Role of Interleukin-15 in Sarcopenia: Future New Target Therapy

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Introduction

The term sarcopenia was first introduced by Rosenberg (1989), refers to decrease in muscle mass with aging (2 Standard Deviations (SD) below the young adults mean). Furthermore, muscle dysfunction is associated with the definition of sarcopenia so that the term sarcopenia with impaired mobility is more applicable clinically. Sarcopenia results in impaired mobility and function, risk of falls and death. Sarcopenia is the leading cause of frailty. Sarcopenia occurs in about 5 to 10% of the population over 65 years old and the cause is multifactorial include illness, decreased caloric intake, impaired blood flow to muscles, mitochondrial dysfunction, decreased anabolic hormone and increased proinflammatory cytokines. It is now known that the key element of sarcopenia is a loss of muscle strength (dynapenia) rather than loss of muscle mass. This leads to a change in the definition of sarcopenia which includes grip strength or function (walking speed or distance) [1,2].

As aging process, there is a significant change in the body composition, the increased of fat mass while the muscle mass decreases with the rate of muscle mass loss of about 1.5% per year at the age of 60 years to 3% per year thereafter. It is also associated with increased serum markers of inflammation and co-factor. Inflamm-aging is characterized by systemic, chronic and low-grade inflammation without any sign of infection that can lead to tissue degeneration. Inflamm-aging was followed by a decrease in the number of T and B lymphocyte, Natural Killer (NK) cells, along with increased tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), IL-1, and C-reactive Protein (CRP) [3]. TNF-α triggers apoptosis in the skeletal muscle contributing to muscle atrophy, as one of the pathophysiological basis of sarcopenia. In contrast, IL-15 is expressed in skeletal muscle and is identified as an anabolic factor in muscle growth. IL-15 also plays a role in reducing adipose tissue mass and progression and survival of NK lymphocytes. IL-15 has anti-apoptotic ability through inhibition of pathways mediated by TNF-α [4,5].

This literature review will deals with the interaction between cytokines especially IL-15 with other proinflammatory cytokines in relation to sarcopenia in elderly.

Sarcopenia Definition

Sarcopenia was originally defined as an excessive loss of muscle mass that is associated with aging. But not all individuals show a uniform muscle mass loss rate. The variation even occurs in the same age group. The decreased of muscle strength was identified to be more involved in the occurrence of sarcopenia than muscle mass. Based on this concept, a number of associations around the world revised the definition of sarcopenia [1,2]. (Table 1)

Definition	Function	Muscle mass
SIG: cachexia-anorexia in chronic wasting disease	Gait speed <0.8 m/s, or other physical performance test	Low muscle mass (2 SD)
EWGSOP	Gait speed <0.8 m/s; grip strength: 40 kg males, 30 kg females	Low muscle mass (not defined)
IWGS Sarcopenia Task Force	Gait speed <1.0 m/s, grip strength	Low Appendicular lean mass (<7.23 kg/m^2 in men, 5.67 in women)
Sarcopenia with Limited Mobility (SCWD)	6-minute walk <400 m, or gait speed <1.0 m/s	Low Appendicular lean mass /height^2
Asian Working Group for Sarcopenia	Gait speed <0.8 m/s; grip strength: 26 kg males, 18 kg females	Low Appendicular lean mass /height^2
Foundation for the National Institutes of Health	Gait speed <0.8 m/s; grip strength: 26 kg males, 16 kg females	Appendicular lean mass/body mass index

Table 1: Comparison of sarcopenia definitions [1].

The European Working Group on Sarcopenia in Older People (EWGSOP) defines 3 levels for sarcopenia: pre-sarcopenia (loss of

muscle mass), sarcopenia (loss of muscle mass followed by either loss of strength or decreased physical performance), and severe sarcopenia (three aspects are met) [2,6]. In some individuals, a single clear cause can be identified whereas other cases are hard to find. Thus, the category of primary and secondary sarcopenia can be useful in clinical practice. Sarcopenia is said to be primary when there is no other cause other than the aging process itself whereas secondary sarcopenia when there are one or more obvious causes. Cachexia is often seen in elderly as a condition of severe muscle mass loss associated with conditions of diseases such as cancer, congestive cardiomyopathic and end stage renal failure. Cachexia has been defined as a complex metabolic syndrome associated with the underlying disease and is characterized by loss of muscle mass with or without loss of fat mass. Cachexia is associated with inflammation, insulin resistance, anorexia and increased catabolism of muscle protein that cannot be managed by nutritional support only. So, most people with cachexia also suffer from sarcopenia but individuals with sarcopenia are not necessarily cachexia. Sarcopenia is one element of cachexia [6,7].

Sarcopenia Prevalence

Since Baumgartner et al. [8], defines sarcopenia as 2 SD below normal - appendicular muscle mass divided by squared height, a number of groups have examined the prevalence of sarcopenia. Five to thirteen percent of elderly people over 60 years' experience low muscle mass with a prevalence of up to 50% in elderly people aged 80 years or older, representing about 50 million populations in the world. As life expectancy increases, the number is expected to increase by 10-fold in 2050 [2,9]. Coin et al. [10] found that 20% of elderly people in Italy had low muscle mass. In Korea, the prevalence of sarcopenia using Baumgartner criteria is 0.8% in women and 1.3% in men over 60 years. In Barcelona, sarcopenia occurs in 33% of elderly women and 10% in men. In Taiwan, sarcopenia occurs in 2.5% of women and 5.4% of men [1].

Using the EWGSOP definition, 4.6% of men and 7.9% of women in Hertfordshire have sarcopenia. In Japan, 21.8% of men and 22.9% of women ages 65 to 89 are sarcopenia. In nursing home residents, 32.8% suffer from sarcopenia. The prevalence of sarcopenia is slightly lower using the International Working Group on Sarcopenia (IWGS) [11]. The Foundation for the National Institutes of Health (FNIH) criteria was based on developing cutoffs using a variety of large epidemiological studies. These criteria are more restrictive with only 1.3 % of men and 2.3 % of women being defined as having sarcopenia [1].

The health cost associated with sarcopenia in 2000 was about 1.5% of total health expenditure. A 10% reduction in the prevalence of sarcopenia will save healthcare costs to 1.1 billion US dollars [7,8].

Alternative Approach to Diagnose Sarcopenia

Based on the operational definition of EWGSOP, the diagnosis of sarcopenia requires a decrease in muscle mass with low grip strength or decreased physical performance. A number of techniques have been used to measure muscle mass such as Dual-Energy X-Ray Absorptiometry (DEXA), Computed Tomography (CT), Magnetic Resonance Imaging (MRI), Ultrasonography (USG), Bioelectrical Impedance Analysis (BIA) and Anthropometry [1]. Sarcopenia screening is important because in the early phase it is often overlooked. The adopted screening method is a 2-step EWGSOP algorithm where patients with a gait speed of ≤0.8m/s will be measured the muscle mass while those with a gait speed of >0.8 m/s will undergo a grip strength check. But research for validation of this algorithm is still limited [9].

Moreover, based on the principle that clinicians prefer a simpler questionnaire than doing more examination to diagnose sarcopenia, Malmstrom and Morley [12] develop SARC-F questionnaire, by assessing the five domains of strength, assistance in walking, rising from a chair, stair climbing and falls. A total score of 10 with each domain is maximum score 2. A score of 4 or more indicates a risk of sarcopenia and appears to be associated with poor outcomes in the elderly [9]. It has been validated by two published studies. Woo et al. [13] Found that SARC-F has predictive capabilities comparable to EWGSOP, IWGS, and the Asian Working Group for Sarcopenia criteria. In Asian populations, it has modest predicted value of physical limitations in 4 years. Cao et al. [14] also provides evidence for the validity of SARC-F which shows that the SARC-F≥4 score is associated with poor physical function and hospitalization due to fall within 2 years thus increasing the strength and usefulness of this questionnaire [1,9,15]. (Table 2)

Component	Question	Scoring
Strength	How much difficulty do you have in lifting and carrying 10 lb (4.54 kg)?	None=0 Some=1 A lot or unable=2
Assistance in walking	How much difficulty do you have walking across a room?	None=0 Some=1 A lot, use aids, or unable=2
Rise from a chair	How much difficulty do you have transferring from a chair or bed?	None=0 Some=1 A lot or unable without help=2
Climb stairs	How much difficulty do you have climbing a flight of 10 stairs?	None=0 Some=1 A lot or unable =2
Falls	How many times have you fallen in the past year?	None=0 1–3 falls=1 ≥4falls=2

Table 2: SARC-F Questionnaire [1].

Sarcopenia Pathophysiology

From a histological point of view, skeletal muscle consists of type I and type II fibers. Type II fast fibers have higher glycolytic potential, lower oxidative capacity and faster response while slow type I fibers are known as fatigue-resistant fibers because they have greater mitochondrial density and capillaries and myoglobin. Sarcopenia is characterized by the dominant atrophy of type II fibers accompanied by smaller and fewer mitochondria. In aging conditions, there is a significant increase in inflammatory markers. Franceschi et al. describes the inflammatory conditions of low-grade chronic inflamm-aging, related to the concept of immunosenescence. Disturbance of regenerative capacity, production, mitochondrial functional changes, muscle inactivity that alters the ability to respond to stress, are important contributing factors to the occurrence of sarcopenia. Inflamm-aging triggers the production of Reactive Oxygen Species (ROS) and tissue damage through the release of cytokines such as TNF-α, IL-1, IL-6 and CRP as well as decreases in T, B and NK cells. These cytokines lead to the occurrence of sarcopenia through activation of The Ubiquitine-Protease System (UPS) [2,3,16]. (Figure 1)

Figure 1: Signaling pathways leading to muscle atrophy [7].

Factors that play a role in the sarcopenia are multifactorial. Unused muscle with aging process is the main underlying cause. Poor blood flow to the muscles, especially the muscle capillaries resulting from reduced production of nitric oxide, is another important cause. The aging process is associated with increased mitochondrial abnormalities that impact on impairment of mitochondrial membrane permeability and apoptosis. Aging is also associated with physiological anorexia, which can lead to weight loss. Losing weight affects 75% loss of fat mass and 25% loss

of muscle and bone mass. Decreased of age-related motor neuron end-plate are also important components for the occurrence of sarcopenia because it not only causes a decrease in muscle mass but also decreases muscle function. Decreased levels of anabolic hormones such as testosterone, Dehydroepiandrosterone (DHEA), growth hormone, and Insulin-Growth Factor 1 (IGF-1); occurs in elderly. It is a potent activator of AKT-mammalian target of rapamycin (mTOR) which is important in the synthesis of muscle protein and reduces muscle degradation by inhibiting the protein Forkhead Box O (Fox-O). Testosterone is an important hormone associated with decreased muscle mass and strength in sarcopenia. Testosterone is not only for protein synthesis but also maintains satellite cells. In addition, low vitamin D levels are associated with severe muscle weakness and risk of falls. In addition, the path of myostatin-activin A is also activated under conditions of sarcopenia. Insulin resistance that occurs in old age and obesity plays an important role in decreasing the availability of glucose and protein for protein anabolism [7,17-19]. (Figure 2)
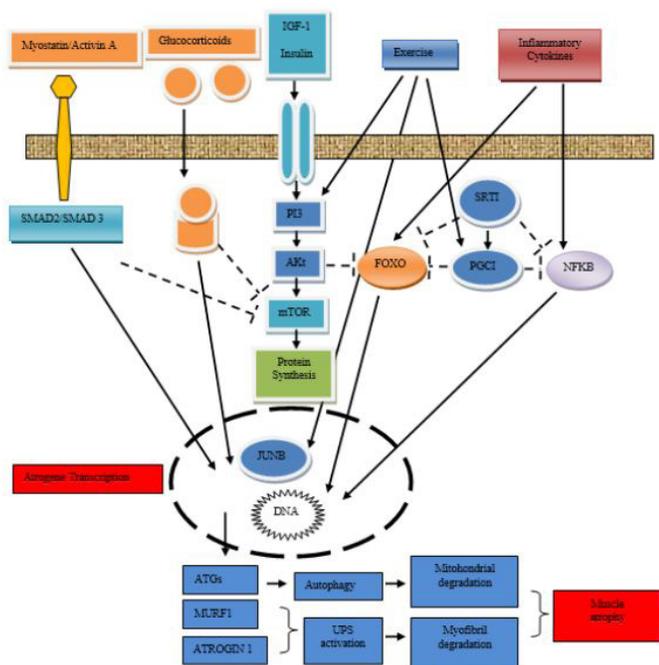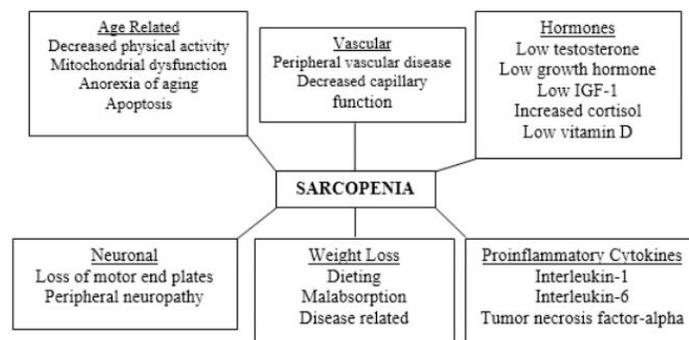

Figure 2: The Cause of Sarcopenia [1].

Cytokines Involved in Sarcopenia

Skeletal muscles are composed by different types of cells including myocytes, fibroblasts, pericytes, adipocytes, motoneuron, and connective tissue. Among these skeletal muscle cells, not only myocytes but also pericytes (including satellite cells) are reported to trigger interactions with surrounding cells and associated with bioactive factor secretion that is myokin. The term myokin was introduced by Pedersen and Fischer (2007), referring to a factor secreted by contracting skeletal myocytes and its levels increase in the bloodstream in response to increased muscle contraction. But many myokines such as IL-6, myostatin, irisin, and others are found secreted by adipocytes, so it called adipo-myokines [2].

The well-known proinflammatory cytokines, IL-6, are also called myokines because, based on findings after physical exercise, their basal plasma concentration increases up to 100 times. IL-6 is produced by many cells such as adipocytes, adipose tissue macrophages, fiber types I and II, as well as secretion by skeletal muscle cells in vitro. IL-6 increases in obesity and aging. The increase of IL-6 in circulation during exercise is not followed by

signs of muscle damage. This is not preceded by an increase in another inflammatory mediator's TNF-α. Furthermore, exercise also increases levels of classic anti-inflammatory cytokines such as IL-1 receptor antagonist (IL-1ra) and IL-10, a TNF-α natural inhibitor. This suggests that elevated levels of exercise-related IL-6 show anti-inflammatory effects. On the other hand, elevated levels of IL-6 are associated with decreased IL-10, so inflamm-aging is common in the elderly. Thus, under these conditions it should be noted that the beneficial effects of IL-6 are normally associated with temporary and short-term production whereas in persistent inflammatory conditions, certain types of cancer and other chronic disease conditions are associated with a systemic increase in IL-6 levels. Other studies have shown that IL-6 and serum amyloid A produced in the liver synergistically improve Muscle Ring Finger-1 (MuRF1) and atrogin-1 expression by inducing the expression of Suppressor of Cytokine Signaling (SOCS-3) as well as interfering with downstream signaling insulin/IGF-1 in the skeletal muscle to trigger muscle atrophy [3,4,20].

It appears that unlike the signaling of IL-6 by macrophage-dependent activation of Nuclear Factor kB (NFkB) signaling pathways, the expression of IL-6 intramuscular regulated by signaling homodimer gp130Rb/IL-6RA that cause activation of glycogen/p38 Mitogen-Activated Protein Kinase (MAPK) and/or Phosphatidylinositol 3-kinase (PI3-kinase) thereby improving glucose uptake and fat oxidation. IL-6 is also known to increase hepatic glucose production during exercise or lipolysis in adipose tissue. So that when IL-6 is produced by macrophages, it will cause an inflammatory response while muscle cells produce and release IL-6 without activating the classical proinflammatory pathways. The paradox about the pleiotropic effect of IL-6 is more dependent on the environment (muscle versus immune cells). Exercise induces an increase in exponential IL-6 plasma concentrations. The peak IL-6 levels are reached at the end of the exercise or some time afterwards. Chronic increase in IL-6 lead to hyperinsulinemia, reduced body mass and impaired insulin to regulate glucose uptake in skeletal muscle. In elderly patients with type 2 DM, the circulating IL-6 level is 2 to 3 times higher than younger and healthier individuals [21,22]. (Figure 3)
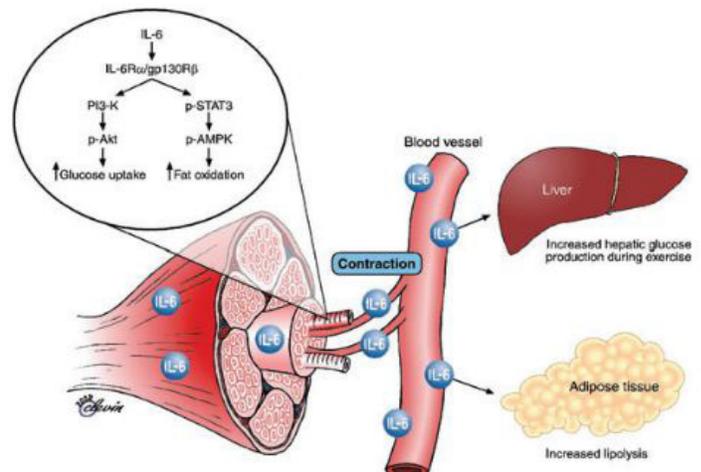

Figure 3: Biological role of contraction-induced IL-6 [17].

TNF-α is a proinflammatory cytokine produced by monocytes, macrophages, and other similar cells such as Kupffer cells and brain microglia. TNF-α is also produced by other cells such as B, T, and NK lymphocytes and adipocytes. In visceral adipose tissue, TNF-α is generated more by adipose tissue macrophages. TNF-α increases with age even in healthy individuals. TNF-α causes apoptosis of T and NK cells [4]. Myoblasts exposure by TNF-α leads to inhibition of myogenic differentiation through enhancement of MyoD proteolysis via UPS pathways. TNF-α is also reported to suppress the Akt/mTOR pathway, causing muscle catabolism [3].

TNF-α has a direct inhibition effect on insulin signaling. Infusion of TNF-α in healthy individual induces insulin resistance in skeletal muscle without the effect of endogenous glucose production. *In vivo*, TNF-α causes insulin resistance indirectly through the release of Free Fatty Acids (FFA) from adipose tissue. Some downstream mediators and signaling pathways associated with insulin regulation activated by TNF-α include C-Jun N-Terminal Kinase (JNK) and IκβKinase (IκβK). This signaling effect is associated with phosphorylation disorders of Akt substrate 160, the earliest identified steps involved in a cascade of insulin signaling that regulate the Glucose Transporter Type 4 (GLUT4) transloca-

tion and glucose uptake. TNF-α and IL-6 have different biological profiles and it is known that TNF-α triggers IL-6 release, but theoretically TNF-α derived from adipose tissue is actually the main trigger for inflammation that triggers insulin resistance [23].

Interleukin-15

Interleukin-15 (IL-15) is a 14 to 15-kDa cytokine that is widely expressed at the level of messenger Ribonucleic Acid (mRNA) and protein in skeletal muscle compared to other muscles. In humans, IL-15 mRNA is more expressed in muscles composed of Type II fibers than muscles with Type I fibers but their own protein content is almost identical in all muscle types [24]. IL-15 is classified as interleukin based on the secondary structure of 4-α-helical and its ability that resembles IL-2 function. The receptors for IL-2 and IL-15 are heterotrimeric and also both contain another subunit, referred to here as IL-2/15Rβ (also known as the IL-2 receptor β-chain (IL-2Rβ), IL-15Rβ and CD122). In addition, the high-affinity forms of the IL-2R and IL-15R contain a third, unique receptor sub-unit: IL-2Rα (also known as CD25) or IL-15Rα, respectively. By contrast, the intermediate-affinity receptors include only the β-chain and the γ-chain. Expression of the IL-15 encoding gene produces translations of 2 isoforms, 21-short amino acids and 48-long amino acids. The long IL-15 isoform should combine intracellularly with its receptor before it is secreted from the skeletal muscle [22,25]. IL-15 requires the presence of IL-15Rα for efficient biosynthesis and secretion [5,26]. (Figure 4)
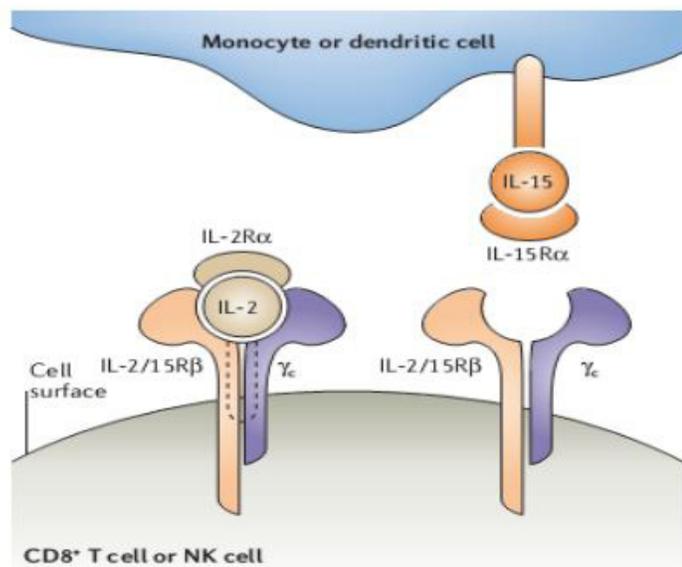

Figure 4: The Structure and interaction of IL-2 and IL-15 with its receptor [26].

In light of the common receptor components and signaling pathways, it was assumed that IL-2 and IL-15 have several similar functions. Indeed, both cytokines stimulate the proliferation of T cells; induce the generation of Cytotoxic T Lymphocytes (CTLs); facilitate the proliferation of, and the synthesis of immunoglobulin by, B cells; and induce the generation and persistence of Natural Killer (NK) cells (Table 3). However, in many adaptive immune responses, IL-2 and IL-15 have distinct, and often competing, roles. IL-2 - through its unique role in Activation-Induced Cell Death (AICD) and its participation in the maintenance of peripheral CD4+ CD25+ regulatory T (TReg) cells-is involved in the elimination of self-reactive T cells, which have a role in the pathogenesis of autoimmune diseases. By contrast, IL-15 is important for the maintenance of long-lasting, high-avidity T-cell responses to invading pathogens, and it achieves this by supporting the survival of CD8+ memory T cells [20].

Properties	IL-2	IL-15
Structure	15.5 kDa; 133 amino acids; four-helix bundle	14 -15 kDa; 114 amino acids; four-helix bundle
Gene structure and location	Four exons; chromosome 4q26	Eight exons; chromosome 4q31
Main site of synthesis	Activated T cells	Dendritic cells and monocytes
Mechanism of regulation of expression	Transcriptional regulation, and stabilization of mRNA	Transcriptional regulation, but mainly post-transcriptional regulation during translation and intracellular trafficking
Receptor	IL-2Rα, IL-2/15Rβand γc are co-expressed by activated T and B cells	IL-15Rα on the surface of monocytes and dendritic cells trans-presents IL-15 to NK cells and CD8+ memory T cells expressing IL-2/15Rβand γc
Function	Proliferation and differentiation of NK cells, and T and B cells; elimination of self-reactive T cells, mediated by AICD and maintenance of TReg cells	Proliferation and differentiation of NK cells, and T and B cells; maintenance of CD8+CD44 memory T cells
Features of mice with knockout of gene encoding cytokine or cytokine-receptor α-chain	Marked enlargement of peripheral lymphoid organs and polyclonal expansion of T- and B-cell populations; associated with autoimmune diseases	Marked reduction in number of NK and NKT cells, and CD8+CD44memory T cells

Table 3: Comparison of human interleukin-2 and interleukin-15 [20].

The most studied IL-15 action regulator pathway is the Janus Kinase Activation of Signal Transducer and Activator of Transcription Proteins (JAK/ STAT) signaling pathway. When IL-15 binds to the IL-2 receptor, Jak isoform (Jak1 and/or Jak3) is auto phosphorylated and then induces STAT3 and/or STAT5

phosphorylation. Overall, the Jak/STAT signaling pathway has a number of intracellular functions with the potential to influence the energy metabolism of different cell types. Other pathway than Jak/STAT cascade have been associated with IL-15 action such as PI3K/Akt and AMPK pathway [19].

IL-15 and IL-15Rα are widely expressed in human skeletal muscle and have anabolic effects *in vitro* and *in vivo* and play a role in reducing adipose tissue mass [5]. Busquets et al. [27] showed that administering IL-15 *in vivo* increased skeletal muscle glucose uptake and IL-15 *in vitro* therapy increased the GLUT4 mRNA content in C2C12 cells. These findings indicate that IL-15 is an important mediator for skeletal muscle growth, hypertrophy and glucose uptake. IL-15 also has an important effect on adipose tissue. IL-15 inhibits adipocyte differentiation in cultures and people with obesity have low blood levels of IL-15. High levels of IL-15 cause lean body type, reduce white adipose tissue and increase the number and function of NK cells. This data supports the conclusion that IL-15 regulates adipose tissue [4,20,28].

With evidence that IL-15 can control glucose and fat metabolism, IL-15 may have an important role in controlling metabolic diseases such as obesity and type 2 DM. A number of studies have shown that exercise increases serum IL-15 concentrations or mRNA levels. The most observed changes associated with serum IL-15 were observations after moderate-intensity resistance exercise. But not all studies show consistent results. After resistance exercise, IL-15 protein levels increased in plasma but IL-15 mRNA levels decreased after 2 hours of intensive strength training [29,30].

The Relation between IL-15 and TNF-α Associated with Sarcopenia

The apoptotic pathway also referred to as an extrinsic pathway is triggered by the interaction between TNF-α and TNF-receptor 1 (TNF-R1) followed by recruitment of adaptor proteins such as Fas-Associated Death Domain (FADD), TNF-Receptor-Associated Death Domain (TRADD) and TNF-Receptor-Associated Factors (TRAFs) that form the Death-Inducing Signalling Complex (DISC) and activate procaspase-8. Cleaved caspase-8 then works downstream to activate caspase-3, resulting in proteolytic events and DNA fragmentation (via caspase-activated DNase, CAD) that result in cellular breakdown. In the presence of apoptotic pressure such as aging, skeletal myocytes may produce anti-apoptotic factors to limit muscle loss. *In vitro* studies have shown that IL-15 causes myosin heavy chain accumulation in differentiated myotubes independent of IGF-1. Quinn et al. (2002) also showed that IL-15 overexpression in cultures stimulates protein synthesis and inhibits proteolysis [5].

Chronic stimulation of IL-15 may result in TNF-R1 downregulation in order to prevent TNF-α-mediated apoptosis as well another proinflammatory cytokines such as IL-1, IL-6, Granulocyte/Macrophage Colony-Stimulating Factor (GM-CSF), chemokines CC-Chemokine Ligand 3 (CCL3), CCL4 and CXC-Chemokine Ligand 8 (CXCL8; known as IL-8). The action of IL-15 is transduced by the cell surface trimeric receptor. IL-15 also interacts with IL-15Rα on the plasma membrane and is presented on adjacent cells and expresses the γc/IL-2Rβ heterodimer. Soluble IL-15Rα (sIL-15Rα) is important in the secretion, stabilization and activity of IL-15. In addition, when acute apoptotic stimuli appear, IL-15Rα can neutralize DISC and trigger the production of anti-apoptotic proteins such as FLICE-Like Inhibitory Protein Long Form (FLIP) and cellular Inhibitor of Apoptosis Protein (cIAPs) through activation of NF-κB [5,26]. (Figure 5)
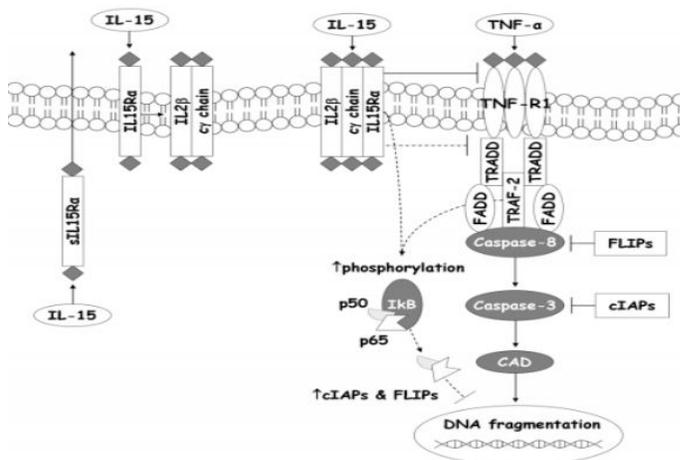

Figure 5: Interplay between IL-5 and TNF- α in skeletal muscle [5].

Therapeutic Approach

Interventions with exercise and nutritional approaches play an important role in the management of sarcopenia. The literature shows that physical exercise can lead to the most significant increase associated with sarcopenia. Other evidence suggests that a combination of physical exercise and nutrition is the key to preventing, treating and slowing the progression of sarcopenia [9,15].

Resistance and aerobic exercise play an important role in preventing and dealing with sarcopenia so it is clear that resistance training is the primary therapeutic strategy to prevent and restore the condition of sarcopenia. Resistance exercises can be done with resistance machines, lifting weights, stretching bands or using their own weight. Resistance exercises can increase muscle strength and mass by increasing protein synthesis in skeletal muscle cells. In the elderly, resistance exercise should be done two or three days/week with at least one set, 8-12 repetition (experts recommend 10-15) in major muscle groups [1,9,31]. Numerous studies have also shown that moderate intensity resistance training can alter IL-15 concentrations in serum or mRNA levels. Running on a treadmill (70% of maximal heart rate for 30 minutes) increases serum IL-15 levels. Resistance training (4 sets, 10 repetitions, intervals 2-3 minutes of rest) showed increased IL-6, IL-10, IL-1 receptor antagonist (IL-1r) and IL-8. While exercise 3 days/week, 75% of 1 maximum repetition, 6-10 repetition can increase levels of IL-15 and IL-15 receptor genes [29].

Yarasheski et al. [32] showed that body muscle mass increased by 1 kg in women and 2.2 kg in men with resistance

training for 3 months. The 2009 Cochrane Review (based on 121 clinical trials) concluded that resistance training increased muscle strength as well as physical performance that included gait speed and getting up from a chair [7].

Bauer et al. [33] recommends an increase in protein intake up to 1.2 grams/kg body weight/day either through diet or protein supplementation for the elderly due to poorer muscle protein synthesis response. The anabolic effects of protein supplements can be maximized by providing efficient nutritional supplements with large amounts (essential amino acids especially leucine) once daily. Another way to optimize postprandial protein anabolism is the provision of "Fast" protein (a rapidly digestible protein analogous to the concept of "Fast" carbohydrates). However, no randomized clinical trials support this particular approach in increasing muscle mass [34]. The β-hydroxy β-methyl butyrate supplement may increase muscle mass although its effect on muscle strength and physical performance is still inconsistent [15]. There is evidence that supplemental amino acids enriched with leucine will increase muscle mass and function [35]. Vitamin D has been shown to improve muscle function in people with low muscle function (<50 nmol) [36].

Little data supports that testosterone can increase muscle mass and strength and improve its function in the vulnerable elderly with hypogonadism. Cardiovascular risk is a major concern in elderly people who receive testosterone therapy. Other risks associated with testosterone therapy include sleep apnea, thrombosis and an increased risk of prostate cancer [7,18]. Selective Androgen Receptor Modulators (SARMs) have shown promise in increasing muscle mass and stair climbing ability. A number of antibodies that modulate myostatin and the activin II receptor are still in clinical trials. A randomized-controlled phase 2 study showed that the humanized monoclonal antibody LY2495655, a myostatin inhibitor, increased the mass and probably improved muscle strength. Ghrelin agonists, which increase food intake and release of growth hormone, are also under study [1,9].

Summary

Sarcopenia is a decrease in muscle mass as aging with implications of impaired mobility and function, risk of falls and death. Sarcopenia is the leading cause of frailty. The prevalence of sarcopenia is keep increasing with the impact of high health costs. The cause of sarcopenia is multifactorial where chronic inflammatory conditions low-grade inflamm-aging plays an important role. Proinflammatory cytokines such as TNF-α, IL-1, IL-6 and CRP lead to the occurrence of sarcopenia by activation of the Ubiquitine-Protease System (UPS). IL-15 is widely expressed in skeletal muscles through inhibition of TNF-α downstream signalling. Interventions with exercise and nutritional approaches play an important role in preventing and as potential therapy for sarcopenia.

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