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Review

Muscle Wasting: Molecular Mechanisms and Promising Therapies

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Abstract

Muscle atrophy, often known as muscle wasting, is a severe disorder marked by a decrease of skeletal muscle mass and strength. It occurs in various pathological states, including chronic kidney disease, cancer, chronic obstructive pulmonary disease (COPD), and heart failure, as well as during extended periods inactivity or aging. Muscle wasting is caused by an imbalance between the production and degradation of proteins, and important regulators including the autophagy-lysosomal pathway, ubiquitin-proteasome system (UPS), and inflammatory cytokines are crucial in this process. Muscle homeostasis is regulated by important signaling pathways, such as the Akt/mTOR and NF-κB pathways. Furthermore, oxidative stress and mitochondrial dysfunction make muscle deterioration worse. By focusing on these molecular pathways, new treatment approaches seek to prevent muscle wasting. Preclinical and clinical investigations have demonstrated the potential of pharmacological treatments, including myostatin inhibitors, anti-inflammatory drugs, and anabolic agents, as well as nutritional therapies and regular exercise. New approaches to muscle regeneration are provided by emerging medicines such as RNA-based methods, gene editing, and stem cell therapy. This study examines the complex molecular processes causing muscle wasting and identifies effective treatment approaches meant to maintain muscular mass and function. Understanding these mechanisms is essential for developing effective treatments that enhance the quality of life for those affected.

Keywords: Muscle wasting, Sarcopenia, Molecular Mechanisms, Therapies

Introduction

Muscle wasting occurs in targeted muscles due to nerve damage or lack of activity but also presents as a systemic effects during periods of short or long duration fasting and during illness[(1)], including chronic kidney disease, cancer, chronic obstructive pulmonary disease (COPD), and heart failure, as well as during extended periods inactivity or aging.(2) This condition considerably lowering quality of life[(1)], increases morbidity and mortality,[(2)] and affects long-term prognosis, immunocompetence, and healing from an illness or damage.[(3)] Muscle atrophy is caused by the molecular activation of protein degradation pathways, specifically autophagy and the ubiquitin–proteasome system (UPS).[(1)] Rapid energy consumption, or hypermetabolism, is one of the more common theories for muscle wasting. Along with this, muscle wasting happens in 80% of cancer patients (known as cancer cachexia).[(1)] Cachexia, also known as muscle wasting, is a condition in which the body's main protein pool skeletal muscle decreases significantly. Internal physiological stressors, such as radiation therapy, severe trauma, cancer/chemotherapy, and severe infection-sepsis, can cause anorexia and/or uncontrollable nausea and vomiting. Age, physical inactivity (disuse), and a reduction in the consumption of vital foods are examples of external variables that contribute to a cycle of poor nutrition. Inadequate intake of nitrogen-rich foods, such as those containing amino acids (NH2-containing compounds) and insufficient absorption of amino acids can result in reduced protein synthesis. Protein reserves are also depleted by large tissue defects and localized and regionalized infections that result in open-draining lesions.[(3)] Muscle wasting has no known cure, despite the fact that a large number of people have some form of muscle weakening.[(2)] Inhibition of important regulators of this process or substances that encourage the production of muscle proteins are of major therapeutic promise for the treatment of many wasting conditions.[(1)] Understanding the

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molecular mechanisms of muscle wasting can provide valuable insights for the development of drugs and therapeutic interventions.[1]This review provides an overview of the mechanistic aspects of muscle wasting and summarizes novel experimental and clinical pharmacological avenues aimed at skeletal muscle.[2]

Epidemiology of Muscle Wasting

Skeletal muscle makes up around half of an average person's entire body weight; muscle also consumes half of the body's metabolism. Every day, a significant amount of intracellular proteins are replaced. The daily breakdown and synthesis of protein in an adult weighing 70 kg is about 280 gm. Skeletal muscle is composed of 75% water, 20% mixed proteins (8% enzymes and 12% myofibrillar proteins, transport channels, membrane proteins, and other proteins), and 5% inorganic salts, pigments, and substrates. Muscle atrophy is accelerated in the context of hypoanabolism (decreased protein synthesis) and hypercatabolism (increased protein breakdown). Immobility is a essential factor contributing to muscle wasting. Muscle wasting from disuse causes a reduction, typically starting within 3 to 7 days of immobilization. After 7 days of bed rest or immobility, strength and endurance drop by 20%, and severe function loss occurs after 1 to 2 months of immobility, which reduces muscle size by 50%. Up to 90% of maximum power may be needed for tasks like climbing stairs in people with severe muscular wasting who experience tiredness related to muscle mass loss. The study indicated that after 21 days, severely ill individuals with sepsis or severe trauma lost 16% of their whole body protein, 19% of their total body potassium, and 17% of their water.[3]

Disease Involved In Muscle Wasting

Muscle wasting are prevalent in many disease states and conditions including aging, cancer cachexia, sepsis, neuropathy, malnutrition, diabetes, liver cirrhosis, multiple sclerosis, obesity, chronic obstructive pulmonary disease (COPD), HIV-acquired immunodeficiency syndrome (AIDS), renal or heart failure, and muscular dystrophies.[4]

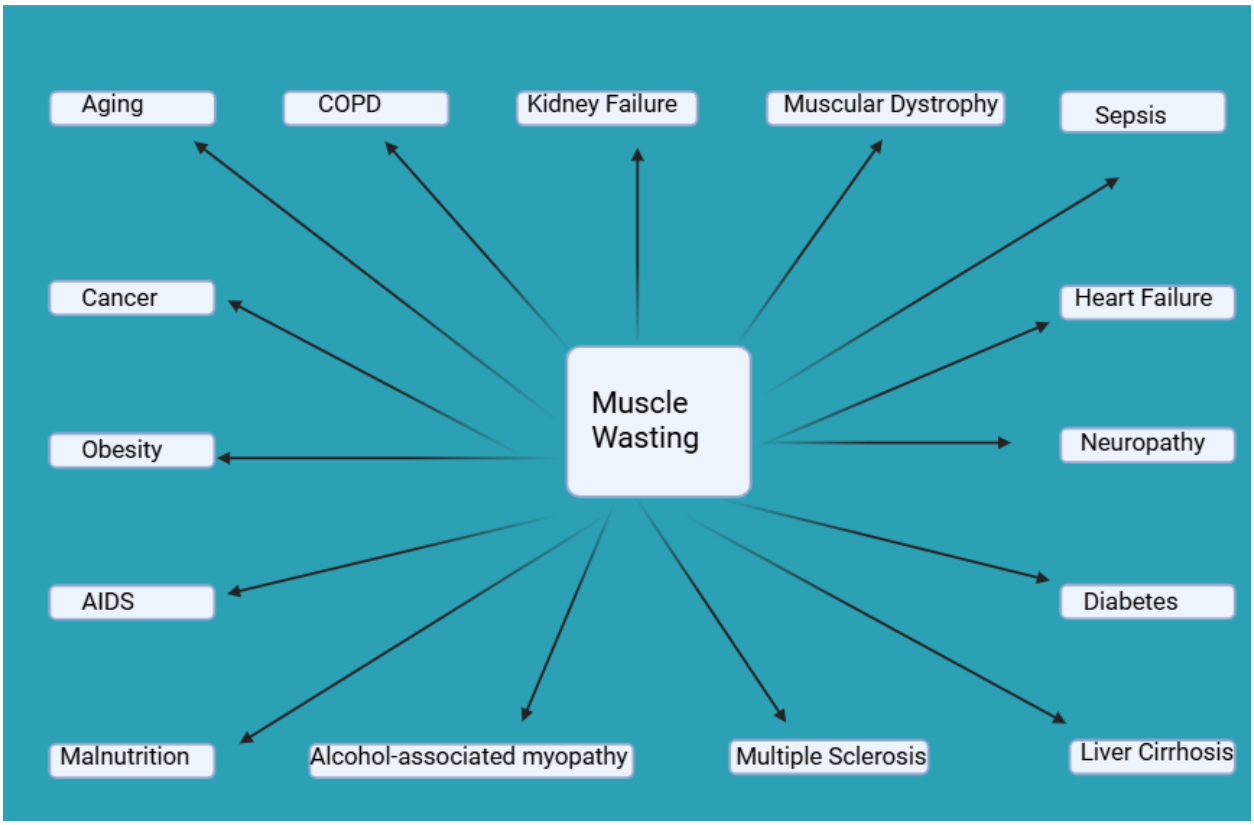

Figure 1: Disease involved in muscle wasting[5]

Cancer

Cancer cachexia is a complex condition characterized by reduction in the mass of skeletal muscle, with or without the reduction of fat mass, that negatively impacts functional status and quality of life. It is caused by the upregulation of catabolic stimuli and systemic inflammation, which inhibits protein synthesis and increases muscle catabolism. The pathophysiological

mechanism of cancer cachexia involves an imbalance in energy and protein resulting from a combination of abnormal metabolism and decreased food intake. This condition also impacts on the process of muscle remodelling. Even though cachexia is among the leading precipitating factors of cancer deaths, there are no available drugs for the treatment of cancer cachexia.[6]

Heart Failure

Cardiac Cachexia is a condition associated with chronic Heart failure, which is defined as involuntary loss of at least 5% of nonoedematous body weight during the preceding 6 to 12 months, i.e. it is a widespread wasting of fat tissue, skeletal muscle and bone tissue, when there is a change in the normal metabolic balance between anabolism and catabolism; this state cannot be rectified by merely changing the amount of food consumed. Skeletal muscle atrophy in chronic heart failure may be caused by hormonal or metabolic abnormalities that favor catabolism over anabolism in addition to decreased physical activity. Decrease in left ventricular function activates various metabolic processes which ultimately cause skeletal muscle wasting and subsequent abnormalities in the metabolism and function of muscles. These individuals' reduced ability to exercise is a result of abnormal metabolic reactions, myocyte apoptosis, and skeletal muscle atrophy. Cardiac cachexia affects 10–19.5% of Heart failure patients, especially those with a reduced ejection fraction, and its prevalence is linked more with neurohormonal dysfunction in Heart failure than the traditional measures of Heart failure.[7]

Aging

Muscle wasting and weakening associated with aging, skeletal muscle damage is one of the most detrimental impacts of aging. The word "sarcopenia" is frequently used to refer to the gradual, progressive decrease of muscle mass that occurs with aging. Its general meaning is "poverty of flesh," and it comes from the Latin words "sarco" and "penia." Sarcopenia is not only defined as the loss of lean tissue mass of skeletal muscle accompanied by a relative decline in the functional properties of muscle tissue, force production and maximum velocity of shortening of muscle fibres and contraction and relaxation rates. After the age of 85, some elderly people may have such a significant loss of strength and bulk that they are unable to perform even the most basic tasks. Age-related alterations in skeletal muscle are unavoidable, but it's not apparent if these changes are permanent or reversible. The loss of individual muscle fibers and a reduction in the size of the surviving muscle fibers result in a reduction in the contractile protein content, which in turn causes a loss of muscle quantity. This age-related decline in contractile tissue is likely due to the rate of protein degradation being greater than the rate of protein synthesis. Skeletal muscle mass decreases as a result of changes in protein synthesis and breakdown. It has been proposed that increased protein breakdown is the fundamental cause of sarcopenia and that muscle protein synthesis may actually rise in a futile attempt to preserve muscle mass. Both a reduction in muscle quantity and a reduction in muscle quality are thought to be linked to the age-related loss in muscular function. As individual muscle fibers are lost and the size of the remaining muscle fibers decreases, the contractile protein composition of the muscle decreases, resulting in a loss of muscle mass. This age-related loss of contractile tissue could be due to the differences in the rates of synthesis of protein and breakdown of protein.[4]

Chronic obstructive pulmonary disease (COPD)

A common symptom experienced by most COPD patients is exercise-intolerance. The exercise ability of 40% of these patients suffers primarily from skeletal muscle changes rather than from lung diseases. COPD is often associated with muscle wasting, as well as a slow to fast shift in muscle fibers, leading to weakness and early onset of muscle fatigue. It is obvious that reducing muscular atrophy during COPD improves the patient's quality of life and survival rate. The causes and processes of muscle loss and remodeling during COPD must be clearly understood in order to effectively address them. Oxidative stress, hypoxemia, Malnutrition, inactivity, and systemic inflammation can all contribute to muscular wasting. Muscle wasting becomes a major problem, especially when systemic inflammation is high. The muscle wasting occurs at least due to increased activity of the ubiquitin proteasome pathway as well as apoptosis. However, the key reason in the loss of muscle mass during COPD with a high degree of systemic inflammation may not be increased protein breakdown but rather the muscle's decreased regeneration ability.[8]

Chronic kidney disease (CKD)

Muscle wasting is a major consequence of chronic kidney disease (CKD), which is defined by an imbalance between the synthesis and breakdown of proteins. Muscle mass loss results from repeated activation of catabolic pathways, including lysosomal proteolysis, caspase-3, the ubiquitin-proteasome system (UPS), and myostatin-mediated processes. Contributing factors include inflammation,

metabolic acidosis, impaired appetite regulation and defective insulin signaling. These mechanisms not only contribute to morbidity but also to mortality of patients with CKD. Targeting these pathways may be an effective treatment strategy to reduce muscle wasting in CKD by preventing protein loss and enhancing muscle metabolism.[9]

Pathways involved in muscle wasting

Ubiquitin–Proteasome Pathway

Most biological proteins are broken down via a multienzymatic process that needs ATP, even though many proteases can hydrolyze peptide bonds without energy. Most proteins targeted for degradation through this process are initially marked for degradation by covalent attachment to the small protein known as ubiquitin. An enzyme called E1 that requires ATP first activates the carboxyl terminus of ubiquitin by converting it to a thiol ester. Activated ubiquitin is then transferred by E1 to one of a class of carrier proteins called E2 proteins, and the carboxyl terminal group of the transferred ubiquitin is joined with the e-amino groups of suitable lysines in the target protein by the action of an enzyme called ubiquitin–protein ligase or E3. Repeated ubiquitin-conjugation processes result in a chain of five or more ubiquitins connected to the protein substrate and subsequently to one another.[10]

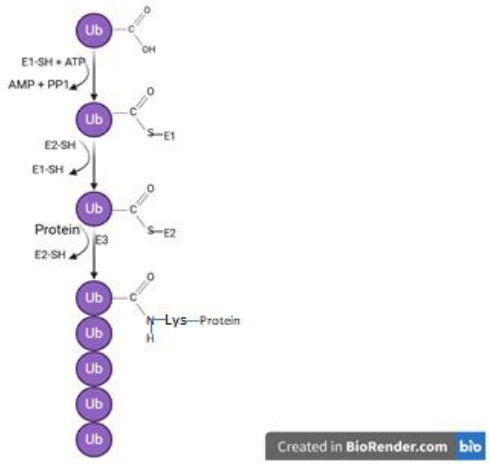

Fig:2 Ubiquitin conjugation[10]

The three enzymes E1, E2, and E3 work together in an ATP-dependent mechanism to conjugate proteins that are meant to be broken down to ubiquitin. The main factor controlling protein substrate selection for degradation arises from the protein's recognition by specific E3 ligases. When a chain of Five ubiquitin proteins is linked to a protein substrate, it forms a recognizable structure for the 26S proteasome. As a result, the ubiquitin chain is released, broken into individual ubiquitins, and the protein substrate unfolds for proteasome injection and peptide digestion. Peptides are broken down into amino acids by cytoplasmic peptidases. A similar mechanism breaks down muscle proteins in catabolic situations.[11]

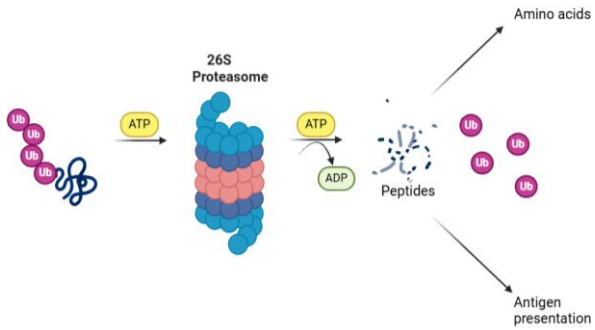

Fig: 3 Protein degradation[11]

Autophagy-lysosome system

Using lysosomal machinery, autophagy is a highly conserved system for breaking down and recycling organelles, long-lived proteins, and bulk cytoplasm. Processes of selective autophagy, such mitophagy (the elimination of mitochondria), are essential. Autophagy had

been reported to be stimulated in different types of pathological muscle wasting conditions such as cancer, ageing, fasting, caloric restriction, sepsis, critical illness, chemotherapy among others. Resistance exercises and endurance naturally stimulate autophagy, contributing to improved glucose homeostatis and overall metabolic benefits. Mitophagy maintains quality of mitochondria control by selectively eliminating damaged mitochondria. Key regulators are parkin, PINK1, Bnip3L and Bnip3, with their dysfunction linked to mitochondrial abnormalities. Muscle wasting is a result of autophagy pathway dysregulation, which is shown in hereditary disease such Vici syndrome and lysosomal storage disorders. EPG5 gene mutations are linked to Vici syndrome, block autophagosome-lysosome fusion, resulting in characteristic myopathic features. Docking to lysosomes and autophagosome biogenesis are regulated by the beclin1/Vps34/Vps15 complex. Specific knockout of Vps15 in muscles has been shown to affect autophagosome-lysosome fusion and thereby leading to autophagic vacuolar myopathy. Targeting autophagy pathways may be therapeutically beneficial, as autophagy reactivation eliminates glycogen buildup in models of lysosomal storage.[12]

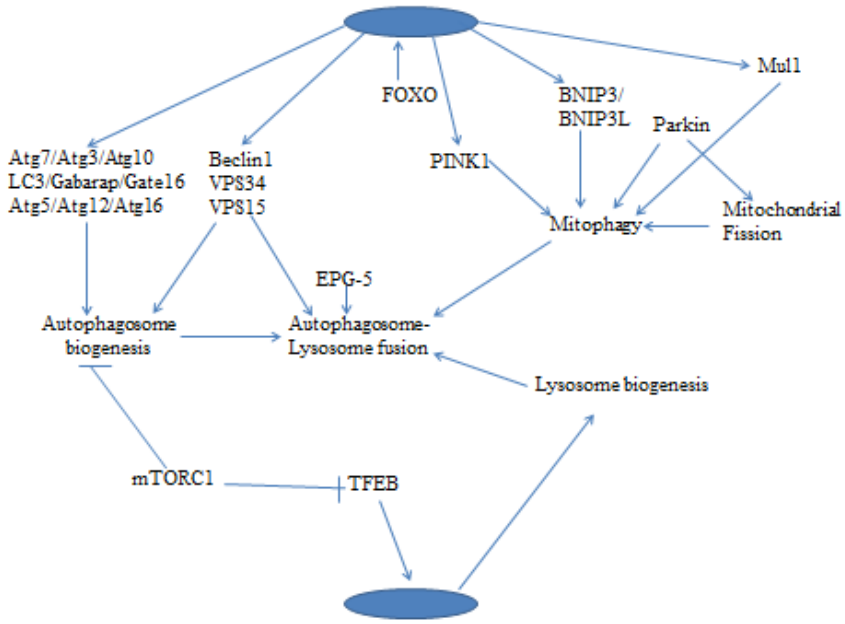

Fig: 4 Signaling modules responsible for autophagy-lysosome pathway in the adult.[12]

NF-κB pathway

NF-κB is an essential transcription factor that controls muscle wasting, apoptosis, and inflammatory reactions. It stimulates the expression of genes linked to muscle wasting by interacting with FOXO transcription factors. Muscle wasting is associated with inflammatory cytokines including TNFα, IL-1, and IL-6 activating NF-κB, which is connected to diseases like sepsis, cachexia, and cancer.[1] TNFα and IL-1 are examples of pro-inflammatory cytokines that cause NF-κB activation, which results in muscle wasting. NF-κB activation promotes protein breakdown in muscle cells by inducing the expression of proteolytic genes such as Atrogin-1 and MuRF1. TWEAK (TNF-like weak inducer of apoptosis) also stimulates NF-κB through binding to FN14, which plays a role in muscle wasting.[13] MuRF1 and Atrogin-1 are two E3 ubiquitin ligases that NF-κB increases the expression of to control inflammation-induced muscle wasting. The pathway also impairs myogenesis by lowering the levels of protein MyoD and Myf-5, which inhibits muscle regeneration. Myogenesis is inhibited by NF-κB activation, which results in poor postnatal muscle development.[13] NF-κB signaling may be inhibited genetically and pharmacologically to enhance muscle health in a variety of settings and stop cytokine-induced muscle wasting. There are ongoing developments for small molecules designed to inhibit IKKβ and NF-κB signaling, and some of these compounds have shown efficiency in reversing muscle wasting.According to the reports, it was found that the natural compound curcumin decreases inflammation and enhances muscle strength as well, which has greater implication for the treatment.[13] Muscle disorders such as Duchenne muscular dystrophy (DMD), sarcopenia, and cachexia are associated with increased NF-κB activation,

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which leads to muscle deterioration. NF-κB activation in these condition is associated with increased levels of pro-inflammatory cytokines and then the activation of proteolytic pathways.[14] TRAF6 plays a crucial role in muscle wasting in cachectic situations by activating NF-κB and integrating upstream inflammatory signals. Nevertheless, it is unclear how many different upstream signals control NF-κB in muscle wasting.[13] Despite attempts, it is still difficult to create effective

NF-κB inhibitors. Clinical success is impeded by problems with specificity and potency.[1] Particularly in DMD models, inhibiting NF-κB with substances like sodium salicylate or NEMO-binding domain peptides has demonstrated potential in minimizing muscle damage.[14]

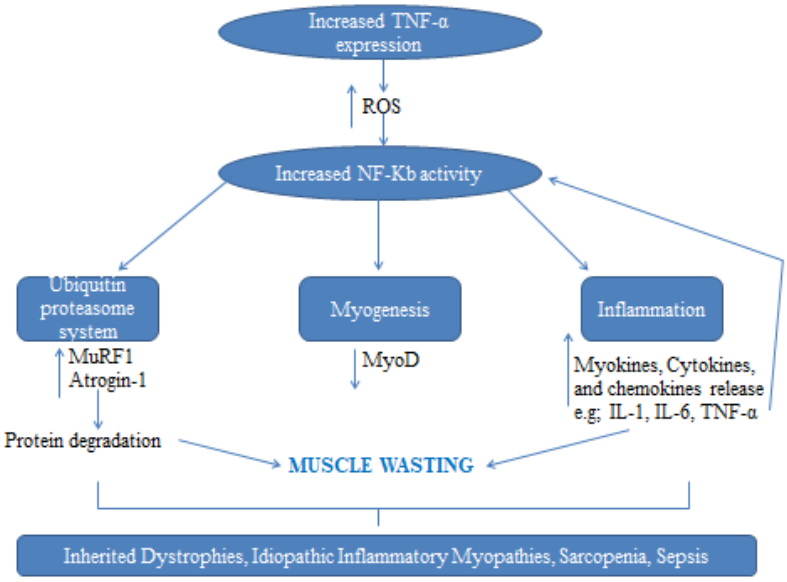

Fig:5 ; NF-κB pathway[14]

mTOR pathway

Muscle wasting is caused by either increased protein breakdown or decreased protein synthesis as a result of causes such as inactivity, illnesses, age, or metabolic disorders. The mTOR pathway regulates muscle hypertrophy by balancing anabolic and catabolic activities. Its activation stimulates protein synthesis, whilst its inhibition causes muscular wasting. mTOR signaling is inhibited by atrophy-inducing signals and Promote defense to muscle wasting under normal physiological conditions.[15] mTORC1 stimulates anabolic processes such as synthesis of protein and lipid production while inhibiting autophagy. Akt signaling is activated and cytoskeletal structure is regulated by mTORC2. For muscle growth and maintenance, mTORC1 activation by growth hormones (such IGF1), amino acids (leucine, arginine), and mechanical stimulation is essential. Atrophy and impaired muscle regeneration are caused by dysregulation of mTORC1 signaling.[16] Cachexia causes loss of muscle and fat tissue, which is common in 80% of cancer patients and raises the death rate. mTORC1 signaling impairment in cancer Cachexia exacerbates muscle deterioration by decreasing protein synthesis and increasing autophagy.The ability of Akt-mTORC1 to repair muscle wasting without influencing tumor growth suggests that it may have therapeutic value.[17] Declining muscle mass, strength, and quality with age is known as sarcopenia.[15] Reduced Akt/mTORC1/p70S6K1 activity in older people affects their anabolic reactions to stimuli like exercise and diet. In aging muscle, chronic mTORC1 activation without autophagy induction leads to atrophy, emphasizing the necessity of balanced mTOR activity.[16] Glucocorticoids enhance catabolic processes by upregulating branched-chain aminotransferase 2 (BCAT2) and atrogenes (such as Atrogin-1 and MuRF-1). By changing myostatin and BCAT2 levels, these hormones inhibit mTOR signaling, which encourages muscle deterioration.[15] By decreasing lean body mass and skeletal muscle index, long-term usage of mTOR inhibitors such as everolimus results in sarcopenia. These inhibitors worsen muscle loss and hinder protein synthesis, particularly in cancer patients receiving treatment.[18] A member of the TGF-β family, myostatin inhibits Akt-mTORC1 signaling, which in turn slows muscle development. Through FOXO activation, it upregulates elements of the ubiquitin-proteasome system, which leads to muscle wasting. Protein synthesis may be regulated by myostatin through both mTOR-dependent and independent pathways.[15] FoxO activation promotes the

breakdown of muscle proteins through ubiquitin-proteasome and autophagy pathways. FoxO activity is inhibited by mTOR, reducing its atrophic effects.[19] Resistance exercise activates mTORC1, which boosts muscle hypertrophy and protein synthesis. Research indicates that mTORC1 signaling is essential for muscle growth after mechanical stress. Mechanisms include nutrient-sensing pathways involving Ragulator and Sestrin2, as well as IGF1 and phosphatidic acid signaling.[20] Activation of Akt-mTORC1 has demonstrated potential for muscle mass restoration in cachectic models.[17] Sarcopenia can be treated by altering mTORC1 activity, which increases anabolic responses and encourages autophagy when needed. Exercise and nutrition: Exercise stimulates mTORC1 and works in concert with protein supplements to promote the health of muscles.[16] Tissue-specific mTOR modulators may improve treatment results with little adverse effects using pharmacological methods. For the study of muscle-wasting mechanisms, mouse models with mTORC1-specific deletion or activation are essential.[19] Muscle mass modulation is revealed by methods such as tamoxifen-induced Akt activation and CT-based skeletal muscle characterization. p70S6K1, 4E-BP1, and eIF2Bε phosphorylation are indicators of mTOR activity. Examine specific mTOR modulators to optimize the pathways involved in protein production and breakdown.[20] Examine how mTOR regulation incorporates mechanical, dietary, and hormonal cues. Create individualized treatment plans that target mTOR for particular muscle-wasting diseases such as glucocorticoid-induced atrophy, sarcopenia, and cachexia.[19]

Myostatin/activin pathway

Myostatin which belongs to the TGF-β superfamily, has the ability to prevent muscle development. Muscle development is negatively regulated by myostatin. It promotes muscle wasting and prevents muscle differentiation.[11] Myostatin and activin attach to the ActRIIB receptor complex that is present on the surface of muscle cell.[21] Myostatin shares receptors with Activin A which is known to be increased under inflammation and is an important factor in muscle wasting.[11] The myostatin/activin signaling pathway activates Smad proteins (Smad2 and Smad3), which causes them to move into the nucleus and control the transcription of genes linked to muscle atrophy.[11] This signaling lowers the activity of Akt, a crucial enzyme that prevents protein breakdown and encourages muscle development. Muscle protein breakdown is promoted by the activation of forkhead transcription factors (FoxO) brought on by the reduction in Akt activity. These factors in turn trigger the production of E3 ubiquitin ligases such as Atrogin-1 and MuRF1.[21] The pathway plays a role in muscle wasting by enhancing protein breakdown via the ubiquitin-proteasome system (UPS).[11] Myostatin levels are elevated in a number of diseases linked to muscular atrophy, including heart failure, cancer, aging, and chronic kidney disease (CKD). Increased breakdown of muscle proteins and a reduction in muscle mass are linked to the myostatin/activin pathway. Activin A which has receptor binding similarities to myostatin also plays a role in muscle wasting and exacerbates the process.[11] Myostatin levels are raised in diseases like cancer cachexia, which leads to muscular wating.[21] A possible treatment strategy to stop muscle wasting is to target the myostatin/activin pathway.[22] Myostatin-neutralizing antibodies, follistatin, and soluble ActRIIB receptors are some of the strategies.[11] Studies have shown that follistatin and other inhibitors can attach to myostatin and stop it from interacting with ActRIIB, which results in increased muscle mass. In experimental models, soluble ActRIIB receptors (sActRIIB) have demonstrated promise in restoring muscle loss.[22] The myostatin/activin-ActRIIB pathway may be pharmacologically blocked to increase muscle growth, strength, and overall patient outcomes.[11] Techniques for myostatin inhibition may enhance muscle growth, function, and reduce muscular atrophy in chronic illnesses. Nevertheless, muscle atrophy remains an unaddressed problem within medical practice despite its critical significance; to this date, there are no drugs available that directly counteract the phenomena. Understanding the myostatin/activin pathway lays the groundwork for creating possible therapies.[11]

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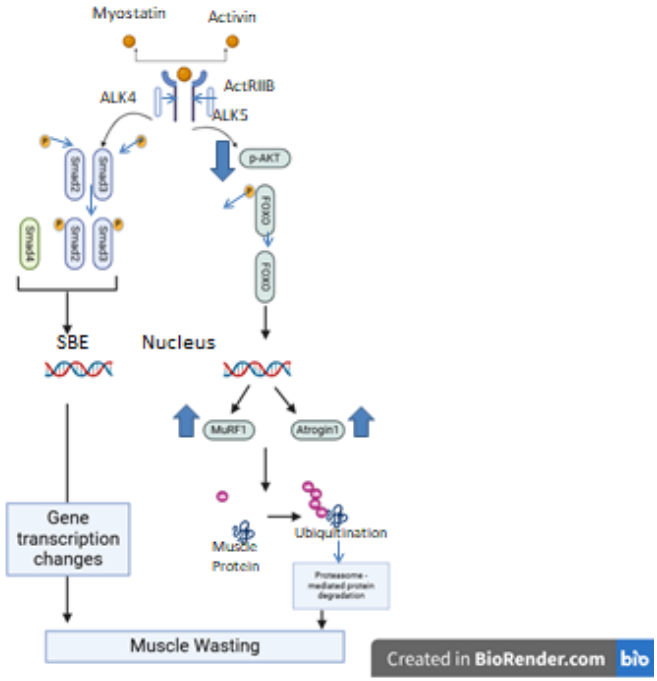

Fig: 6 Myostatin/activin pathway[11]

Insulin-like growth factor-1 (IGF-1) pathway

Insulin-like growth factor-1 (IGF-1) is essential for muscle metabolism and is especially important when it comes to muscular wasting, which is a common occurrence in diseases like chronic heart failure (CHF). IGF-1 is necessary for the maintenance of muscle mass. It does this by triggering intracellular signaling pathways, particularly the PI3K/Akt pathway, which prevents muscle wasting and encourages muscular growth. Muscle-specific ubiquitin ligases involved in protein breakdown, such as MAFbx and MuRF1, are inhibited by IGF-1. IGF-1 stimulates signaling pathways that support muscle cell development and survival by acting through its receptor. It prevents FoxO transcription factors from being activated, which is linked to increased proteolysis and muscle wasting. When FoxO factors are phosphorylated, their nuclear translocation is inhibited, which lowers the transcription of genes that encourage muscle breakdown.[23] The decline in IGF-1 serum levels that occurs with aging is linked to sarcopenia, or age-related muscle loss. IGF-1 signaling can be disrupted by chronic low-grade inflammation, which is frequently observed in older persons and is marked by increased cytokines such as IL-6 and TNF-α. This can further contribute to muscle wasting.[24] IGF-1 is a possible therapeutic drug because of its ability to prevent muscle wasting.[23] It has been demonstrated that localized IGF-1 expression in skeletal muscle maintains muscular growth and repair.[24] Techniques to improve IGF-1 signaling or IGF-1 administration itself may help prevent muscle loss in a number of circumstances, such as chronic diseases and cancer cachexia.[25] In muscle cells, the PI3K/Akt pathway is crucial for enhancing protein synthesis and preventing protein breakdown.[23] Akt activation promotes protein synthesis via activating mTOR, a key regulator of muscle hypertrophy and cell development.[24] Proteolytic pathways are adversely regulated by IGF-1 signaling, especially the autophagy-lysosomal and ubiquitin-proteasome systems.[25] IGF-1 signaling can be adversely regulated by microRNAs (miRNAs), including miR-29b, which suggests a possible therapeutic target for muscle wasting.[24] Muscle wasting can result from myostatin overproduction, which can reverse the benefits of IGF-1.In chronic inflammatory diseases like cancer cachexia, inflammatory cytokines like IL-6 might hinder the function of IGF-1. IGF-1's signaling pathways, especially the PI3K/Akt/mTOR pathway, are essential for maintaining muscle mass. Knowing these pathways helps researchers develop possible treatment approaches to stop muscle wasting in a variety of disease.[25]

Promising therapies in muscle wasting

Exercise

Exercise training has been recommended for healthy older adults, as well as many patients suffering from chronic disease, including those with diabetes mellitus, heart failure, or cancer.[26] Many muscle-wasting conditions can benefit from physical activity, but sarcopenia is particularly one where exercise can have long-term

positive effects on muscular function, lowering the risk of falls and enhancing older people's independence and quality of life.[4] When comparing high-speed circuit training to hypertrophy training, the short physical performance battery value significantly improved by 20%. Patients having total hip replacement may benefit from interval walking training as a home-based training program to avoid muscle wasting brought on by decreased daily activity. In older adults, respiratory muscle exercise improved maximum inspiratory pressure, diaphragm thickness, and mobility.[26] While aerobic exercise training has significant positive impacts on cardiovascular fitness, resistance (strength) training is the most effective exercise for maintaining or increasing muscular strength and reducing the rate of muscle mass loss.[4] Exercise can alter the epigenetic profile of muscle over time by demethylating DNA regions to boost transcription of good genes and hypermethylating DNA in promoter regions of harmful genes to inhibit their expression. Even in the absence of muscle mass growth, enhanced neuromuscular function can lead to sustained or enhanced muscle strength and power. Exercise helps regulate systemic glucose homeostasis by increasing glucose absorption independent of insulin sensitivity. It also uses other fuels, such fatty acids, to provide substrate for oxidative phosphorylation and ATP generation.[27] Exercise is the only treatment that has been shown to reverse or prevent muscle wasting, but it is difficult to apply to broad populations since it requires qualified trainers, sufficient facilities, and motivated patients. Long-term adherence is challenging because many patients are either too ill to engage in exercise programs successfully or dislike exercising.[28] The implementation of exercise prescription as the bedside standard of treatment may be accelerated by a focus on identifying biomarkers associated with significant clinical outcomes that are also directly influenced by exercise. Exercise will be handled as a regular "drug" with the appropriate dosage and prescription. Finding the processes behind variations in muscle mass response to training or resilience to muscle wasting might guide customized exercise regimens to maximize recovery.[27]

Nutrients

Nutrition supplements has been demonstrated to affect physical performance, strength, and muscle mass in both chronic illness patients and older, healthy persons. In older persons, n-3 PUFA treatment[29] can reduce the loss of muscle mass and function, perhaps avoiding sarcopenia and maintaining physical independence. Supplements with high levels of whey protein, leucine, and vitamin D may help maintain muscle mass while losing weight and lower the risk of sarcopenia. Consuming some foods, like ricotta cheese, may enhance sarcopenia indicators and slow down the loss of muscle mass. According to preclinical studies, bioactive substances such as quercetin, AGT251, baicalin, and epigallocatechin-3-gallate have the ability to prevent muscle wasting and its associated indicators.[26] Muscle wasting is linked to increased oxidative cell damage, decreased protein synthesis, and increased protein breakdown (catabolism). Nutritional intervention is one strategy that may have direct therapeutic relevance for muscle wasting. This includes the use of protein powders and certain amino acids to reduce muscle protein losses and create an intracellular environment that is suitable to protein synthesis. It has been demonstrated that nutritional supplements with anti-inflammatory components such eicosapentanoic acid (EPA) and polyunsaturated fatty acid (PUFA) are more advantageous for malnourished individuals than nutritional supplements by themselves.[4] High-quality protein sources that provide the amino acids needed for muscle growth and repair include eggs, dairy products, lean meats and plant-based proteins. Muscle protein synthesis (MPS) is primarily stimulated by leucine, a branched-chain amino acid (BCAA). Leucine-rich foods, such as dairy, whey protein, and certain meats, should be prioritized in the diet. Muscle loss can be reversed by taking BCAA supplements, particularly leucine, in a number of situations, such as chronic illnesses or periods of inactivity. Providing a full spectrum of essential amino acids (EAAs) can help promote muscle growth and recovery, especially when taken during exercise.[30] Muscle protein synthesis (MPS) may be effectively stimulated by certain protein sources, such as whey protein.[28] A good nitrogen balance and continued muscle synthesis and repair are supported when protein consumption is distributed uniformly throughout the day.[30] Physical exercise or resistance training, which increases muscle mass and strength, is more effective when paired with nutritional therapies.[28] There is significantly less evidence supporting the effectiveness of nutritional supplements, especially protein and amino acids, in counteracting disuse atrophy. Unloading reduces the increase in muscle and whole body protein synthesis brought on by amino acids. Maintaining a body composition that supports a healthy metabolic profile during periods of inactivity, such as bed rest, may not be possible with supplements alone along with a eucaloric diet. During bed rest, exercise improved body composition, preserved muscle mass, and decreased fat mass—even when there was a slight negative energy balance.[31] Aging-related changes in glutamine metabolism are believed to be a reflection of increased

proteolysis in elderly as well as in diseased skeletal muscle and in critically ill patients.[4] When it comes to treating muscle wasting, nutrition is especially important for populations that are at risk, such as older adults, those with chronic illnesses, and people receiving medical treatment.[28] Maintaining muscle mass requires enough hydration, which also improves exercise performance and promotes general health. Vitamin D, calcium, and magnesium are examples of micronutrients that are essential for muscle function and should be included into the diet to promote muscle health. Protein powders, amino acid formulations, or specialty nutritional beverages are examples of nutritional supplements that may be helpful, particularly for people who have trouble eating enough meals. High-quality protein and amino acid supplements, careful nutrient scheduling, making sure sufficient calorie and micronutrient consumption, and taking into account functional meals or supplements when necessary are all effective dietary methods for treating muscle wasting.[30]

Anti-Inflammatory Drugs

In mice, direct suppression of NF-κB signaling prevented the loss of muscle mass caused by tumors or denervation. Using a monoclonal antibody against Fn14 to treat tumor-bearing mice effectively increased survival and stopped the loss of muscle, fat, and body weight. Soluble TNFα receptor or IL-6 receptor antibody treatment had a considerably less noticeable impact; it improved the cachectic phenotype but was unable to totally stop the animals' muscle wasting.[29] Several other clinical trials examining the effects of TNFα inhibitors or soluble TNFα receptors failed to demonstrate an improvement in body weight, appetite, or muscle volume, despite an early study showing positive effects of a TNFα inhibitor (thalidomide) on muscle loss and weight loss in cancer patients. An IL-1α-specific humanized monoclonal antibody (Xilonix/MABp1) that inhibited IL-1α signaling enhanced lean body mass (LBM); nevertheless, the study did not include a control group. The humanized IL-6 monoclonal antibody ALD518 improved tiredness but had no impact on LBM; this was probably because it helped with anemia. An current trial in cancer patients is examining whether the JAK1/2 inhibitor ruxolitinib, which blocks downstream signaling of IL-6, improves muscle wasting. The synthesis of prostanoids and prostaglandins depends on cyclooxygenase (COX) inhibitors, which are another class of medications that have a strong effect on systemic inflammation. Meloxicam, a COX2 inhibitor, decreased the muscle mass loss that rheumatoid arthritis caused in rats. This reduction may have been linked to a significant decrease in the expression of Trim63 (MuRF1) and FBXO32 (MAFbx). Celecoxib, an inhibitor of COX2, produced conflicting findings. In one research, it had no impact on LBM, while in another, it increased grip strength and LBM while lowering blood TNFα in cancer patients.[2]

Angiotensin-Converting Enzyme (ACE) Inhibitor

Angiotensin II (Ang II) was initially shown to produce a substantial decrease in body weight in rats by increasing skeletal muscle proteolysis and decreasing food intake. ACE inhibitors have been used to prevent subsequent strokes and treat cardiovascular disease. Ang II infusion speeds up the degradation of proteins and reduces IGF-I signaling. Atrogene expression, 20S proteasome activity, and ubiquitin-conjugated protein levels are all markedly elevated in Ang II-induced muscle wasting. Even with ACE inhibitory treatment, plasma Ang II levels in patients with CHF and CKD can increase by a factor of two to five. Ang II may cause older people to lose muscular mass. ACE drugs would enhance muscular function by altering endothelial and metabolic function, promoting angiogenesis, and reducing inflammation. ACE inhibitors can help prevent several types of muscle wasting by raising IGF-I levels and mitochondrial counts. ACE inhibitors lower the chance of weight loss in heart failure patients. ACE inhibitors increase the ability to exercise in both younger and older heart failure patients, although they often do not increase grip strength. Long-term use of ACE inhibitors may slow the loss of muscular strength and walking speed in elderly hypertension patients. This causes a considerable increase in lower limb muscle mass compared to those who use other antihypertensive medications.[32] ACE inhibitors may help reduce the decline in muscular strength and walking speed. They have been associated with improvements in mobility and endurance, potentially lowering the risk of sarcopenia by enhancing muscle function.[33] Before suggesting ACE inhibitors to prevent further atrophy in sarcopenia, more research would be needed, focusing on sarcopenic patients rather than just elderly individuals. Given that ACE inhibitors are linked to cardiovascular benefits and that underlying cardiovascular issues are widespread in older adults, these medications are already regularly recommended. Before suggesting ACE inhibitors particularly for sarcopenia, more research is required.[32]

Anabolic Steroids

Steroid hormones called testosterone or testosterone derivatives work by attaching to cytosolic receptors, which increases muscle mass and protein synthesis. Research on

testosterone and its derivatives in various malnutrition-related disorders has recently surfaced. The majority of research on the use of these anabolic drugs in patients with cachexia has focused on individuals with HIV/AIDS and COPD, where beneficial benefits on body weight, LBM, and some functional parameters have been reported. For many years, oxandrolone, a modified testosterone derivative with little androgenic effects, has been authorized as an oral anabolic for men and women who have lost weight due to caabolic disorders, infections, or surgery. Nandrolone decanoate, an anabolic steroid frequently misused by sportsmen, has been tested in many studies in patients with cachexia and wasting and was licensed to boost red blood cell formation in patients with renal failure. According to a number of placebo-controlled studies, nandrolone decanoate may have anabolic benefits in individuals with wasting related to COPD or HIV.[34] Anabolic androgenic steroids, such as testosterone and its synthetic analog derivatives, have been used to enhance muscle growth in individuals with a variety of chronic conditions and are given for male hypogonadism. It has been demonstrated that anabolic androgenic drugs improve muscle protein synthesis, lean body mass, and muscular strength through both direct and indirect actions on androgen receptors. Increased protein synthesis in skeletal muscle may be the cause of increases in muscle mass and weight gain.[35] These drugs have caused side effects such as decreased concentrations of high-density lipoproteins, increased concentrations of transaminase (particularly when combined with nandrolone), hypogonadism (shown by decreased systemic testosterone concentrations), and interactions with oral anticoagulants, oral hypoglycemics, and adrenal steroids that necessitate adjusting the dosage of these medications.[34] The possibility for severe side effects and the relative lack of tissue selectivity of androgenic anabolic steroids are important factors to take into account while treating them.[35] The potential for nonsteroidal selective androgen receptor modulators (SARMs) to produce advantageous anabolic effects in a tissue-selective manner while avoiding many undesirable side effects associated with steroidal agents has contributed to the recent acceleration of their development. Recent reviews have examined the pharmacology, therapeutic potential, and mechanisms of action of androgen receptors in a variety of SARMs under development. Importantly, SARMs do not function as substrates for the metabolic conversion of estrogens or dihydrotestosterone, which limits the risk of gynecomastia and benign prostatic hyperplasia in males and masculinization in females. Aryl propionamide SARMs have been found in preclinical investigations to improve skeletal muscular strength, enhance lean body mass, raise total bone mineral density, and decrease body fat and bone loss in rats. Ostarine is the SARM that is presently undergoing the most clinical development; it has successfully passed a phase IIb study in cancer cachexia patients. Ostarine showed a positive safety profile and was linked to a dose-dependent increase in lean body mass and improvements in functional performance in a phase II proof-of-concept trial between postmenopausal women and older males.[35] To determine the clinical and long-term effectiveness of any of the medicines mentioned in this article, further information is often required. Only rigorous, suitably powered phase III studies in the future will be able to meet this demand.[34]

β2-Adrenergic agonists

The positive effects of β2-agonists on muscle mass may be due to increased blood flow and stimulation of muscle protein synthesis. Slow-release salbutamol improved respiratory muscle strength in HF patients, but it had no effect on quadriceps strength or exercise capacity, according to a small, randomized, placebo-controlled study. Clenbuterol substantially improved muscular strength and lean mass and lean-to-fat ratio in HF patients compared to the placebo group. Gaining more muscle mass does not always result in gaining more muscular strength; only the latter is thought to be linked to a higher quality of life.[36] Powerful anabolic drugs known as β2-agonists cause skeletal muscle growth

and may be used therapeutically to treat muscle-wasting conditions such as neuromuscular illnesses, cancer cachexia, sepsis, and thermal damage. β2-agonists have been shown in several trials to reduce and/or restore muscle mass loss and related weakness in both human patients and animal models. The cAMP/PKA/CREB and cAMP/Epac/Rap pathways are stimulated by β2-adrenergic receptor activation, which results in enhanced protein synthesis and inhibition of muscle wasting pathways. A slow-to-fast muscle fiber type change is linked to β2-agonist-induced skeletal muscle growth. Myostatin inhibition and IGF-1 overexpression are two important regulators of skeletal muscle mass that are coordinated by β2-Agonist-induced production of PGC-1α4. Despite its advantages, long-term use of β2-agonists has been associated with negative side effects such tachycardia, cardiac enlargement, and increased collagen deposition in the heart muscle. According to clinical research, β2-agonists may help individuals with Becker and Duchenne muscular dystrophy gain more muscle mass

and strength. In MDX mice, formoterol enhances muscular function without making muscles more tired. Salbutamol raises the expression of the SMN protein in spinal muscular wasting, indicating that it may have therapeutic uses beyond hypertrophy. When β2-Agonist is administered, muscle wasting is decreased in sepsis, COPD, cancer cachexia, and chronic heart failure. β2-agonists are not widely used therapeutically for muscle wasting diseases due to long-term safety concerns and possible cardiac adverse effects.[37] β-Agonists have been suggested as pharmacological treatments to reduce muscle atrophy and rebuild muscle mass in diseases including COPD, burns, sepsis, and cancer cachexia. Clenbuterol and other β-agonists have the potential to cure muscle-wasting illnesses since they enhance skeletal muscle mass and decrease body fat. By promoting protein synthesis and preventing muscle proteolysis, clenbuterol therapy has demonstrated positive benefits on muscle wasting in animal models of cancer cachexia. β-Agonists may play an essential role in muscle maintenance and remodeling by simulating the effects of normal innervation in denervated muscles. Clinically, β-Agonists can improve muscle regeneration and function following injury or reconstructive surgery. Clenbuterol restored muscle mass and function in old rats, suggesting that it might be used therapeutically to treat sarcopenia. Research on the effects of β-agonists on motor neuron degeneration, ALS, and muscular dystrophy has revealed that they promote muscle growth and slow the course of the illness. Long-term therapeutic usage of β-agonists is limited due to their unfavorable cardiovascular side effects, which include tremors and elevated heart rate, despite their ability to grow muscle. More recent β-agonists, such as formoterol, have been created to reduce cardiovascular risks and promote muscle growth.[38]

Investigational Drugs of Muscle Wasting

Enobosarm

Enobosarm, commonly known as ostarine or GTx-024, is a selective androgen receptor modulator (SARM) that is non-steroidal and accessible orally.[39] When it binds, it causes conformational changes in the androgen receptor, which modulates the receptor without causing the negative effects of testosterone or other anabolic steroids.[40] In healthy older men and postmenopausal women, enobosarm has demonstrated a dose-dependent improvement in total lean body mass and physical function. Additionally, it has proven to be effective in reducing muscle wasting linked to cancer cachexia. In cancer patients, a phase II clinical trial revealed improvements in insulin resistance and muscular function (as determined by stair climbing) without any obvious toxicity or adverse effects.[39] POWER 1 and POWER2 phases 3 trials were conducted, aiming at determining the effectiveness of Enobosarm in the prevention of the degradation of muscles in non-small-cell lung cancer (NSCLC) patients receiving first chemotherapy. The POWER II experiment did not reveal a substantial gain in stair climb power, however the POWER trials did indicate an increase in lean body mass.[40] Although anabolic androgenic drugs, like testosterone, enhance lean body mass, their usage is limited due to their adverse effects. Enobosarm is a non-steroidal SARM that has anabolic effects without harming the skin, hair, or prostate. However, Enobosarm is at present not being developed further for cancer cachexia treatment due to mixed outcomes of Phase III trials.[40]

OHR/AVR118

OHR/AVR118 is an anti-inflammatory, broad-spectrum peptide-nucleic acid immune modulator that inhibits the production of cytokines (such TNF and IL-6) as well as cellular proinflammatory chemokines.[39] It is thought to have cytoprotective and immunomodulatory qualities, while the exact mode of action is yet unknown.[41] During a Phase II study, this medication stabilized body weight, body fat, and muscle mass in patients with advanced cancer and cachexia. It also significantly increased hunger without causing any negative side effects. According to the study, OHR/AVR118 reduces the negative effects of chemokines and cytokines, which have a direct effect on muscle metabolism. In addition to treating cancer cachexia, this medication has been used to treat AIDS cachexia, helping to reduce a number of the illness's symptoms.[39] A double blind, placebo controlled Phase II study using OHR/AVR118 of 4 ml/day for 28 days has been done on cancer related anorexia and cachexia in patients with advanced solid tumors, impacted on anorexia and gastrointestinal symptoms. Due to its limited sample size and single-arm interventional design without a placebo group, the trial had disadvantages.[40] The Phase II study that had been conducted in the Ottawa, Canada in 2013 (NCT01206335) involved 18 patients suffering from advanced solid tumors to assess multiple cachexia symptoms, including appetite loss, early satiety and reduced nutritional intake. These said secondary outcomes comprised alteration of inflammatory proteins, hormonal balance, and impacts on testosterone level, thyroid stimulating hormone level, and C reactive protein level. The study found that weight, body mass, and muscle mass stabilized, and that people's appetites and quality of life improved. The information was presented in December

2013 at the annual conference of the Society for Cachexia and Wasting Disorders.[41] Also there was enhancement on mean body weight, body fat and muscle mass. However, the published abstract lacked safety data and a precise definition of muscle mass stabilization.[42]

Anamorelin

Anamorelin (RC-1291; ONO-7643) is a new molecule that is still in clinical trial designed to function as an orally active selective agonist of the ghrelin receptor.[43] Anamorelin is a novel non-peptide drug, which emulates the ghrelin action of activating the growth hormone, increasing the appetite, and regulating integrated feed intake incentives.[40] Anamorelin is thought to help cancer patients who suffer from anorexia and cachexia by boosting appetite and triggering anabolic hormone pathways that encourage muscle growth.[43] A randomized, double-blind, placebo-controlled, phase I research was conducted to evaluate anamorelin, and after six days of therapy, a substantial dose-related increase in body weight was found.[40] The 12-week assessment showed significant improvements in lean body mass along with total body weight from phase II studies of anamorelin done on cachectic patients with advanced or incurable cancer and from phase III trials conducted on cachectic non-small cell lung cancer patients with no cure options.[43] When compared to the placebo group, the 12-week anamorelin therapy resulted in a favorable increase in appendicular lean body mass.[40] Since then, two international phase III studies have been carried out: ROMANA 1 (NCT01387269) and ROMANA 2 (NCT01387282). Anamorelin significantly increased lean body mass but not hand-grip strength in individuals suffering from cachexia due to advanced non-small-cell lung cancer. These trials evaluated the safety and effectiveness of anamorelin therapy over a 12-week period when compared to a placebo.[40] Anamorelin-treated patients had improvements in their non-dominant handgrip strength, as well as higher insulin-like growth factor-1 concentrations and quality of life, especially in the areas of sleep, nausea, sleepiness, and sense of well-being, compared to placebo-treated patients. The safety and effectiveness of anamorelin therapy for a lengthy exposure duration (24 weeks) in lung cancer patients with a mean age of 62 years were validated by the ROMANA 3 safety extension trial.[40] Furthermore, the FAACT A/CS domain score, a 12-item anorexia–cachexia symptom burden scale, showed a notable and long-lasting improvement.[43]

ALD518

The humanized monoclonal antibody ALD518 (Alder Biopharmaceuticals, Inc., Bothell, WA) has a high binding affinity for both human and monkey IL-6.[42] Cancer fatigue and cachexia are now being treated with a humanized anti-IL-6 antibody (ALD518).[44] The impact of interleukin inhibition on the symptoms of cancer cachexia has been investigated in other research on anti-inflammatory therapies.[40] ALD518 has pharmacokinetics that are almost dose-proportional and a lengthy elimination half-life of 21–31 days. Adverse clinical characteristics, changes in food intake or body weight, or significant blood and urine laboratory safety tests were not seen in preclinical animal investigations with intravenous (i.v.) single- and multiple-dose ALD518.[42] In a recent phase I study, the safety of ALD518 given as a single intravenous infusion of 80, 160, or 320 mg was assessed in nine patients with advanced cancer whose circulating C-reactive protein levels were greater than 10 mg/l. ALD518 boosted hemoglobin and albumin, corrected tiredness, and showed a tendency to strengthen hand grips.[44] After receiving a single dosage of ALD518 in a small cohort of patients with advanced cancer, a Phase I research found statistically significant changes in hand grip strength and weariness.[42] An 8-week intravenous dose of anti-IL-6 (called ALD518) reduced the loss of lean body mass and enhanced the quality of life for patients with advanced non-small cell lung cancer (NSCLC), according to preliminary findings from a phase II double-blind experiment.[40] Cachexia was characterized as having a life expectancy of at least four months, a weight loss of at least five percent during the previous three months, and an increased C-reactive protein concentration.[42] For ALD518 no dose-limiting effects have been reported. There has been one recorded major adverse event of rectal bleeding, which is thought to be connected. The most frequent side effects are hemoptysis, chest discomfort, and dyspnea.[42] Because these data are so preliminary, care must be used when interpreting them.[44]

Future Perspectives

Myostatin and activin-A antagonists (and maybe SARMs) are the most promising medications to treat systemic atrophy. While these agents can increase muscle mass in people, their use as therapies requires way more validation. Determining the effectiveness of muscle increasing therapies is difficult due to several issues. Determining strength, nitrogen balance, or endurance in older or sick individuals is particularly difficult. Additionally, preventing the abuse of muscle-building treatments to improve sports performance will be the final challenge. Despite these significant obstacles, further research into

therapies for muscle atrophy is crucial due to the potential medicinal advantages.[1] Future research must include fundamental mechanism investigations and more high-quality clinical studies. More extensive and mechanism-based research is also needed in the future. The main questions revolve around whether and how nutrition therapies reverse the severe muscle wasting process to generate better conclusions. More study is necessary to understand the central processes governing muscle wasting, since this might lead to a new therapeutic approach. It is yet unknown if myostatin signaling plays a major role in muscle wasting during acute illness and if it may be addressed therapeutically.[45] New research outcomes present innovative viewpoints to the field which leads the community to investigate several intriguing questions that aim to discover therapeutic targets and drugs for future studies. A possible strategy is the creation of a novel class of IGF1 mimetics that selectively stimulate the Akt pathway in skeletal muscle. Furthermore, to assess the function of this pathway in muscle development and its potential in treatment methods, we need a better knowledge of which mTOR downstream targets are essential regulators of protein synthesis.[46] Knowing the processes governing muscle mass can help identify potential therapy targets for both inherited and non-inherited disorders that cause muscle loss, as well as for enhancing quality of life as people age. Future studies should concentrate on clarifying the complex interactions among signaling pathways, muscle metabolism, and systemic variables in order to provide targeted treatments. However, there are currently no effective pharmacological therapies for atrophying muscle in the clinic, despite continuous scientific attempts.[47]

Conclusion

NF-κB, mTOR signaling, the autophagy-lysosome route, the ubiquitin-proteasome system, and the myostatin/activin pathway are some of the molecular pathways that induce muscle wasting. It is frequently linked to conditions including aging-related sarcopenia, cancer, heart failure, chronic kidney disease, and COPD. The fundamental reason is frequently an imbalance between the production and breakdown of proteins, which is impacted by hormone dysregulation, inflammatory cytokines, and physical inactivity. Currently, there are no authorized pharmaceutical therapies that specifically target muscle wasting, despite the fact that this illness has a substantial influence on morbidity, mortality, and quality of life. Various therapeutic approaches for muscle wasting include exercise programs and nutritional interventions as well as anti-inflammatory drugs and ACE inhibitors and anabolic steroids and β2-adrenergic agonists and the investigational drugs Enobosarm and OHR/AVR118 and Anamorelin and ALD518. Exercise proves to be the greatest non-drug intervention that helps boost muscle protein synthesis and improves metabolic outcomes as well as functional ability. Maintaining muscle mass, especially in older persons and those with chronic diseases, requires nutritional support, notably in the form of protein and amino acid supplements. Several agents exhibit promising outcomes during preclinical and early clinical trials for drug treatment methods that target NF-κB, mTOR, IGF-1 and myostatin pathways. Future studies should concentrate on clarifying the complex interactions between these pathways, finding biomarkers for early identification and monitoring of development, and creating focused treatments with few adverse effects. Scientists must better comprehend molecular systems to generate medical applications that enhance treatment results for patients whose muscles deteriorate due to various diseases.

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