synovium, which alter the balance of cartilage matrix degradation and repair (Sutton *et al.*, 2009). These events lead to excess production of the proteolytic enzymes

Systemic and OA Risk Factors:
Age
Obesity, overweight and sedentary lifestyle
Mechanical factors
Joint trauma, joint instability, joint overuse, increased joint laxity - increased stiffness of periarticular ligaments and tendons
Anatomic factors, joint shape and conformation
Genetics, epigenetics
Metabolic disease
Diabetes mellitus – formation of advanced glycation end-products (AGEs), oxidative stress
Endocrine disease (inherited or acquired)
Disorders of bone turnover
Disorders of blood clotting (haemophilia)
Previous septic arthritis (joint infection)
Previous rheumatoid arthritis (RA)
Gout or other forms of inflammatory crystal deposition in joints

Figure 7.1 *Systemic and OA risk factors.*

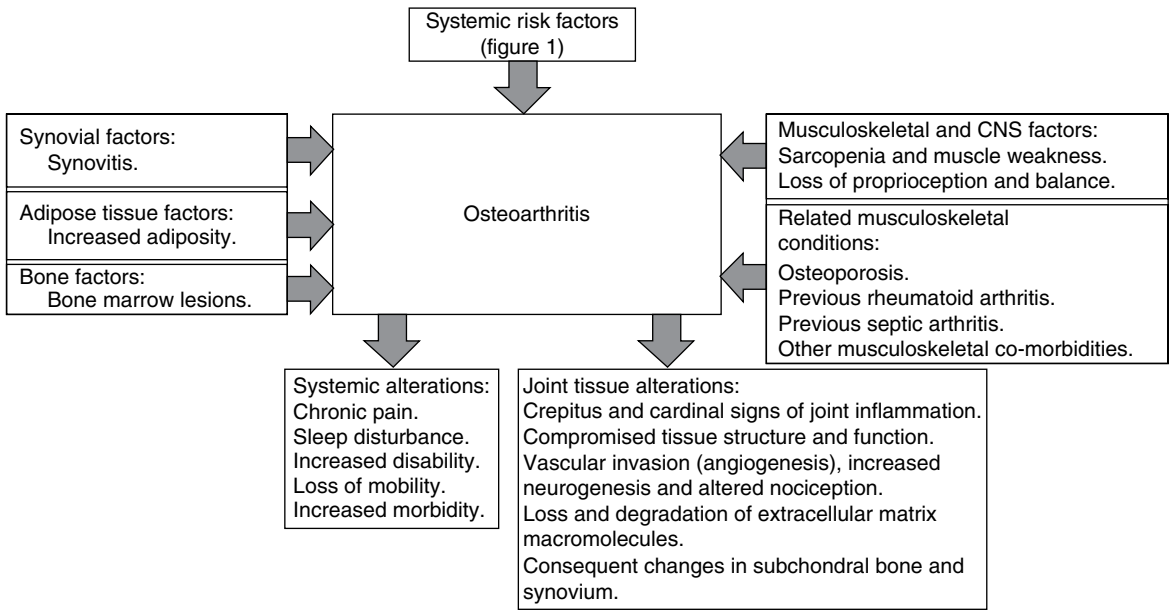

Figure 7.2 *Factors that contribute to the development and progression of OA.*

responsible for cartilage breakdown (Sellam *et al.*, 2010). Cartilage degeneration induces further synovial inflammation, creating a vicious circle. The progressing synovitis will then exacerbate clinical symptoms and joint degradation in OA (Sellam *et al.*, 2010).

7.3 Antioxidants and the Inflammatory Microenvironment

Antioxidants are naturally occurring reducing agents capable of inhibiting the oxidation of biological molecules. Oxidation reactions in living cells produce free radicals; reactive oxygen species (ROS) and their derivatives. These dangerous and harmful chemical products can accumulate over time, causing extensive structural damage or even cell death. The cytotoxic effects of

ROS can cause a variety of health problems including inflammatory disease, tissue necrosis, organ failure, atherosclerosis, infertility, birth defects, premature aging, mutations, and malignancy (Parke and Sapota, 1996). ROS production initiates an "inflammatory state" which unless quenched may result in chronic inflammatory disease states, for example, arthritis, hepatitis, nephritis, myositis, scleroderma, lupus erythematosus, or multiple system organ failure (Parke and Sapota, 1996). However, ROS can also be involved in the *initiation* of inflammatory responses (Gloire *et al.*, 2006). For example, ROS such as H_2O_2 can stimulate the transcription factor NF-κB, which is crucial for cellular processes such as inflammation, immunity, cell proliferation, and apoptosis (Schreck *et al.*, 1991). Therefore, ROS mediated upregulation of NF-κB can cause dysregulation of many inflammatory responses. NF-κB. ROS are also linked to mitochondria and the inflammasome (Zhou *et al.*, 2011). The inflammasome is a protein complex that stimulates caspase-1 activation to promote the processing and secretion of proinflammatory cytokines (Ogura *et al.*, 2006). This multiprotein oligomer consists of caspase 1, PYCARD, NALP, and sometimes caspase 5 (also known as caspase 11 or ICH-3). Inflammasome-dependent inflammatory responses can be triggered by a variety of stimuli including infection, tissue damage, and metabolic dysregulation (Tschopp, 2011). Recent work suggests that mitochondria are involved in integrating distinct signals and relaying information to the inflammasome. Dysfunctional mitochondria generate ROS, which is required for inflammasome activation. Interestingly, mitochondrial dysfunction has been linked to OA (Blanco *et al.*, 2004; Terkeltaub *et al.*, 2002). Analyses of mitochondrial electron transport chain activity in chondrocytes from OA affected cartilage show decreased activity of complexes I, II, and III compared to normal chondrocytes (Blanco *et al.*, 2011). Therefore, it is possible that mitochondrial dysfunction in arthritis is exacerbated by ROS and catabolic processes that alter cellular metabolism. The inflammasome is negatively regulated by autophagy, which is a catabolic process that removes damaged or otherwise dysfunctional organelles, including mitochondria (Tschopp, 2011). Autophagy has been shown to be a protective mechanism in normal cartilage, and its aging-related loss is linked with cell death and OA (Carames *et al.*, 2010). These studies suggest that the connections between mitochondria, metabolism, and inflammation are important for cell function and that malfunctioning of this network is associated with many chronic inflammatory diseases. ROS generation and inflammasome activation are linked with mitochondrial dysfunction and may explain the frequent association of mitochondrial damage with inflammatory diseases.

Antioxidants in foods and natural products are thought to interfere with inflammatory reactions by inhibiting ROS formation, scavenging free radicals, or removing ROS derivatives. They do this by being oxidized themselves, so antioxidants are often reducing agents such as vitamin C (ascorbic acid), vitamin E, thiols (glutathione), or a variety of plant polyphenols. Living cells maintain a complex and interrelated protective system of antioxidant vitamins, minerals such as selenium and manganese as cofactors, and glutathione to protect themselves from the harmful effects of ROS (Meister, 1994a, b). Cells also use a variety of antioxidant enzymes such as catalase, superoxide dismutase, and various peroxidases to quench and control cellular levels of ROS. Deficiency in antioxidants, or inhibition of the antioxidant enzyme systems, may cause oxidative stress and may damage or kill cells. Oxidative stress is an important component of many diseases. Therefore, the biology of ROS and antioxidants is widely investigated in the context of understanding the role of these chemicals in chronic diseases characterized by oxidative stress.

The redox state of chondrocytes is relevant in the context of OA because they exist in an avascular microenvironment, with low nutrient and oxygen levels (Mobasheri *et al.*, 2002, 2008). Although chondrocytes rely on glycolysis (Archer *et al.*, 2003), some of the metabolic functions of these cells are oxygen dependent (Henrotin *et al.*, 2003; Henrotin and Kurz, 2007). Oxygen is mainly supplied by diffusion from the synovial fluid (Mobasheri *et al.*, 2002; Pfander and Gelse, 2007). Consequently, the lack of oxygen means that chondrocytes display a metabolism adapted to anaerobic conditions (Henrotin *et al.*, 2003; Henrotin and Kurz, 2007; Lafont, 2010). There is little published information about the regulation of antioxidant enzymes within cartilage. Equally, little is known about the transport of antioxidants from the circulation to chondrocytes. However, some transport of nutrients, oxygen, and antioxidants to chondrocytes is thought to occur by diffusion from subchondral bone (Imhof *et al.*, 2000) and the synovial microcirculation (Levick, 1995). The role of subchondral bone in the pathogenesis of cartilage damage has been underestimated (Imhof *et al.*, 2000). There is increasing evidence that vascular pathology plays a role in the initiation and/or progression of OA (Findlay, 2007). In pathological conditions, oxygen tension in synovial fluid is subject to fluctuation as blood flow may be reduced by venous occlusion and stasis, vascular shunt, and fibrosis in synovium and/or by the development of microemboli in the subchondral vessels (Findlay, 2007). In response to oxygen variations induced through ischemia/reperfusion injury, mechanical stress, immunomodulatory, and inflammatory mediators, chondrocytes produce abnormal levels of ROS that are more usually produced by immune cells (Henrotin *et al.*, 1992, 2003; Henrotin and Kurz, 2007). The main ROS produced by chondrocytes are NO and superoxide anion that generate derivative radicals, including peroxynitrite and hydrogen peroxide (H_2O_2) (Hiran *et al.*, 1997, 1998). NO and its redox derivatives appear to have a number of different functions in both normal and pathophysiological joint conditions (Abramson, 2008b). Low NO concentrations have protective effects on other cell types and the literature

that deals with this area is beyond the scope of this chapter. Chondrocytes stimulated with pro-inflammatory cytokines produce large amounts of NO, which have been implicated in OA and has the capacity to inhibit extracellular matrix production by interfering with important autocrine and paracrine factors (Studer *et al.*, 1999). The published literature suggests important roles for NO in inflammation and pain associated with OA but this area is highly controversial and more work needs to be done to clarify the role of NO in joint health and disease (Abramson, 2008a). NO is synthesized by nitric oxide synthase (NOS) enzymes. Chondrocytes express both endothelial (eNOS) and inducible (iNOS) forms of the enzyme. NO production is stimulated by cytokines (i.e., IL-1β, TNF-α), interferons (i.e., interferon γ: IFN-γ), and lipopolysaccharides (LPS). In fact, the increased expression of iNOS and cyclo-oxygenase-2 (COX-2) in OA is largely due to the increased expression of pro-inflammatory cytokines, particularly IL-1β, which act in an autocrine/paracrine fashion to perpetuate a catabolic state that leads to progressive destruction of articular cartilage (Abramson *et al.*, 2001). In contrast, NO production is inhibited by growth factors such as transforming growth factor β (TGF-β).

In healthy cartilage, chondrocytes are thought to maintain robust defense mechanisms against attack by NO, free radicals, and ROS. However, as discussed earlier, responses to ROS generation will be dependent on redox status at the cellular level and influenced by systemic levels of inflammatory mediators, if present. When the oxidant level does not exceed the reducing capacities of cells, ROS are strongly involved in the normal physiological control of cellular functions including signal transduction. In contrast, in some pathological situations, when the cellular antioxidant capacity is insufficient to detoxify ROS, oxidative stress may occur degrading not only cellular membranes and nucleic acids, but also extracellular components including proteoglycans and collagens. This is likely to happen in certain OA phenotypes. Furthermore, ROS can modify proteins by oxidation, nitrosylation, nitration, or chlorination of specific amino acids, leading to impaired biological activity, changes in protein structure, and accumulation of damaged proteins in the tissue.

A further point that needs to be made in connection with oxidative stress is the fact that redox sensitive transcription factors (e.g., NF-κB) are upregulated, which might result in an uncontrolled inflammatory response. Oxidative stress may also cause cell death and release of cellular content into extracellular environment, activating clearance mechanisms in the microenvironment. Altogether, degradation products and cellular material containing oxidized molecules may contribute to the exacerbation of synovial inflammation and form a vicious circle, constituted by newly formed ROS and further degradation products.

7.4 Inflammaging

"Inflammaging" is defined as "low-grade chronic systemic inflammation established during physiological aging" (Franceschi and Bonafe, 2003). The aging phenotype is characterized by immunosenescence and is explained by an imbalance between inflammatory and anti-inflammatory pathways, which results in a "low grade chronic pro-inflammatory status" (Franceschi *et al.*, 2007). Inflammaging is thought to be a driving force behind many forms of age-related pathologies, such as neurodegeneration, atherosclerosis, metabolic syndrome, diabetes mellitus, and sarcopenia (Franceschi and Bonafe, 2003). There is increasing evidence to suggest that inflammaging is associated with inflammatory diseases of the musculoskeletal system (i.e., osteoporosis, OA, and RA) (Berenbaum, 2013; Lencel and Magne 2011; Sellam *et al.*, 2013). In this context, humans and other animals must maintain homeostasis as they age, despite incessant attack from both intrinsic and extrinsic stimuli (Goto, 2008). Increased longevity results in a reduced capacity to mount inflammatory responses to infections and coordinate efficient anti-inflammatory responses to antigens and other noxious agents in our food and environment. Molecular evidence points to a disturbed interplay between autophagy and inflammasomes (Salminen *et al.*, 2012a). Declined autophagic capacity in aging cells impairs the process of cellular housekeeping. This leads to protein aggregation, accumulation of misfolded proteins, and the formation of dysfunctional mitochondria, which increases the generation of ROS thus promoting oxidative stress. In turn, oxidative stress can induce the assembly of inflammasomes (Salminen *et al.*, 2012b). Nod-like receptor protein 3 (NLRP3) is the major immune sensor for cellular stress signals. NLRP3 inflammasome-dependent inflammatory responses are triggered by a variety of signals of host danger, including infection, tissue damage, and metabolic dysregulation (Tschopp, 2011; Zhou *et al.*, 2011). Inflammatory signals activate inflammasome-dependent responses and caspases, predominantly caspase-1, which cleaves the inactive precursors of interleukins, thus stimulating their elevated secretion and activity (Salminen *et al.*, 2012a). Consequently, these cytokines promote inflammatory responses and accelerate the aging process by inhibiting autophagy, which is believed to be a protective mechanism in cartilage. Autophagy may be a protective or homeostatic mechanism in normal cartilage (Lotz *et al.*, 2011). However, in OA it is associated with a reduction and loss of Unc-51-like kinase 1 (ULK1), an inducer of autophagy, Beclin1, a regulator

of autophagy, and microtubule-associated protein 1 light chain 3 (LC3), which initiates autophagy and increases chondrocyte apoptosis (Carames *et al.*, 2010).

7.5 Nutrigenomics

Nutrigenomics is the study of the effects of foods and food constituents on gene expression (Figure 7.3) (van Ommen and Stierum, 2002). This field of study has emerged because of the modern realization that the health effects of food-derived substances start at the molecular level (van Ommen, 2004; van Ommen and Stierum, 2002). Therefore, nutrigenomics is a form of personalized nutrition that involves tailoring diets to an individual's genetic makeup, considering genetic variation, allergies, and intolerances (van Ommen, 2007). The changes in gene expression translate to changes in the proteome and metabolome and consequently result in an altered metabolic state, which may have beneficial health effects. An important aim of nutrigenomic research is defining the relationship between genes and nutrients from basic biology to clinical states. We often overlook the fact that nutrigenomics and systems biology apply the same set of tools and technologies. The nutrigenomics approach extracts relevant differences, which become leads for further hypothesis driven and mechanistic research. The application of systems biology approaches in nutritional research aim to describe the physiological responses of culture models, experimental animals, and human subjects by exploiting the datasets, focusing on biochemical pathways, molecular targets for therapy, and potential biomarkers. Within this nutrigenomic framework, the term "nutritargeting" can be applied. Nutritargeting is defined as the targeting of a nutrient or nutrients to specific "target" tissues and is analogous to the term "drug targeting" (Biesalski and Tinz, 2008). There is a good scientific rationale for this intuitive idea. Some tissues are able to accumulate and utilize micronutrients selectively. For example, the antioxidant vitamin C is selectively accumulated in astroglial cells in the brain and in the lens of the eye (where it fulfills antioxidative and metabolic functions, facilitating the formation of collagen structures) (Biesalski and Tinz, 2008. Dehydroascorbic acid, the oxidized form of vitamin C, can enter the cell via the glucose transporter GLUT1 (Troadec and Kaplan, 2008). GLUT1 is expressed in tissues as a consequence of low oxygen pressure leading to upregulation of HIF1-α (a finding that is well documented in cancer cells; Airley *et al.*, 2007). These observations highlight the importance of vitamin C and its oxidized form dehydroascorbate in clinical nutrition, particularly in critically ill patients (Biesalski, 2008; McGregor and Biesalski, 2006).

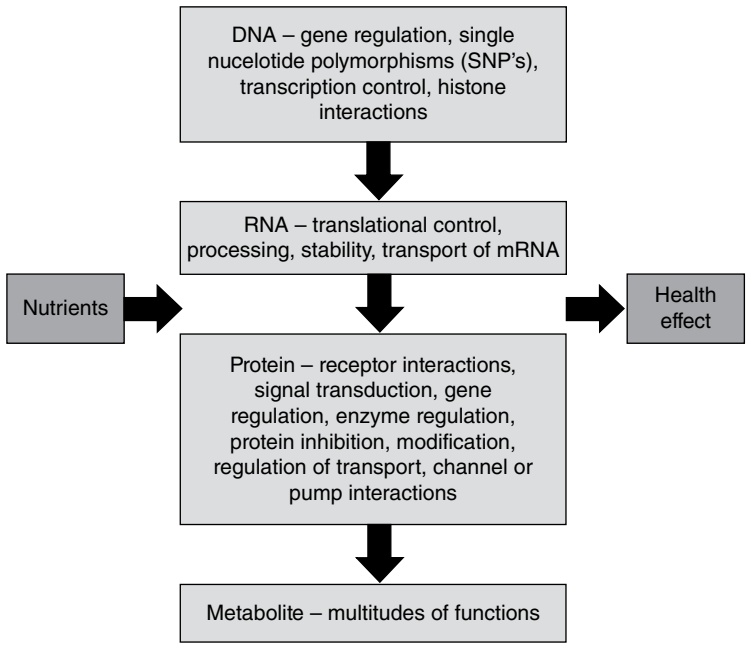

Figure 7.3 *Nutrigenomics. The study of the effects of nutrients on gene expression.*

Approximately 40% of the body's ascorbate is stored in skeletal muscle because this tissue is relatively abundant and its cellular concentration is ten-fold higher than the plasma level. The concept of nutritargeting relates to the gradual accumulation of micronutrients in target tissues using specific "carriers" or removal of the main barriers to absorption and tissue accumulation. For example, naturally occurring curcumin, which is poorly absorbed, exhibits increased bioavailability when complexed with polysorbate. "Nutritargeting" may play an important role in diseases where either systemic absorption is not possible (e.g., malabsorption/ maldigestion) or where significant local deficits occur, which may not adequately be supplied by the systemic application of that nutrient (Biesalski and Tinz, 2008). One of the goals of nutrition research is to optimize health and prevent or delay disease (van Ommen *et al.*, 2009). Research that targets certain aspects of the overarching drivers of health (metabolism, oxidation, inflammation, and stress responses) may be instrumental in creating knowledge for maintaining health and preventing disease through nutrition (van Ommen *et al.*, 2009).

We have discussed the importance of oxidative stress and inflammaging in cartilage biology in two recently published book chapters (Mobasheri *et al.*, 2013, 2014). The remaining part of this chapter will deal with inflammation in muscle and its relevance to OA. We also review some data of the literature that focuses on the effects of nutrients and polyphenols on muscle.

7.6 Muscle Inflammation in OA

An often-overlooked contributor to the progression of OA is sarcopenia and muscle weakness. Muscular support for the joint is important for the health of the whole joint organ. A considerable body of data shows that there is a strong correlation between muscle weakness and the presence of OA in patients (Palmieri-Smith *et al.*, 2010; Segal *et al.*, 2010), and indeed, muscle weakness is a better predictor of knee OA than joint space narrowing itself (McAlindon *et al.*, 1993). Although correlation does not imply causation, animal models confirm that experimentally induced muscle weakness does precipitate joint degeneration (Egloff *et al.*, 2014; Rehan Youssef *et al.*, 2009). It also seems logical that some of the amelioration of OA claimed to occur with moderate exercise could be because the joint receives more support from the strengthened (trained) musculature (Roos *et al.*, 2011). Skeletal muscle itself is well known to be vulnerable to the effects of cytokines (Roubenoff *et al.*, 2003) and these are, in turn, well known to increase with aging (Table 7.1). It is of note that changes of cytokines can include both those typically thought of as pro and anti-inflammatory, and that "successful aging" (i.e., aging without co-morbidity, is still associated with increased inflammatory activity; Krabbe *et al.*, 2004).

There is substantial evidence from studies of rodent models that skeletal muscle is highly sensitive to regulation by factors in the circulation. Experiments have shown that age-related deficits in muscle (loss of mass and contractile force generation, and impaired regeneration) can be restored by exposure of the tissue to young blood (Conboy *et al.*, 2005). Furthermore, recent work has shown that the protein growth differentiation factor (GDF)-11, as well as the hormone testosterone, which are both systemically depleted with aging, are key contributors to the rejuvenation of muscle function by young blood (Sinha *et al.*, 2014a, b). Other circulating factors are also likely to influence muscle function with aging. Consistent with the inflammaging hypothesis, injection of the pro-inflammatory cytokines TNF-α or IL-6 into rodents induces muscle atrophy (Fujita *et al.*, 1996; Haddad *et al.*, 2005; Janssen *et al.*, 2005; Li *et al.*, 2005). Transgenic mice over expressing IL-6 exhibit muscle atrophy resembling early-onset sarcopenia (muscle wastage or loss), which was prevented by regular subcutaneous injection of an IL-6 receptor-blocking antibody (Tsujinaka *et al.*, 1996). Both TNF-α and IL-6 have been reported to be increased in the human circulation with aging (Bartlett *et al.*, 2012; Forsey *et al.*, 2003), and in older people, circulating IL-6 and C-reactive protein (CRP) concentrations were inversely correlated with muscle strength, while the anti-inflammatory protein α1-antichymotrypsin was found to protect against losses of muscle strength and mass (Schaap *et al.*, 2006).

An area garnering rising interest connected with inflammaging is the nutraceutical intervention concept, that is, supplementation of dietary non-medicinal extracts from herbs, spices, fruits, vegetables, teas, and other sources to deliver bioactive compounds that ameliorate age-related chronic inflammation. Certain dietary interventions such as these may modify the circulating milieu of cytokines and growth hormones, and thus act to maintain or restore muscle mass and function in older people. It is hoped that interdicting the age-related increase in muscle cytokines and downstream weakness will improve joint mobility in the elderly through reductions of both sarcopenia itself and of joint degeneration. Polyphenols, a class of compounds found in some edible plants, are under active investigation for their potential to reduce chronic inflammation. In plants, polyphenols function as antimicrobials, stress response factors, and pigments. However, they also induce structure-specific responses in mammalian cells, either directly or via secondary metabolites. At physiological doses, polyphenols have been shown to modulate ion channels (Wallace *et al.*, 2006), inhibit pro- inflammatory NF-κB signaling (Kundu *et al.*, 2006) and cyclooxygenase and lipoxygenase activities (Kimura *et al.*, 1985; Kundu *et al.*, 2006), suppress intracellular reactive oxygen species (Lombardo *et al.*, 2013), interact with enzymes involved in redox signaling

Table 7.1 *Cytokines linked to aging. A number of cytokines have been shown to change abundance as humans and non-human animals age. The arrows indicate whether levels tend to increase or decrease during aging. Asterisks indicate those cytokines typically thought of as "anti-inflammatory" (Marietta* et al.*, 1996; Yogesha* et al.*, 2009) (IL3), (Hart* et al.*, 1989; Nolan* et al.*, 2005) (IL4), (Marie* et al.*, 1996) (IL-4, IL-10, and IL-13).*

Significantly associated with aging	Not significantly associated with aging
↑ TNF-α (Diniz *et al.*, 2010; Fagiolo *et al.*, 1993; Morrisette-Thomas *et al.*, 2014; Mooradian *et al.*, 1991; Paganelli *et al.*, 1994)	MCP1 (Morrisette-Thomas *et al.*, 2014)
↓ IFN-γ (Paganelli *et al.*, 1994; Rink *et al.*, 1998)	IL-7 (Nikolich-Zugich, 2008)
↑ IL-18 (Morrisette-Thomas *et al.*, 2014)	IL-8 (Morrisette-Thomas *et al.*, 2014)
↑ hsCRP (Krabbe *et al.*, 2004; Morrisette-Thomas *et al.*, 2014)	IL-12 (Morrisette-Thomas *et al.*, 2014)
↑ IL-1 (Paganelli *et al.*, 1994; Rink *et al.*, 1998)	
↓ IL-2 (Gillis *et al.*, 1981; Rink *et al.*, 1998)	
↑ IL-3* (Paganelli *et al.*, 1994; Rink *et al.*, 1998)	
↑ IL-4* (Paganelli *et al.*, 1994)	
↑ IL-6 (Ershler *et al.*, 1993; Fagiolo *et al.*, 1993; Fernandez-Real *et al.*, 2001; Morrisette-Thomas *et al.*, 2014; Paganelli *et al.*, 1994)	
↑ IL-10* (Cakman *et al.*, 1996; Miles *et al.*, 2008; Morrisette-Thomas *et al.*, 2014; Rink *et al.*, 1998)	
↓ IL-15 (Morrisette-Thomas *et al.*, 2014)	
↑ IL-18 (Morrisette-Thomas *et al.*, 2014)	
↑ MCP-1 (Miles *et al.*, 2008)	
↑ 6Ckine (Miles *et al.*, 2008)	
↑ Eotaxin-1 (Shurin *et al.*, 2007)	
↑ MIG (Shurin *et al.*, 2007)	

(Buryanovskyy *et al.*, 2004; Lu *et al.*, 2006; Takahashi *et al.*, 2012), influence cellular metabolism, autophagy, and protein acetylation (El-Mowafy and Alkhalaf, 2003; Gu *et al.*, 2014; Pietrocola *et al.*, 2012), and bind directly to microRNAs (Baselga-Escudero *et al.*, 2014). As little as 200 ml of red wine is reported to potentially contain sufficient polyphenols to modulate ATP dependent potassium channels (Mosca *et al.*, 2002). Potassium channels are well known to be expressed by both joint chondrocytes (Mobasheri *et al.*, 2007) and a variety of mammalian muscle cell types (Wellman *et al.*, 1999).

A wide range of polyphenols are potentially of interest to the study of muscle inflammaging and nutrigenomics, including quercetin and its glycosylated/methylated derivatives, which are found in many different common fruits and vegetables, including onions and apples; curcumin, from the Indian spice turmeric, which is a core component of the Ayurvedic and Unani traditional medical systems; gingerol, from ginger, which is closely related to turmeric; resveratrol, from red grapes, and epigallocatechin gallate (EGCG), from green tea. These structures have been reported to inhibit pro-inflammatory signaling *in vitro* and *in vivo*, and while the existing literature is somewhat limited in respect to their actions on skeletal muscle, those studies that have been performed have shown some interesting results. Long-term dietary supplementation of mdx mice (a widely used genetic model of muscular dystrophy) with quercetin significantly reduced the progression of the dystrophy phenotype (Hollinger *et al.*, 2014). The limb immobilization/suspension rodent model is frequently used for the study of skeletal muscle atrophy; muscles thus unloaded show increased proteasomal/apoptosomal activity, indicating atrophy. Daily injection of hindlimb-immobilized rats with curcumin was found to abrogate the muscle atrophy response (Vazeille *et al.*, 2012). Oral supplementation with resveratrol also maintained muscle mass and protected against metabolic dysfunction in a rat muscle unloading model (Momken *et al.*, 2011). There is accumulating evidence that polyphenols may inhibit the induction of atrophy by factors involved in inflammaging. An *in vitro* model of muscle showed significantly less atrophy when treated with resveratrol and TNF-α together, compared with TNF-α treatment only (Wang *et al.*, 2014). This study highlighted the Akt/mTOR/FoxO1 signaling pathway as a regulatory target of resveratrol in alleviating TNF-α-induced atrophy. However, long-term dietary supplementation of mice with resveratrol did not prevent age-related sarcopenia, indicating that other polyphenols may be better candidates for use as interventions in aging (Jackson *et al.*, 2011). The green tea polyphenol, EGCG, has come to the fore as an anti-atrophic polyphenol following several studies over

the last decade. Although EGCG supplementation in the diet did not protect against primary muscle atrophy in an aged rat hindlimb-immobilization model, EGCG-supplemented rats showed significantly increased muscle recovery after remobilization (Alway *et al.*, 2014). Loss of force in a mouse model of muscle unloading was also reduced by dietary EGCG supplementation (Ota *et al.*, 2011), and EGCG delivered either through the diet or by subcutaneous injection protected against muscular dystrophy in mdx mice (Dorchies *et al.*, 2006; Nakae *et al.*, 2008). In mice with tumor-driven cachexia, EGCG attenuated muscle atrophy and suppressed NF-κB signaling in muscle (Wang *et al.*, 2011). The induction of myotube atrophy markers in a physical *in vitro* model of muscle unloading (three-dimensional clinorotation) was significantly inhibited by treatment by EGCG (Hemdan *et al.*, 2009) and EGCG treatment also significantly reduced serum starvation-induced myotube atrophy (Mirza *et al.*, 2014). The evidence that is presently available therefore points towards EGCG (or green tea) as a promising dietary intervention to potentially reduce muscle dysfunction and atrophy in aging. A trial was conducted in sarcopenic Japanese women; the subjects either underwent a program of exercise, were supplemented with green tea catechins, or undertook both interventions together. Interestingly, the only group to show a significant increase in leg muscle mass (2% increase after 3 months) was the combined catechins and exercise group, neither catechins alone nor exercise alone were effective (Kim *et al.*, 2013). The structurally similar cocoa polyphenol, (-)-epicatechin, has also been reported to protect against sarcopenia in mice (Gutierrez-Salmean *et al.*, 2014), and normalize aberrant metabolic processes in skeletal muscle of patients with systemic age-related conditions (Ramirez-Sanchez *et al.*, 2013). In addition to these promising reports on EGCG and (-)-epicatechin, there are hundreds of polyphenols relevant to the human diet that have not been studied in the context of skeletal muscle atrophy, and other anti-sarcopenic compounds may remain among this unexplored pool of potential bioactives. Also of interest is the non-polyphenolic organosulfur compound diallyl sulfide, found predominantly in garlic, which was found to inhibit muscle atrophy in mice with cancer cachexia, and also led to increased muscle weights in healthy control subjects (Olivan *et al.*, 2011).

In summary, there is clear evidence that inflammaging exerts effects on muscle that contribute to progression of OA, and several promising candidate plant-derived bioactive molecules may beneficially modulate one or more aspects of the inflammaging/muscle weakness/joint degradation trinity in the development of OA (Figure 7.4). Of these compounds, EGCG from green tea is arguably best evidenced to improve muscle function, and further study is warranted for diallyl sulfide from garlic, curcumin from turmeric, (-)-epicatechin from cocoa, and quercetin from onions and apples.

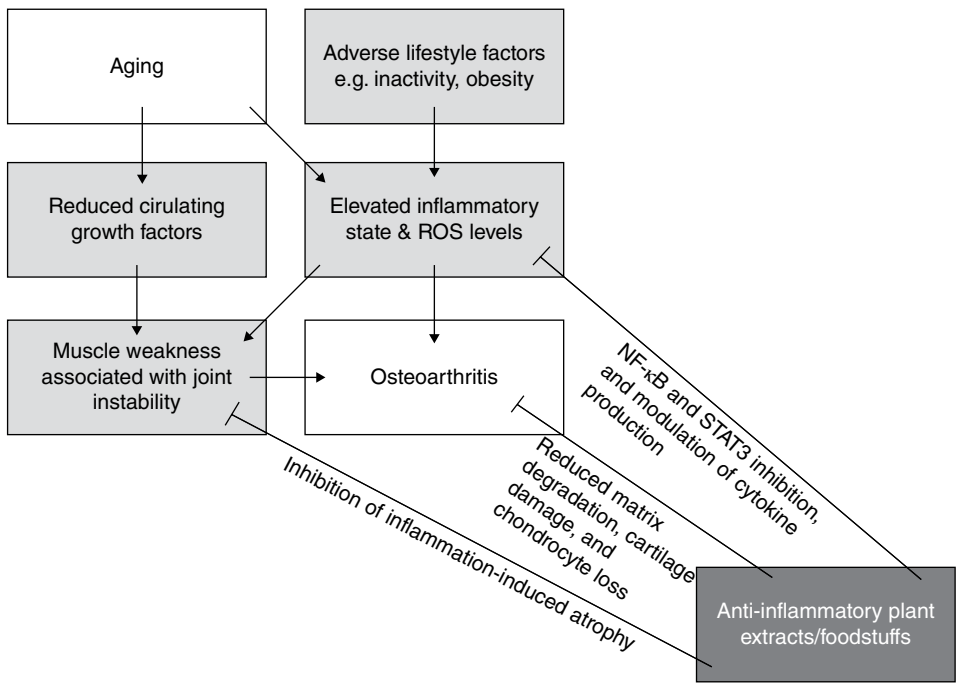

Figure 7.4 *The relationship between aging, OA and anti-inflammatory nutraceuticals, functional foods, and natural plant products/extracts.*

7.7 Conclusions

Nutraceuticals, functional foods and dietary supplements have become important areas of research and clinical practice in orthopedics and rheumatology. The elderly population is rapidly growing and expanding throughout the developed and developing worlds. Therefore, the use of herbal and complementary medicines for the treatment of persistent musculoskeletal pain will continue to increase. Therefore, it is important that patients and health-care providers are aware of the evidence for or against these approaches. Some of the published evidence suggests that several herbal medicines and dietary supplements have the capacity to alleviate the pain of OA and RA. For several treatments, the risk-benefit profile is encouraging. Some herbal remedies are inhibitors of NF-κB and may be able to reduce the consumption of NSAIDs. Nutraceuticals, functional foods and dietary supplements may be used to supplement some of the benefits from existing pharmaceutical treatment modalities for OA. In such situations the aim is to reduce the frequency of consumption and dosages of conventional drugs such as NSAIDs, which have significant side-effects. However, the objective is not to replace NSAIDs altogether because they not only provide pain relief, but also possess valuable anti-inflammatory activity. However, patients with OA routinely use prescribed and alternative products at the same time. There is potential for adverse drug interactions and patients should be made aware of the risks associated with taking multiple products. Also, many nutraceuticals and functional foods have not been tested properly in rigorous clinical trials examining the efficacy of herbal remedies are needed before definitive recommendations regarding the application of these modalities can be made.

The European Food Safety Authority (EFSA) based in Parma, Italy has recently issued new guidelines and proposed new scientific requirements for health claims related to the maintenance of joints and to the reduction of the risk of developing OA. EFSA has proposed that clinical trials of functional foods and nutraceuticals should be designed in new and innovative ways to demonstrate a "beneficial physiological effect" on healthy joints. According to these new guidelines, only clinical trials designed to demonstrate a beneficial physiological effect on joints or a reduction in joint degradation in people without OA should be accepted as indicative. These guidelines present some major new challenges to the scientific and clinical communities. Furthermore, they create a number of opportunities for new types of clinical trials. Studies performed in non-diseased (but including high risk) population subgroups in which the incidence of OA is the outcome measure could be used for substantiation of health claims relating to the normal maintenance of the joint. Whilst attempting to address these requirements, we need to discriminate between food and non-food supplements. Studies dealing with "non-foods" will require a much more traditional pharmacological design compared to studies on "foods". Clearly, addressing these issues requires new strategies and large scale clinical studies lasting several decades. Such new trials will require radical rethinking of the concept of clinical trials in the OA research community. Human studies will be necessary for substantiation of clinical data and study groups should be representative of the entire population. The hierarchy of evidence should also be considered; for example, double blind interventional studies are of greater significance compared to observational studies and reproducibility of the effect much be demonstrated. In addition, demonstrating efficacy of food supplements to organizations such as EFSA will require data on tolerance and safety, specifically gastric tolerance, hepatotoxicity, renal toxicity, and allergenicity.

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