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Role of Il-6 And Igf-1 in SarcopeNIA

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A B S T R A C T

Background: Sarcopenia is a syndrome characterized by decreased muscle mass and decreased muscle strength and muscle function. Oxidative stress and inflammatory processes are known to contribute to sarcopenia by releasing the catabolic stimuli interleukin-6 (IL-6) and insulin-like growth factor (IGF). Methods: The method used is a literature review by collecting appropriate articles from the PubMed and Google Scholar databases. Results: Low IL-6 can trigger satellite cell activity and myotube regeneration, whereas if IL-6 production increases chronically, it triggers muscle wasting. Changes in muscle size are the result of changes in the synthesis and degradation of muscle protein. IGF-1, where signal changes are strongly related to muscle size. IGF-1 binding to the receptor causes intracellular phosphorylation of the adapter protein Shc or insulin receptor substrate (IRS-1). Conclusion: The role of IGF-1 and IL-6 can be helpful as diagnostic and prognostic parameters for sarcopenia.

Kata kunci:

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A B S T R A K

Latar belakang: Sarkopenia adalah sindrom yang ditandai dengan penurunan massa otot disertai penurunan kekuatan otot dan atau fungsi otot. Stres oksidatif dan proses inflamasi dikenal sebagai faktor pemicu untuk sarkopenia dengan melepaskan rangsangan katabolik interleukin-6 (IL-6) dan IGF1. Metode: Metode yang digunakan adalah literature review dengan mengumpulkan artikel-artikel yang sesuai dari data base PubMed dan google sholar. Hasil: IL-6 yang rendah dapat mencetuskan aktivitas sel-sel satelit dan regenerasi myotube, sedangkan bila produksi IL-6 meningkat secara kronik mencetuskan muscle wasting. Perubahan ukuran otot merupakan dampak dari perubahan sintesis dan degradasi protein otot. IGF-1 dimana perubahan sinyal berhubungan kuat dengan ukuran otot. Ikatan IGF-1 pada reseptor menyebabkan fosforilasi intracellular adaptor proteins Shc atau insulin receptor substrate (IRS-1). Kesimpulan: Peran IGF-1 dan IL-6 dapat berguna sebagai parameter diagnostik dan prognostic terhadap kejadian sarcopenia.

INTRODUCTION

Sarcopenia is a muscle disease characterized by a general and progressive loss of skeletal muscle mass and strength.(Keller, 2019)Various serious impacts caused by sarcopenia include falls, fractures, hospitalization, decreased functional status, reduced quality of life, risk of postoperative infection, susceptibility to nosocomial infections, risk of community pneumonia, 90-day mortality in patients with aspiration pneumonia, disability, vulnerability (frailty), morbidity and mortality.(Ascenzi et al., 2019; Nelke et al., 2019)

The etiopathogenesis of sarcopenia is very complex and is a multifactorial process. However, in the aging process, the factors that play a major role in sarcopenia are low-grade systemic inflammation and loss of muscle protein homeostasis.(Bonato et al., 2020; Petermann-Rocha et al., 2020)

Il-6 promotes skeletal muscle development by stimulating protein synthesis and inhibiting protein catabolism. At the same time, IGF-1 can prevent muscle mass loss, strength, and changes in nerve and muscle interactions. Low IGF-1 levels were found in elderly patients.(Beaudart et al., 2017)

METHODS

The method used is a literature review by collecting appropriate articles from the PubMed and Google Scholar databases.

DISCUSSION

IL-6 in Sarcopenia

IL-6 is a pleomorphic pro-inflammatory cytokine that is produced during an inflammatory process.(Barbiera et al., 2020) IL-6 deregulation is associated with chronic inflammatory conditions. Interleukin 6 is a multifunctional cytokine, playing a role in pro-inflammatory and anti-inflammatory. IL-11, *Leukemia Inhibitory Factor* (LIF), *Cardiopin-1* (CL-1), *Oncostatin M* (OSM), *Ciliary Neurotrophic Factor* (CNTF), *Cardiotrophin-1* (CT-1), and *Cardiotrophin-like Cytokine* (CLC) stimulate target genes including differentiation, survival, apoptosis, and cell proliferation. The IL-6 structure has an IL-6 R receptor and an IL-6 receptor complex.(Belizário et al., 2016)

IL-6 signal transmission via mIL-6R (classical signal pathway) or sIL-6R (trans signal pathway). Classical signaling is manifested primarily in leukocytes and liver cells, which express mIL-6Rα and gp 130 and promote an anti-inflammatory response. Conversely, *trans-signaling* may be manifested primarily in all hgp 130- *expressing cells* and lead to a pro-inflammatory response.

Skeletal muscle produces a number of growth factors, cytokines, and myokines that play a major role in regulating inflammatory processes and skeletal muscle regeneration. IL-6 is a cytokine produced by skeletal muscle. (Belizário et al., 2016)

Low IL-6 levels can trigger satellite cell activity and *myotube regeneration,* whereas if IL-6 production increases chronically, it triggers *muscle wasting.* This difference in effect is due to the *cross-talk* of the IL-6/IL-6 receptor and the gp 130 signal trans-signal pathway, which does not cause regenerative and anti-inflammatory effects of the classic IL-6 receptor signaling pathway. IL-6 is associated with cells expressing both IL-6R gp 130-associated membranes and triggering the activation of the JAK/STAT signaling pathway/this type of signaling is called classical signaling. In cells expressing only gp130 but not IL-6R, IL-6 binds to soluble IL-6R (sIL-6R) and binds to gp130 to trigger intracellular signaling activity. This type of signaling is called trans-signaling. (Picture 1) (Belizário et al., 2016).

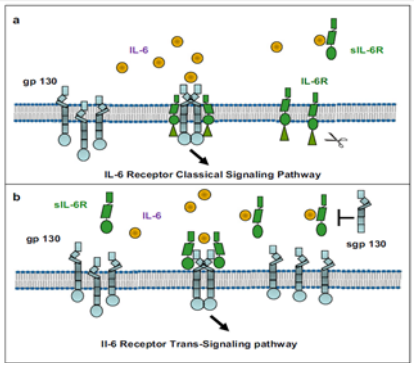

Figure 1. Classic Signal Path and Trans Signal (Belizário et al., 2016)

IL-6 is a double-edged sword and displays a complex biological profile. In general, IL -6 can have pro and anti effects inflammation and can exert hyperbolism or catabolism depending on the target structure, dominant cytokine environment, and mode of release, whereas in inflammatory aging, there is prolonged exposure to IL-6 signaling, which is involved in the pathogenesis of sarcopenia.(Nelke et al., 2019)

IL-6 as a pro-inflammatory and catabolic effect

IL-6 induces muscle atrophy by inhibiting muscle anabolism and homeostasis and directly mediates muscle catabolism. This can be seen in transgenic mice that chronically express IL-6, showing muscle mass loss marked by increased catepsin activity. Using IL-6 receptor antibodies reduces the detrimental effects of IL-6 on muscle. *Knockout* mice did not significantly differ in muscle catabolism from wild-type mice under experimentally induced sepsis. This suggests that the single action of IL-6 is insufficient to trigger muscle wasting.

The catabolic effects of IL-6 depend on interactions that mediate the inflammatory response synergy with other mediators. IL-6 mediated muscle catabolism depends on chronic exposure to IL-6 and the concomitant activity of other pro-inflammatory cytokines such as TNF-α. (Nelke et al., 2019)

IL-6 as anti-inflammatory and anabolic effects

IL-6 as the main myokine, which after exercise, the skeletal muscle will release IL-6 to restore muscle homeostasis. IL-6 signaling is required for skeletal muscle regeneration and hypertrophy by regulating satellite function and enhancing glucose metabolism. Exercise causes IL-6 to induce anabolism through the release of Ca2+ from the sarcoplasmic reticulum. IL-6 levels are essentially unchanged, whereas strenuous exercise such as a marathon triggers a TNF-α response. (Nelke et al., 2019)

In sarcopenia, the IL-6 signal switches to a pro-inflammatory profile due to aging skeletal muscle function (Figure 2). Exposure to pro-inflammatory cytokines triggers pro-inflammatory effects and muscle catabolism via IL-6 signaling. In sarcopenia, there is a disturbance in the release of pulsatile IL-6 in response to exercise, which reduces the anti-inflammatory effect and interferes with muscle anabolism. (Nelke et al., 2019)

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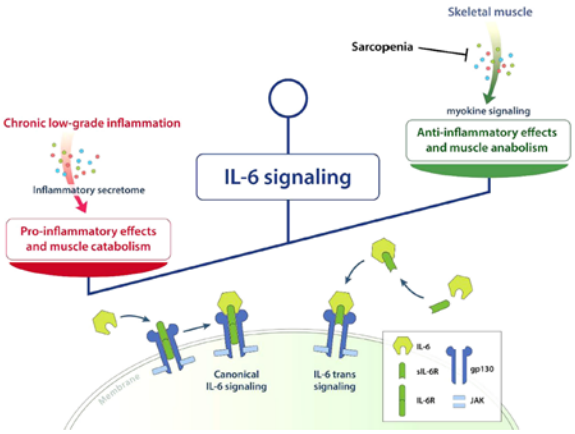

Figure 2. IL-6 Signal Scale on aging [2]

Rachim R, et al. evaluated IL-6 levels in the elderly to the degree of sarcopenia, age, and comorbidities in 82 old patients at the geriatric clinic of Wahidin Sudirohusido Hospital.(Rachim et al., n.d.) it was found that IL-6 levels increased according to the degree of sarcopenia p<0.001 (normal; 52.81µg/L, *probable sarcopenia* ; 67.47 · µg/L, *sarcopenia* ; 135.36µg/L, *severe sarcopenia* ; 287.99µg/L) . IL-6 levels also increased with increasing: age p<0.001 (age 60-74 years: µg/L, age≥75 years; 139.5µg/L), number of comorbidities; p≤0.001 (1-3 comorbid; 52.86µg/L, ≥4 comorbids:120.84µg/L).(Petermann-Rocha et al., 2020)

Some studies look at levels of inflammatory cytokines on sarcopenia in the elderly. Systematic study review and meta-analysis by Bano G, et al (Bano et al., 2017) looked at levels of pro-inflammatory cytokines; IL-6, CRP, and TNFα in sarcopenic patients from 17 studies with a total of 11249 participants (3072 sarcopenia groups and 8177 control groups), it was found that *C-Reactive Protein* (CRP) levels increased significantly in sarcopenic patients (SMD = 0.51; 95 %CI 0.26-0.77; p<0.0001; I^2 = 96%), while IL-6 levels did not differ significantly between sarcopenia and controls (SMD=0.35; 95% CI-0.19- 0.89; p=0.21; I^2 = 97%). There was no increase in TNFα levels in sarcopenia compared to the control group (SMD=028; 95% CI -0.26 0.83; p=0.31; I^2 = 97%).(Liguori et al., 2018; Pratiwi et al., 2019)

CRP and IL-6 are catabolic stimuli that trigger sarcopenia. CRP levels correlate with IL-6 levels in the elderly. This is based on research by Aryana Suka IGP, et al. in elderly with sarcopenia in the Buleleng Bali village community, it was found that IL-6 levels correlated with CRP (r=0.43;p=0.001 pa (r=0.40;p=0.011) and total muscle mass (r=-0.25;p=0.026) after adjustment for BMI variables. (Gusti Putu Suka Aryana et al., 2018)

Another study conducted showed a significant relationship between IL-6 and decreased muscle mass, muscle strength, function, quality, and functional adaptation.(Grosicki et al., 2020) In line with the study found high levels of inflammatory markers in IL-6, CRP, and TNF-α associated with decreased strength and muscle mass.(Tuttle et al., 2020) Research conducted by Erfin et al [17] in the elderly population at RSMH Palembang showed a significant negative correlation between serum IL-6 levels with muscle mass and physical performance.(Erfin et al., 2021)

IGF-1

IGF-1 is a growth hormone that plays an important role in skeletal muscle myogenesis and increases the proliferation capacity of *muscle satellite cells* (MSC). In addition to being created in the liver as a systemic growth factor, IGF-1 is also produced by tissues other than the liver, such as muscles, which have an endocrine function. IGF-1 levels decreased 1.88ng/ml/year in men and 2.13ng/ml/year in women.(Ascenzi et al., 2019)

Different pre-pro-peptides form the IGF-1 protein, there are two different promoters, and the *differential splicing* of the IGF-1 gene forms several different IGF-1 isoforms in the *N-terminal signal peptide (class 1 or 2) and the C -terminal* extension. *Terminal extension peptide* (E-peptide Ea or Eb) in the form of IGF-1 Ea and IGF-1 Eb. Both can inhibit sarcopenia through molecular mechanism activity.(Grosicki et al., 2020) (Figure 3)

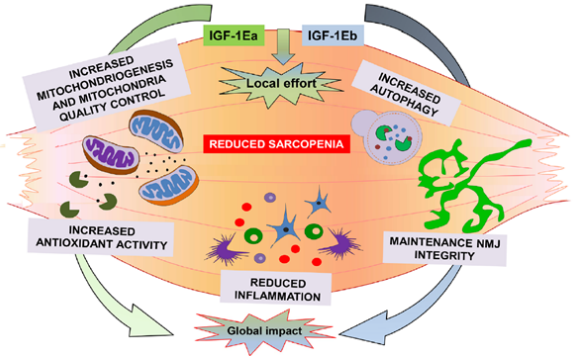

Figure 3. The activation mechanism of IGF-1Ea and IGF-1Eb inhibits sarcopenia [18]

Muscle expresses IGF-1 1Ea or IGF-1Eb to prevent sarcopenia via two-way activation of *Peroxisome proliferator-activated receptors -coactivator 1* (PGC-1) and autophagy to protect cells against organelle malfunction and aggregated proteins during aging. PGC-1α induces mitochondriogenesis and stimulates specific gene programs to ensure the maintenance of muscle mass and adaptability (i.e., fiber type specification, *Neuro Muscular Junction* (NMJ) stability, and reduced inflammation. IGF-1Ea expression stimulates additional pathways (AMPK, SIRT1) to maintain the phenotype's functional hypertrophy during aging. (Tuttle et al., 2020) (fig 4)

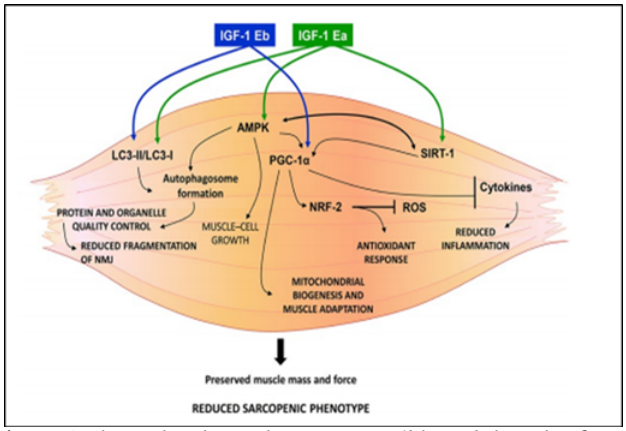

Figure 4. The molecular pathway responsible and the role of IGF-1 in preventing sarcopenia.(Musarò & Scicchitano, 2019)

The transmembrane IGF-1 receptor (IGF-1R) is a tyrosine kinase receptor that activates several pathways, namely *Phosphoinositide-3 Kinase* (PI3K)/ protein kinase (PKB or AKT), Ras/Raf/*Mitogen-Activated Protein Kinase* (MAPK), and Shc. This pathway involves cell growth, *proliferation, differentiation*, life expectancy, metabolism, gene transcription, and protein transition.(Erfin et al., 2021)

The molecular mechanism of IGF-1 is related to the receptor, which activates the MAPK pathway and the P13-kinase pathway. Activation of the MAPK pathway causes increased proliferation and migration of satellite cells. Activation of the P13-Kinase pathway leads to the differentiation and synthesis of muscle fiber proteins.(Musarò & Scicchitano, 2019) (image 5)

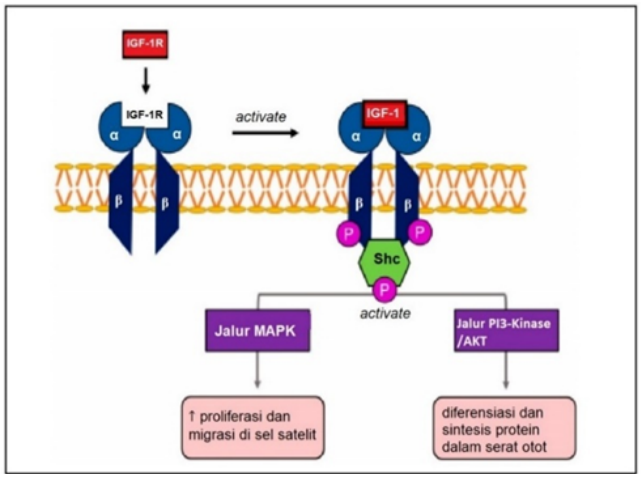

Figure 5. Molecular mechanism of IGF-1. IGF-1 interacts with its receptor (IGF-1R)(Musarò & Scicchitano, 2019)

Structure of IGF-1

IGF-1, known as somatomedin C, is a hormone similar in molecular structure to the insulin that has anabolic effects in adults. IGF-1 is the protein encoded in humans by the IGF-1 gene. IGF-1 consists of 70 amino acids in one chain with three intramolecular disulfide bridges with a molecular weight of 7.649 Daltons. IGF-1 is produced primarily by the liver; production is stimulated by growth hormone (GH) and is produced throughout life. The highest production of IGF-1 occurs during puberty, and the lowest during infancy and old age.(Ascenzi et al., 2019)

Synthesis and Circulation of IGF-1

IGF-1 is produced primarily by the liver as an endocrine hormone and in target tissues in a paracrine/autocrine manner. IGF-1 production is stimulated by growth hormone (GH). It can be inhibited by malnutrition, growth hormone insensitivity, lack of growth hormone receptors, or failure of post-GH receptor signaling pathways, including SHP2 and STAT5B. About 98% of IGF-1 is invariably bound to one of 6 binding proteins (IGF-BP). IGFBP-3, the most abundant protein, accounts for 80% of all IGF binding. IGF-1 binds to IGFBP-3 in a 1:1 molar ratio. IGFBP-1 is regulated by insulin. Protein intake increases IGF-1 levels in humans. Variations in the circulating levels of growth hormone (GH) and insulin-like growth factor-1 (IGF-1) are caused by insulin levels, genetic makeup, time of day, age, gender, exercise status, stress levels, nutritional levels, and body mass index (BMI), disease state, ethnicity and estrogen status.

Mechanism of Action of IGF-1 in the elderly

GH and IGF-1 are part of the *hypothalamic-pituitary axis,* which regulates somatic growth and aging. The peak at puberty supports fat-free muscle mass (*lean*) and fat mass. During aging, GH and IGF-1 levels decrease, which is termed somatopause. IGF-1 receptors are present in almost all cells, the receptors are tyrosine kinases that activate many pathways, including *Phosphoinositide 3 Kinase* (P13K), *Protein Kinase B* (PKB or AKT), Ras/Raf/*Mitogen-Activated Protein Kinase* (MAPK), and Shc. This pathway involves cell growth, proliferation, differentiation, survival, metabolism, gene transcription, and protein translation. IGF-1 has an important role in mitochondrial function. Mitochondria play a major role in cell function. As a producer of ATP from the process of metabolism of carbohydrates, fats, and amino acids, mitochondria also play a role in calcium homeostasis, apoptosis, inflammation, and heat production. As a major role as a regulator of aging, mitochondrial regulation of the GH/IGF-1 Axis. IGF-1 also plays a role in mitochondrial biogenesis.(Erfin et al., 2021)

The role of mitochondria is in the form of cellular respiration, energy production through the pair cycle of tri-carboxylic acid with OXPHOS, calcium homeostasis, cell replication, apoptosis, generation, and protection from ROS. This function is fundamental during growth and development and plays a major role during aging. Age induces mitochondrial dysfunction and reduces GH/IGF-1 secretion and action; the exact causality between these two processes has not been established. IGF-1 levels peak during puberty and then fall with age; concurrently, mitochondrial metabolism in the brain (cognition), muscle (sarcopenia), and skeletal tissue have detrimental consequences (osteopenia).

In mice that experience IGF-1 deficiency, it is associated with mitochondrial dysfunction through increased lipid peroxidase, protein carboxylation, intra-mitochondrial ROS in hepatocytes, reduced mitochondrial membrane potential, and oxidative phosphorylation. Administration of IGF-1 to old (130 days) rats for 30 days improved mitochondrial membrane potential, oxygen consumption rate, *proton leak*, cytochrome oxidation, and ATPase complex. Small doses of GH for 8 weeks in old Wistar rats aged 22 months increased circulating IGF-1, protein synthesis in mitochondria and increased the action of antioxy and *catalase enzymes, glutathione peroxidase, glucose 6 phosphate peroxidase* (G6PDH) and reduced oxidative damage (measured by 8-OHdG levels in skeletal muscle. This is because GH induces anabolic activation of AKT, mTOR, p70S6K, Myf-5 factor, inhibits p21, p38, *muscle ring finger-1* (MuRF-1) as a catabolic signal. (Erfin et al., 2021)

It was also reported that a decrease in GH/IGF-1 signaling in old rat muscle was associated with mitochondrial dysfunction. Given antioxidants, Gh and IGF-1 serum levels increased associated with the repair of cristae and mitochondrial structures. IGF-1 reduces mitochondrial cardiomyocyte dysfunction in obese mice. IGF-1 overexpressing transgenic mice boosted glucose absorption, ATP generation, and aconitase activity while decreasing lipid peroxidation, protein carbonyl ROS production, and apoptosis. Cardiomyocyte-specific IGF-1 induces the expression of *Cytochrome c* (Cyt c), *Peroxisome proliferator Activated receptor Gamma Coactivator 1* α (PGC-1α), *Mitochondrial Uncoupling Proteins* (UCP2), which are

equally important intracellular Ca 2+ regulator of *Sarco/endoplasmic reticulum protein* Ca2+-ATPase-2a (SERCA 2a) and Na+Ca2+ exchange. Mitochondrial dysfunction in cortical bone osteocytes in *GH receptor null* (GHRKO) mice is described as decreased mitochondrial membrane potential, reduced ATP production, and reduced maximal respiration. Overall, GH/IGF-1 signaling involved in mitochondrial function has multiple facets in important tissues, organs, and age-dependent presentations.(Erfin et al., 2021)

Based on the theory of aging, the presence of free radicals produced by electron transfer chains in mitochondria or through cytosolic nitrate oxidant metabolism can produce oxidative damage to DNA, proteins, and lipids and further accelerate aging. Mitochondria produce ATP and free radicals resulting from oxidative phosphorylation. In young adults, *reactive oxygen species* (ROS) are neutralized by antioxidant systems such as superoxide dismutase, a metalloprotein that converts superoxide into hydrogen peroxidase and molecular oxygen. There are three superoxide dismutases, namely: Cu/Zn -SOD, located mainly in the cytosol, Mn-SOD located in mitochondria, EC-SOD extracellular. Catalase is a heme protein located primarily in peroxisomes and mitochondrial membranes. In aging, the antioxidant system decreases so that ROS increases which will cause a decrease in *Oxidative Phosphorylation* (OXPHOS), ATP is formed low, and ROS is formed increases which cause damage to proteins and enzymes. Accumulation of damaged proteins and enzymes will disrupt mitochondrial function during aging. Mitochondrial dysfunction is associated with decreased GH/IGF-1 signaling and various age-related diseases. Many reports show that GH/IGF-1 signaling controls the expression and activity of antioxidant enzymes and regulates oxidative stress levels. *Thioredoxin-interacting protein* (TXNIP) was identified as a new target of IGF-1 and insulin action. There is TXNIP oxidative stress back and forth from the nucleus to mitochondria. TXINP inhibits proliferation by activating *Apoptosis Signal Regulating Kinase 1* (ASK1) signaling and tumor suppressor function in cancer. TXNIP is a major regulator of ROS signaling and is involved in the pathogenesis of various autoimmune and degenerative diseases. Antioxidants given to old animals can increase GH and IGF-1 levels. Multiple mechanisms are associated with muscle degeneration in sarcopenia, but the main role is loss of mitochondrial integrity in myocytes and dysfunction of mitochondrial quality control mechanisms. Mitochondria act directly or indirectly with other cellular components (such as endoplasmic reticulum, peroxisomes, and lysosomes/vacuoles) as well as the extracellular environment by releasing several biomolecules.(Levine et al., 2014)

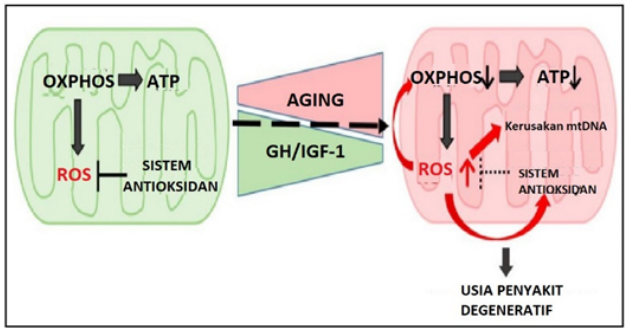

Figure 6. Mitochondria produce ATP and ROS (Ascenzi et al., 2019)

IGF-1 with Sarcopenia

The decline in strength and muscle mass in the aging process is a complex process that until now has not been able to explain the mechanism of change from the biomolecular level to the cellular level. Sarcopenia's pathophysiological mechanisms include reduced protein synthesis capacity (anabolic resistance). Aging is associated with decreased levels of testosterone, IGF-1, and insulin resulting in decreased protein synthesis through decreased activity of the IGF-1/Akt/mTOR pathway. The rate of protein synthesis that decreases in the aging process is also accompanied by a decrease in the repair capacity (*repair mechanisms*) of skeletal muscles. The processes of autophagy and apoptosis are also disrupted in sarcopenia, resulting in an imbalance between protein synthesis and degradation processes. A progressive decrease in muscle mass will lead to atrophic conditions, and the process of apoptosis will occur when the size of the muscle fiber has reached a minimum critical value. The process of apoptosis is accompanied by denervation and loss of neurons. Denervation and loss of neurons lead to decreased muscle strength capacity and metabolism. Resistance training can increase muscle mass in the elderly by activating the AMPK-SIRT1-PGC-1α pathway and stimulating protein synthesis via the PI3K-AktmTOR pathway. Activating the AMPK-Sirt-PGC1α pathway stimulates mitochondrial biogenesis, muscle fiber gain, and regeneration.(Wiedmer et al., 2021)

The effect of IGF-1 isoforms on muscle growth and sarcopenia.(Ascenzi et al., 2019) This study analyzed the effect of overexpression of IGF-1Ea and IGF-1Eb isoforms on muscle growth and their ability to prevent sarcopenia. Local muscle expression of IGF-1Ea or IGF-1Eb prevents sarcopenia without causing side effects to other tissues and organs. Research using transgenic rats showed an increase in muscle expression of the IGF-1 isoform, maintaining the ability of muscles to function as an endocrine organ, thus contributing to maintaining IGF-1 levels. The higher expression level of the IGF-1 protein in mice, namely IGF-1Ea, compared to IGF-1Eb, may be responsible for the hypertrophic phenotype of the IGF-1Ea isoform. IGF-1Ea and IGF-1Eb, apart from promoting muscle growth, can fight against sarcopenia, activating pathways usually affected during aging, namely autophagy and PGC-1-mediated signaling. This pathway controls two important destabilizing factors associated with sarcopenia: reducing mitochondrial dysfunction, which is responsible for excessive ROS production and maintenance of NMJ integrity, important for muscle function and muscle-nerve interactions. (Wiedmer et al., 2021)

Role of IGF-1 in Skeletal Muscle Atrophy

IGF-1 is the primary anabolic hormone that stimulates the PI3K signal, which acts as a regulator of muscle hypertrophy. IGF-1/PI3K increases muscle protein synthesis and inhibits proteasomal and lysosomal protein degradation. The IGF-1/PI3K/Akt signal also plays a role in inhibiting the caspase involved in protein degradation. In contrast, the effect of the signal on protein degradation involving calpain cannot be concluded. There is a reduction in these signals during conditions of atrophy that occur during denervation, *unloading,* and joint mmobilization; however, the P13K signal does not change during the process of muscle atrophy that occurs due to age. Overexpression of IGF-1 or injection of IGF-1 can inhibit muscle atrophy due to aging, although there is an increase in anabolic resistance to IGF-1. IGF-1 expression increases biochemically by GH; besides that IGF-1

expression degrades its half-life/ bioactivity, which is regulated negatively or positively by a number of IGF-1 binding proteins known as *IGF-1 binding proteins* (IGFBPs), namely albumin. (Ahmad et al., 2020)

In muscle, the most widely expressed IGF-1 isoforms are IGF-1Ea and mechano-growth factor (MGF, also called IGF-1Ec). In skeletal muscle, the basal mRNA level of IGF-1Ea is higher than that of MGF. The IGF-1 receptor (IGF-1R) is a receptor tyrosine kinase that is expressed on muscle fibers and muscle stem cells (satellite cells). (Ahmad et al., 2020)

IGF-1 has a more dominant role in muscle hypertrophy. The IGF-1/ *Phosphatidylinositol3-Kinase* (PI3K/Akt) pathway is involved in regulating protein synthesis and degradation. The main signaling pathway is via IGF-1, whereas MGF modulates protein synthesis and degradation rate during muscle atrophy.(Levine et al., 2014)

Role of IGF-1 in Muscle Protein Synthesis and Degradation

Changes in muscle size are the result of changes in the synthesis and degradation of muscle protein. IGF-1 for both processes, where signal changes are strongly related to muscle size. The binding of IGF-1 to the receptor causes *intracellular phosphorylation of the adapter protein Shc* or *insulin receptor substrate* (IRS-1) to activate two main pathways:

A. RAS/RAF/MEK/ERK is known as *Mitogen-Activated Protein Kinase* (MAPK) signaling.
B. PI3K/Akt

The IGF-1/PI3/Akt pathway plays a major role in muscle fiber size and the anabolic mechanisms underlying muscle hypertrophy. Translocation of PI3K to phosphorylated IRS-1 results in PI3K phosphorylation, which then causes *Phosphoinositide Dependent Kinase- 1* (PDKI) phosphorylation which then phosphorylates serine/threonine kinase Akt (known as protein kinase B). Akt is involved in several cellular processes including proliferation, metabolism and regulation of cell size. This pathway plays a major role in the size of the muscle fiber. (Ahmad et al., 2020)

IGF-1 Signaling in Aging Muscle

Aging is associated with skeletal muscle atrophy, a loss of muscle mass and strength called sarcopenia. This is determined by a combination of two processes: loss of muscle fibers and atrophy of muscle fibers resulting in loss of motor units. In unused conditions, type 1 muscle fibers are more dominantly affected. During aging, type 2 muscle fibers are more susceptible to atrophy and necrosis than type 1 fibers. (Levine et al., 2014)

Loss of muscle mass in aging may be caused by decreased physical activity, oxidative stress, low-grade chronic inflammation, and changes in systemic serum proteins. Low-grade chronic inflammation in aging is associated with increased plasma levels of IL-6 and TNF-α.

These IL-6 and TNF-α cytokines inhibit IGF-1 signaling, thus playing a major role in muscle atrophy associated with systemic inflammation in aging. IL-6 can also inhibit mTOR without affecting Akt phosphorylation. TNF-α interferes with GF-1R sensitivity and increases MuRF-1 expression by activating a transcription factor, namely *nuclear factor kappa-light-chain-enhancer of activated B -cells* (NF-kβ). The anabolic potency decreases with age due to an increase in pro-inflammatory cytokines.

Changes in IGF-1/PI3K/Akt signal can be caused by decreased expression, bioactivity, receptor availability, and inhibition along the IGF-1/PI3K/Akt pathway.(Ascenzi et al., 2019)

IGF-1 Signaling Pathways

IGF-1 plays a role in regulating the anabolic and catabolic pathways of skeletal muscle. In the anabolic pathway, IGF-1 increases skeletal muscle protein synthesis through the PI3K/Akt/mTOR and PI3K/Akt/GSK3β pathways, while its catabolic role is through PI3K/Akt, which inhibits FOXO and suppresses transcription of *E3ubiquitin ligase* which regulates the *Ubiquitin Proteasome System* (UPS). UPS causes protein degradation in skeletal muscle.

Several studies in cell culture models, experimental animals, and humans have shown that cytokines and IGF-1 play a role in regulating cell growth. Changes in IGF-1 signaling in skeletal muscle can affect the size and function of muscle fibers.(Yoshida & Delafontaine, 2020)

Following are the pathways of protein synthesis and degradation mediated by IGF-1 in skeletal muscle (figure 7). Most of the IGF-1 in the body is bound to IGFBP and IGFALS. IGF-1 binds to IGF-1R, causing IRS-1 and P13K to be recruited and activated. P13K converts P1P2 to P1P3, which activates PDK1 and Akt. Akt activates protein synthesis through activation of the S6 ribosomal protein and translation initiation factor eIF4E *downstream of* mTORC1 and activation of catenin and eIF2B *downstream of* GSK3β. Akt can suppress UPS activity through FoxO inhibition. MuRF-1 expression is induced by cytokines such as TNF-α via the NFkβ pathway. MuRF-1, also known as *RING finger* 1 muscle, is an E3 ubiquitous *ligase* that mediates protein polyubiquitination and targets degradation by the 26S proteosome.(Yoshida & Delafontaine, 2020)

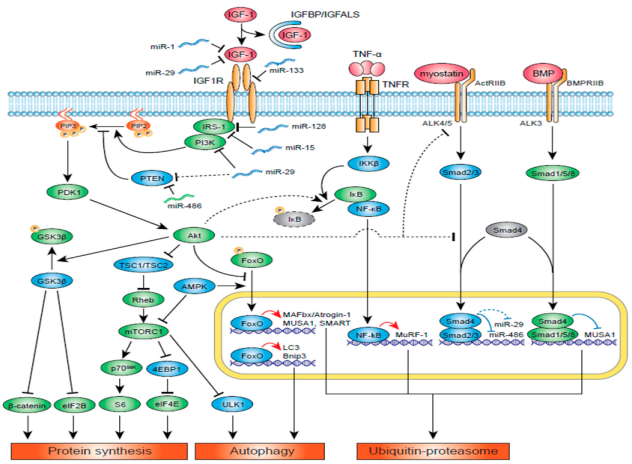

Figure 7. IGF-1 signaling pathway(Wiedmer et al., 2021)

IGF-1/Akt controls two protein synthesis pathways through mTORC and GSK3β. In conditions of muscle atrophy, these pathways decrease.

CONCLUSION

Inflammation has a crucial role in advancing sarcopenia. This disorder changes the metabolism of cellular proteins

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and causes muscle atrophy due to an abnormally high ratio of proteolysis to synthesis. The aging process is marked by an increase in pro-inflammatory cytokines, such as IGF-1 and IL-6, which both play a major role in developing sarcopenia, which is a loss of muscle mass.

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