
CELLULAR MECHANISMS BEHIND MUSCLE LOSS

Module 2

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CELLULAR MECHANISMS BEHIND MUSCLE LOSS



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SKELETAL MUSCLE DECLINE WITH AGE: PHYSIOLOGICAL & FUNCTIONAL CHANGES

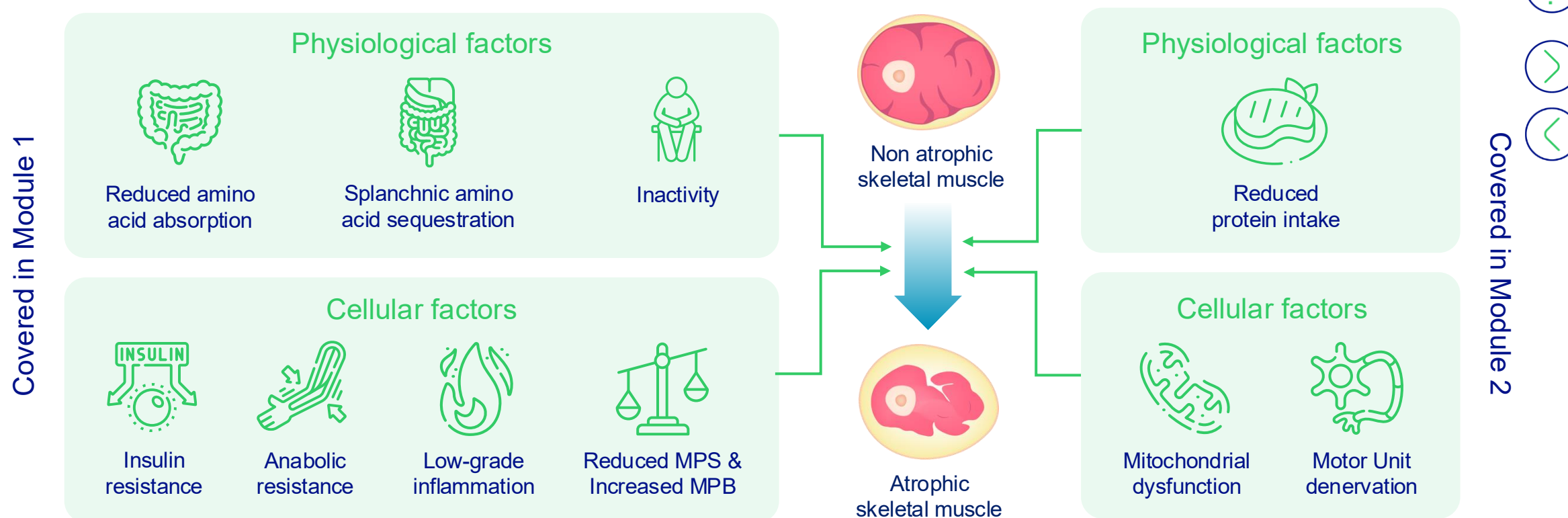
1.1. Skeletal muscle decline with age



SKELETAL MUSCLE DECLINE WITH AGE: PHYSIOLOGICAL & FUNCTIONAL CHANGES

Skeletal muscle decline with age

Aging-related muscle loss is a complex biological process influenced by various factors.^{1,2}



* MPB: muscular protein breakdown, MPS: muscular protein synthesis.

1. Granic A, et al. Hallmarks of ageing in human skeletal muscle and implications for understanding the pathophysiology of sarcopenia in women and men. Clin Sci (Lond). 2023 Nov 29;137(22):1721-1751.

2. McKendry J, et al. Mitigating disuse-induced skeletal muscle atrophy in ageing: Resistance exercise as a critical countermeasure. Exp Physiol. 2024 Oct;109(10):1650-1662.



MOLECULAR MECHANISMS BEHIND IMPAIRED PROTEIN SYNTHESIS

[2.1. Effect of protein intake on muscle synthesis](#)

[2.2. Nutrient sensing](#)

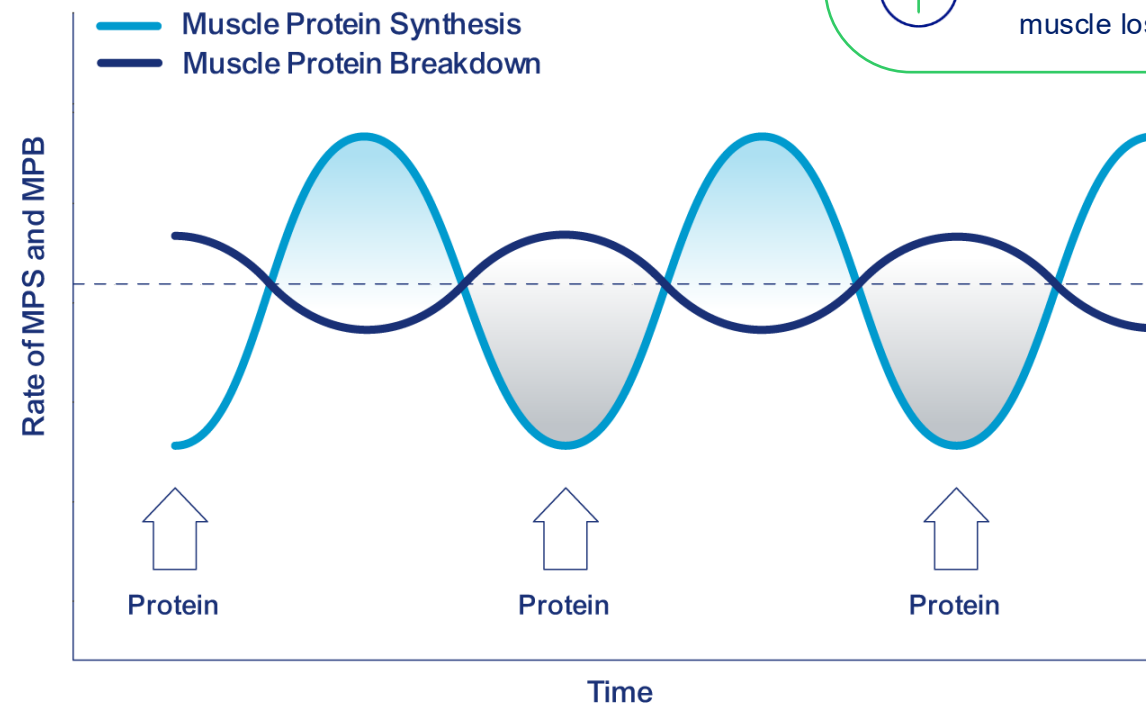
[2.3. Age-related dysregulation of autophagy pathways](#)

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MOLECULAR MECHANISMS BEHIND IMPAIRED PROTEIN SYNTHESIS

Effect of protein intake on muscle synthesis

- Protein intake triggers muscular protein synthesis.¹
- Nutrients availability are sensed by **mTOR** (mammalian Target Of Rapamycin).²
- Amino acids increase MPS via mTOR pathway activation.³
- Aging results in a diminished anabolic response to protein intake and aminoacidemia.¹



Schematic representation of muscle protein metabolism in response to protein intake. Based on information from ¹

1. Breen L et al. Skeletal muscle protein metabolism in the elderly: Interventions to counteract the "anabolic resistance" of ageing. *Nutr Metab (Lond)*. 2011;8(1):68.
 2. Dibble CC, et al. Signal integration by mTORC1 coordinates nutrient input with biosynthetic output. *Nat Cell Biol*. 2013 Jun;15(6):555-64.
 3. Torre-Villalvazo I, et al. Protein intake and amino acid supplementation regulate exercise recovery and performance through the modulation of mTOR, AMPK, FGF21, and immunity. *Nutr Res*. 2019 Dec;72:1-17.

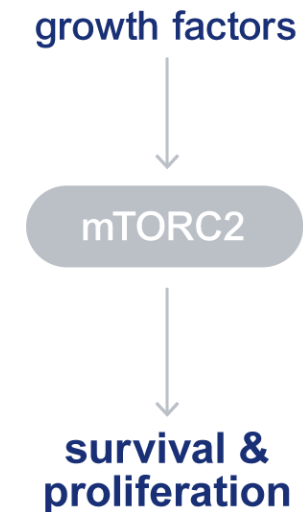
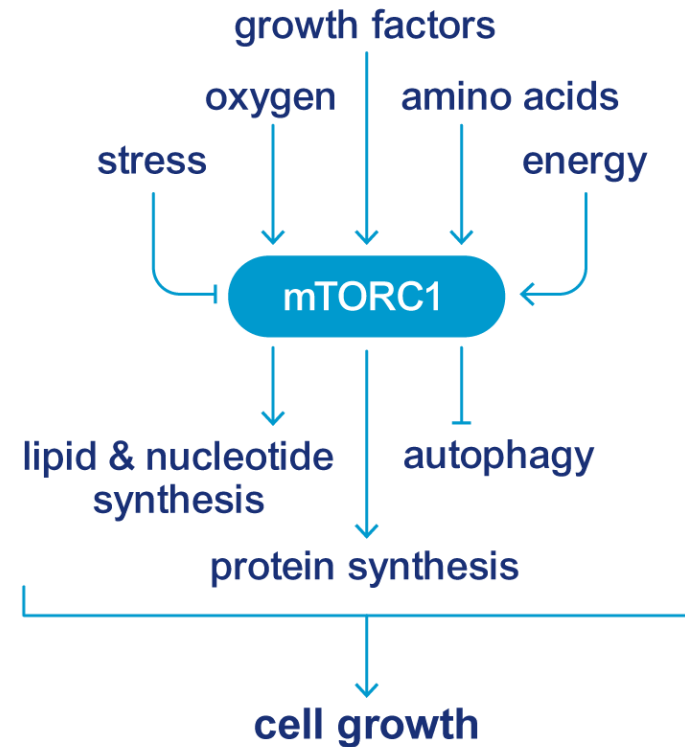


MOLECULAR MECHANISMS BEHIND IMPAIRED PROTEIN SYNTHESIS

Nutrient sensing (1/2)

mTOR can function in two different protein complexes: mTORC1 and mTORC2.^{1,2}

mTORC1 and mTORC2 integrate signals from nutrient availability, growth factors and environmental conditions to balance anabolic and catabolic processes.¹⁻³



Schematic mTORC1 and mTORC2 signaling pathways. Based on information from ¹



1. Saxton RA, et al. mTOR Signaling in Growth, Metabolism, and Disease. Cell. 2017 Apr 6;169(2):361-371.
 2. Goul C, et al. The molecular basis of nutrient sensing and signalling by mTORC1 in metabolism regulation and disease. Nat Rev Mol Cell Biol. 2023 Dec;24(12):857-875.
 3. Bodine SC. The role of mTORC1 in the regulation of skeletal muscle mass. Fac Rev. 2022 Nov 11;11:32.

Nutrient sensing (2/2)



mTORC1 is **over activated** in aging human skeletal muscle cells.¹⁻³

However, hyperphosphorylation of mTOR does not result in an increased protein synthesis.^{2,3}

There are many unanswered questions regarding mTORC1 and proteins synthesis in aged cells:

- What drives persistent mTORC1 activation?
- Why doesn't chronic activation of mTORC1 increase muscle protein synthesis?
- ...



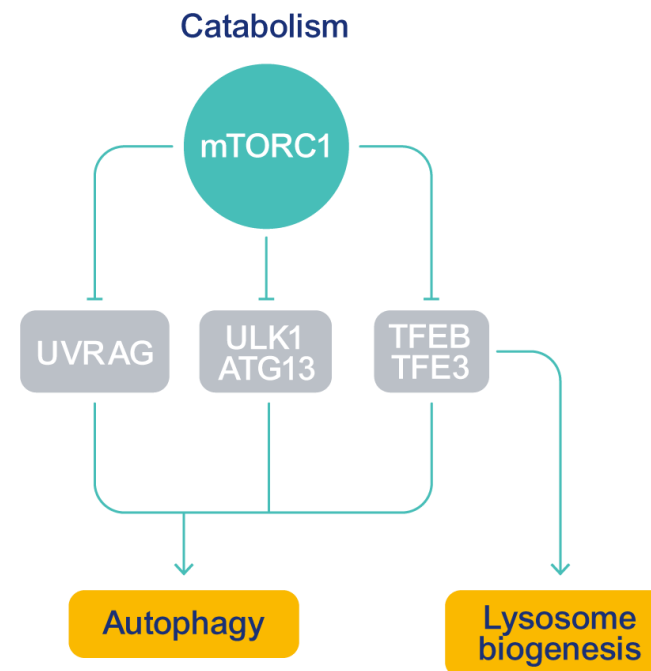
Age-related dysregulation of autophagy pathways (1/2)

Overactivation of mTORC1 suppresses **autophagy**, which is a vital **cleanup process** that recycle aberrant proteins and organelles.¹

Aging is accompanied by chronic, **low-grade inflammation** (“inflammaging”) and elevated **oxidative stress**,² which can **activate mTORC1** signaling.^{3,4} This may further inhibit the autophagic process.

Sustained inhibition of autophagy contributes to:

- Increased dysfunctional mitochondrial content.⁵
- Insulin resistance.⁶



mTORC1 catabolic signaling. mTORC1 represses catabolic routes. Based on information from ⁷

1. Mizushima N, et al. Autophagy: renovation of cells and tissues. Cell. 2011 Nov 11;147(4):728-41.
 2. Liguori I, et al. Oxidative stress, aging, and diseases. Clin Interv Aging. 2018 Apr 26;13:757-772.
 3. Li M, et al. Multi-mechanisms are involved in reactive oxygen species regulation of mTORC1 signaling. Cell Signal. 2010 Oct;22(10):1469-76.
 4. Lee DF, et al. IKK beta suppression of TSC1 links inflammation and tumor angiogenesis via the mTOR pathway. Cell. 2007 Aug 10;130(3):440-55.

5. Tang H, et al. mTORC1 underlies age-related muscle fiber damage and loss by inducing oxidative stress and catabolism. Aging Cell. 2019 Jun;18(3):e12943.
 6. Kitada M, et al. Autophagy in metabolic disease and ageing. Nat Rev Endocrinol. 2021 Nov;17(11):647-661.
 7. Liu GY, et al. mTOR at the nexus of nutrition, growth, ageing and disease. Nat Rev Mol Cell Biol. 2020 Apr;21(4):183-203.

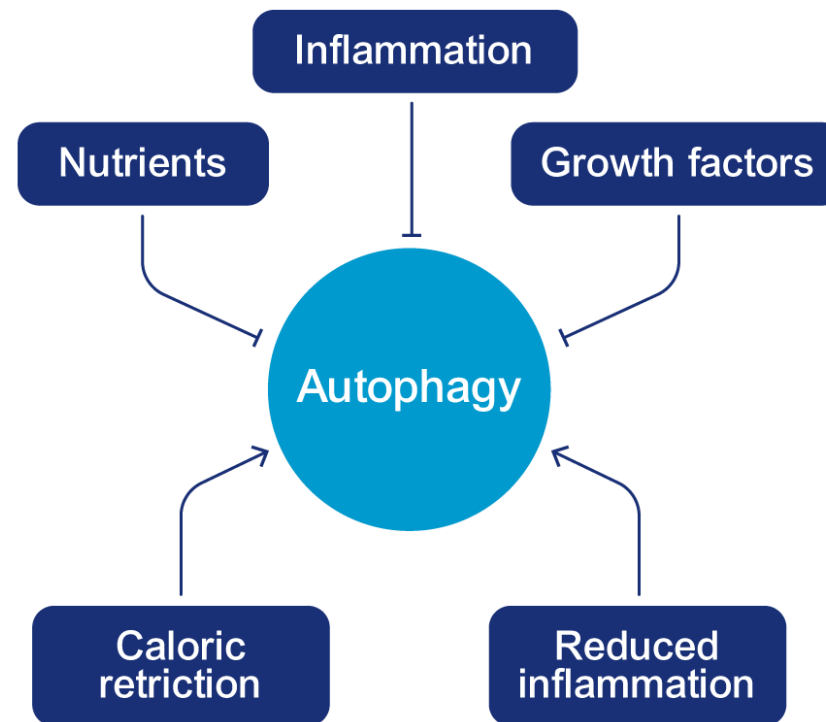


Age-related dysregulation of autophagy pathways (2/2)

Autophagy can be positively influenced by interventions such as caloric restriction and inflammation control.

Caloric restriction increases autophagy. It is achieved by directly activating ULK (key for autophagy initiation), and by inhibiting mTORC1 signaling.¹

Anti inflammatory strategies such as treatment with NSAID leads to increased autophagy.²



Summary

- ✓ **Protein**, mostly **leucine**, intake triggers **muscular protein synthesis**.
- ✓ **Aging**, as well as **nutrient deprivation** result in muscle **atrophy**.
- ✓ In aging muscle, nutrient sensing becomes impaired, further promoting muscle loss.
- ✓ The **mTORC1** protein complex integrates multiple signals to **regulate protein synthesis** and cellular growth.
- ✓ Available amino acids activate mTORC1.
- ✓ mTORC1 inhibits autophagy, a key process for recycling damaged organelles and misfolded proteins.
- ✓ The **mTORC1** signaling pathway is complex and both **chronic activation** and **prolonged inhibition** can lead to **muscle atrophy**.





MOLECULAR PATHWAYS LINKING INFLAMMATION TO MUSCLE LOSS

[3.1. Impact of inflammation on muscle synthesis](#)

[3.2. Inflammation and increase in muscle degradation](#)

[3.3. Summary](#)



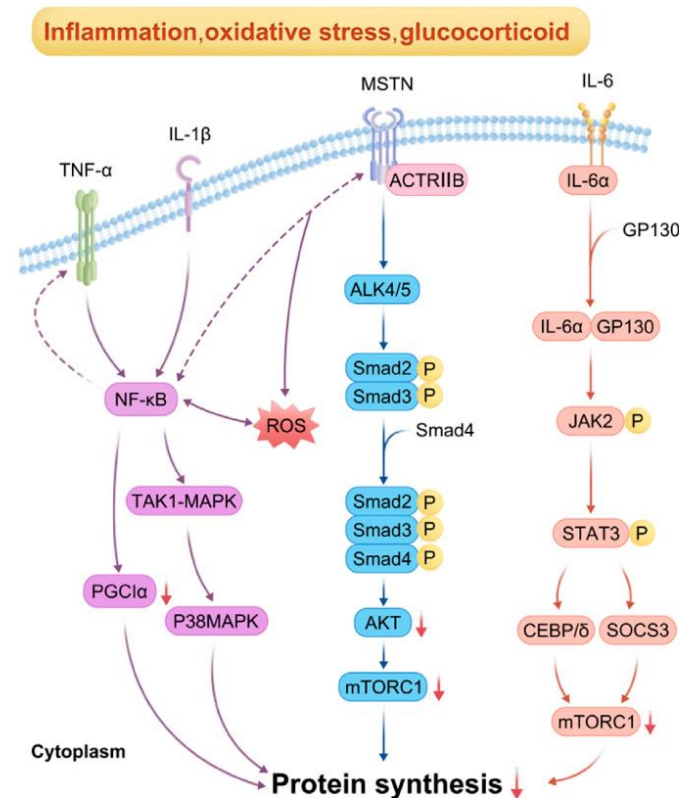
MOLECULAR PATHWAYS LINKING INFLAMMATION TO MUSCLE LOSS

Impact of inflammation on muscle synthesis

Inflammation impairs **muscle protein synthesis**, particularly post-meal anabolic responses by increasing $\text{TNF-}\alpha$.¹

The proinflammatory cytokines, particularly interfere with mTORC1 activation through various pathways.²

- $\text{TNF-}\alpha$ and IL-1 activate **NF- κB** which:
 - signals to reduce protein synthesis
 - activates expression of MSTN
- **MSTN** signals to **reduce mTORC1 activity** and activates the NF- κB pathway.
- IL-6 reduces mTORC1 activity.



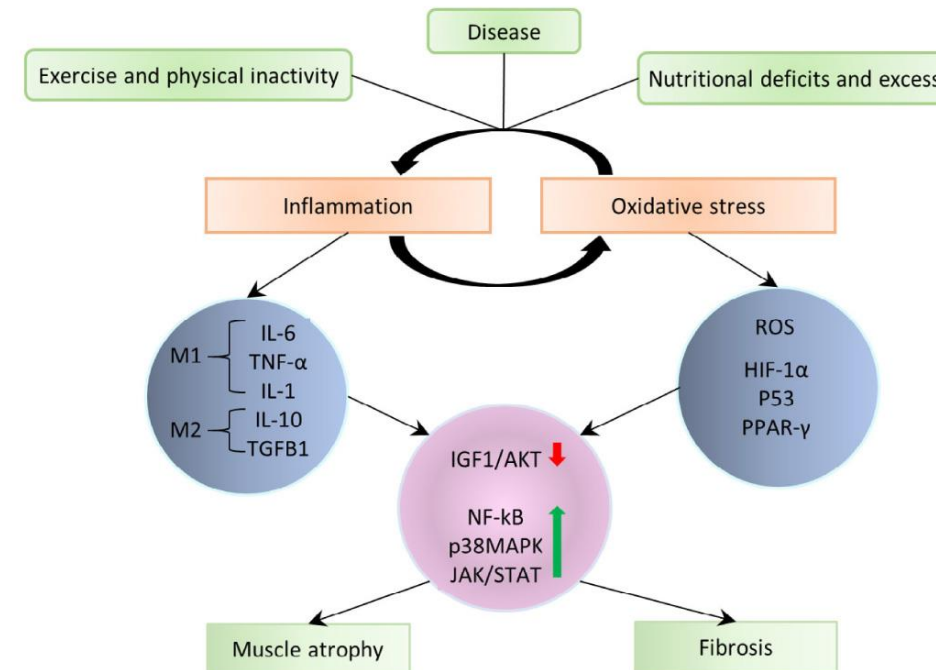
Mechanisms linking inflammatory pathways to reduced protein synthesis.²

1. Draganidis D, et al. Inflammaging and Skeletal Muscle: Can Protein Intake Make a Difference? J Nutr. 2016 Oct;146(10):1940-1952.
 2. Chen P, et al. Analysis of the mechanism of skeletal muscle atrophy from the pathway of decreased protein synthesis. Front Physiol. 2025 Apr 25;16:1533394.

MOLECULAR PATHWAYS LINKING INFLAMMATION TO MUSCLE LOSS

Inflammation and increase in muscle degradation

- In chronic inflammation, proinflammatory cytokines activate the **NF-κB** signaling pathway.¹⁻³
- Similarly, oxidative stress leads to increased production of reactive oxygen species (ROS) and subsequently, activation of **NF-κB** as well as inhibition of the **AKT/mTOR** pathway.^{4,5}
- **NF-κB** activation turns on the **ubiquitin-proteasome system** which in excess leads to muscle protein breakdown.^{1,2}
- Inhibition of **mTOR** pathway decreases protein synthesis and promotes autophagy.⁶



Inflammation and oxidative stress in muscle damage.⁴

1. Draganidis D, et al. Inflammaging and Skeletal Muscle: Can Protein Intake Make a Difference? J Nutr. 2016 Oct;146(10):1940-1952.
 2. Granic A, et al. Hallmarks of ageing in human skeletal muscle and implications for understanding the pathophysiology of sarcopenia in women and men. Clin Sci (Lond). 2023 Nov 29;137(22):1721-1751.
 3. Mourkioti F, et al. NF-κB signaling in skeletal muscle: Prospects for intervention in muscle diseases. Journal of Molecular Medicine, 2008 86(7), 747-759

4. Mukund K, et al. Skeletal muscle: A review of molecular structure and function, in health and disease. Wiley Interdiscip Rev Syst Biol Med. 2020 Jan;12(1):e1462.
 5. Powers SK, et al. Oxidative stress and disuse muscle atrophy: cause or consequence? Curr Opin Clin Nutr Metab Care. 2012 May;15(3):240-5.
 6. Zhao Y, et al. ROS signaling under metabolic stress: cross-talk between AMPK and AKT pathway. Mol Cancer. 2017 Apr 13;16(1):79

MOLECULAR PATHWAYS LINKING INFLAMMATION TO MUSCLE LOSS

Summary

- ✓ Inflammation is not just a consequence but a **central driver** of age-related muscle degeneration.
- ✓ Proinflammatory cytokines interfere with mTORC1 activation through multiple signaling pathways.
- ✓ Inflammation suppresses muscle protein synthesis, leading to increased muscle loss.
- ✓ In chronic inflammation, **NF-κB activation** triggers the **ubiquitin-proteasome system**, accelerating proteolysis and muscle wasting.
- ✓ NF-κB stimulates MSTN expression which further blocks mTORC1 signaling.





ECM DYSFUNCTION

[4.1. The muscular extracellular matrix](#)

[4.2. The role of ECM on muscle regeneration](#)

[4.3. The effect of age on muscular extracellular matrix dysfunction](#)

[4.4. Summary](#)

ECM DYSFUNCTION

The muscular extracellular matrix

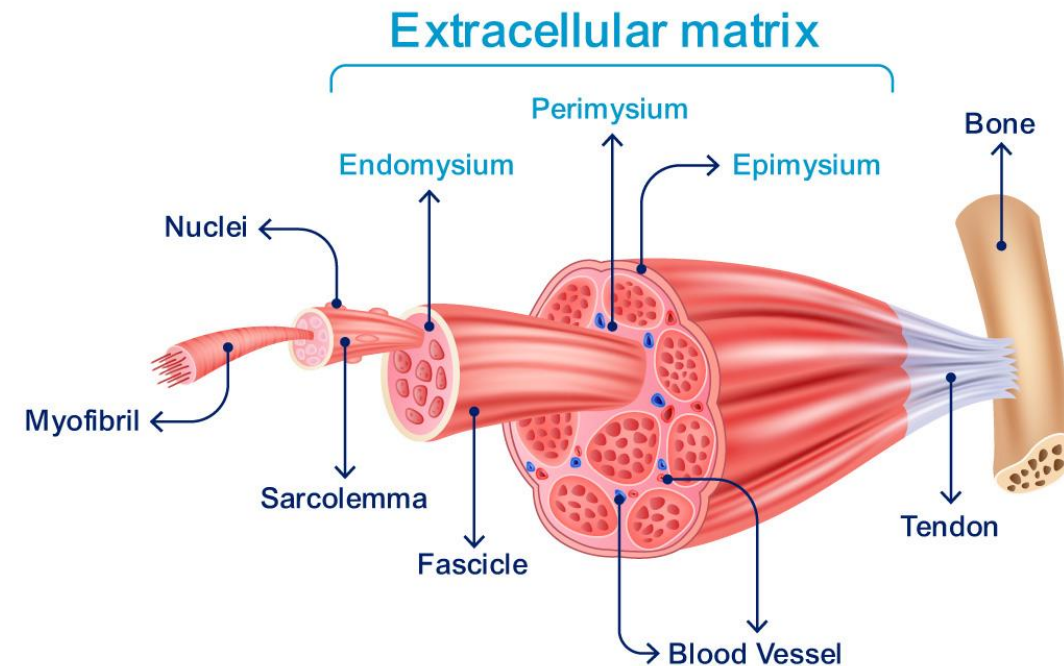
The muscular **extracellular matrix (ECM)** is the **scaffold** structure that holds together the muscle's myofibers, blood vessels and nerves.¹

COMPOSITION¹

- Collagenous glycoproteins
- Non-collagenous glycoproteins
- Proteoglycans
- Glycosaminoglycans

FUNCTIONS^{1,2}

- Force transmission
- Initiator of signaling pathways
- Maintenance and repair of muscle fibers following injury



Schematic representation of the ECM disposition in skeletal muscle.³

1. Mahdy MAA. Skeletal muscle fibrosis: an overview. Cell Tissue Res. 2019 Mar;375(3):575-588.

2. Kragstrup TW, et al. Structural, biochemical, cellular, and functional changes in skeletal muscle extracellular matrix with aging. Scand J Med Sci Sports. 2011 Dec;21(6):749-57.

3. Gotti, et al. Hierarchical fibrous structures for muscle-inspired soft-actuators: A review. Applied Materials Today. 2020;20:100772.

ECM DYSFUNCTION

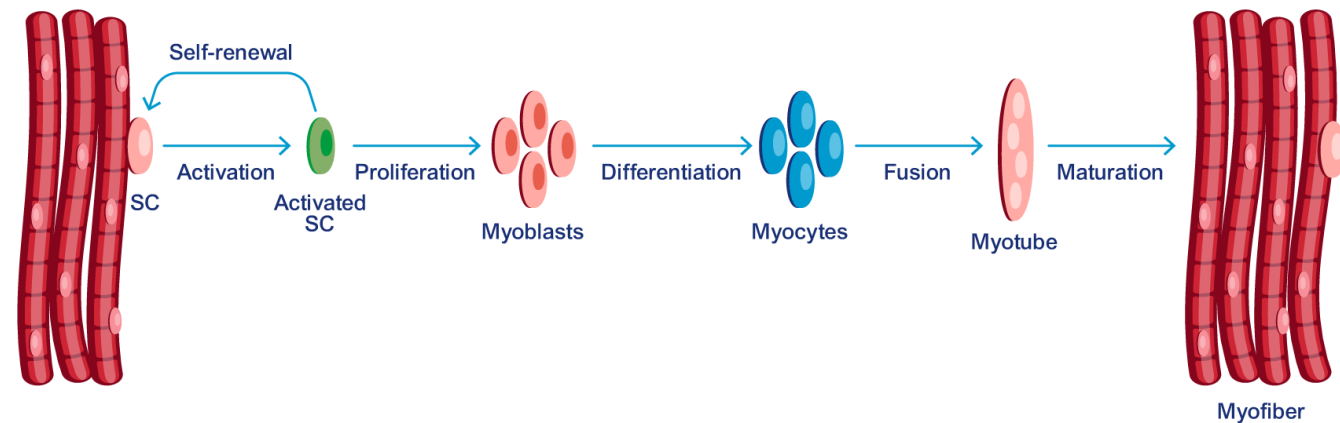
The role of ECM on muscle regeneration

The ECM plays a key role in muscle repair.¹

After injury, the **ECM undergoes remodeling** which result in a temporary ECM that creates an optimal microenvironment for satellite cells differentiation.^{1,2}

The ECM regulates signal transduction, influencing, various cell types, including satellite cells.³

Satellite cells (muscle stem cells) reside within the ECM and are activated by different stimuli: mechanical stress, oxidative stress, endocrine factors and inflammatory factors.⁴



Schematic illustration of satellite cell-mediated muscle regeneration. Satellite cells once activated undergo proliferation. A subset of cells self-renew to restore the satellite-cell pool, while others commit and differentiate to myofibers. MPC: myogenic precursor cells, SC: satellite cell. Based on information from⁴

1. Mahdy MAA. Skeletal muscle fibrosis: an overview. Cell Tissue Res. 2019 Mar;375(3):575-588.
 2. Mann CJ, et al. Aberrant repair and fibrosis development in skeletal muscle. Skelet Muscle. 2011 May 4;1(1):21.
 3. Kragstrup TW, et al. Structural, biochemical, cellular, and functional changes in skeletal muscle extracellular matrix with aging. Scand J Med Sci Sports. 2011 Dec;21(6):749-57.
 4. Tidball JG. Regulation of muscle growth and regeneration by the immune system. Nat Rev Immunol. 2017 Mar;17(3):165-178.

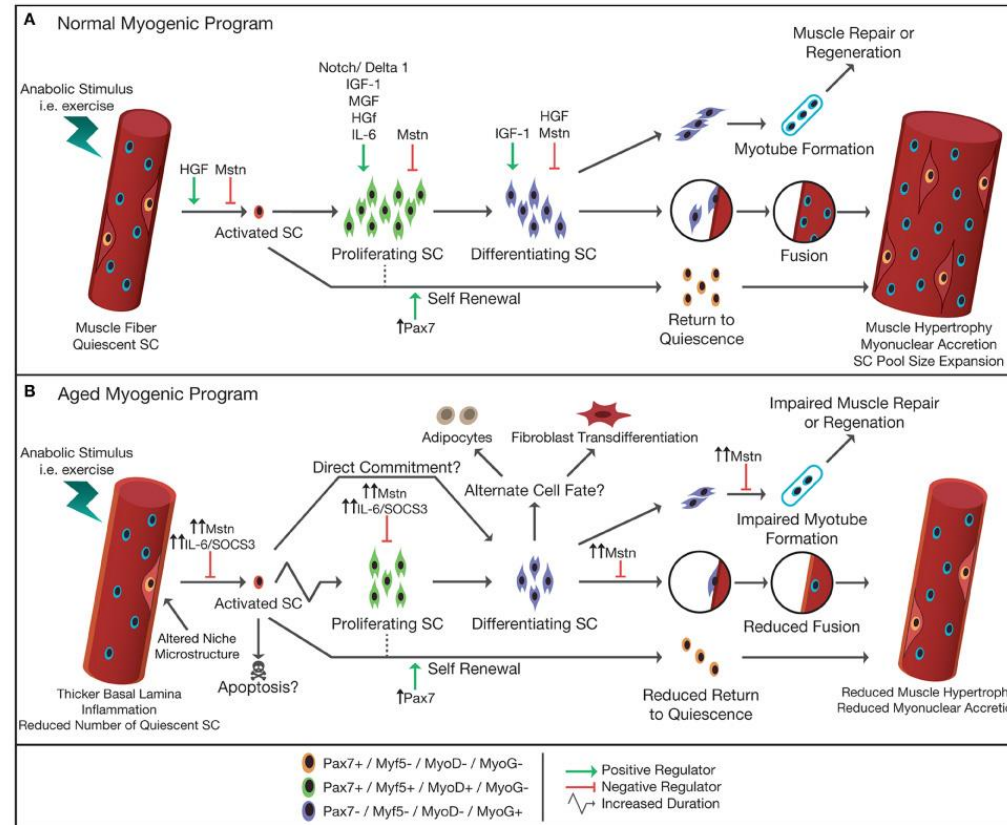
ECM DYSFUNCTION

The effect of age on muscular extracellular matrix dysfunction

Aging alters the skeletal muscle extracellular matrix (ECM) by:

- **Increasing collagen content**,¹
- **Enhancing collagen cross-linking** causing stiffness,¹
- **Reducing the number of satellite cell**,¹⁻²
- Increasing levels of **myostatin** and **pro-inflammatory cytokines** that affect satellite cells function and impair muscle regeneration.²

Structural and cellular changes in the ECM impair muscle regeneration reducing muscle function and mobility in older adults.¹



Normal vs. aged muscle regeneration after anabolic stimulus. In adult muscle, satellite cells remain dormant until stimulated by exercise, then proliferate to support repair or return to rest. In aged muscle, reduced satellite cell numbers, disrupted niches, and elevated inflammation and myostatin impair their activation and fusion, limiting muscle repair and growth.²

1. Kragstrup TW, et al. Structural, biochemical, cellular, and functional changes in skeletal muscle extracellular matrix with aging. Scand J Med Sci Sports. 2011 Dec;21(6):749-57.
2. Snijders T, et al. Satellite cells in human skeletal muscle plasticity. Front Physiol. 2015 Oct 21;6:283.

Summary

- ✓ The extracellular matrix (ECM) has a key role in muscle repair.
- ✓ The ECM provides **structural support** and **regulates** muscle **function**.
- ✓ ECM remodels after injury, creating a microenvironment that promotes satellite cell activation and differentiation.
- ✓ **Satellite cells** (muscle stem cells) enable **muscle regeneration**.
- ✓ The aging process is associated with a **decline in satellite cell** number and function.
- ✓ Aging stiffens the muscle extracellular matrix, reducing repair capacity and force transmission.





MOTOR UNIT DYSFUNCTION

[5.1. The effect of age on motor unit number](#)

[5.2. MU remodeling](#)

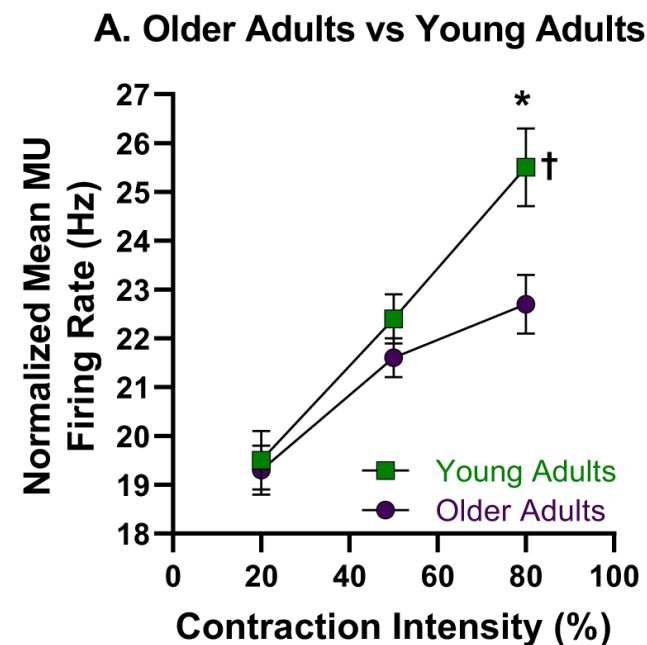
[5.3. Summary](#)

MOTOR UNIT DYSFUNCTION

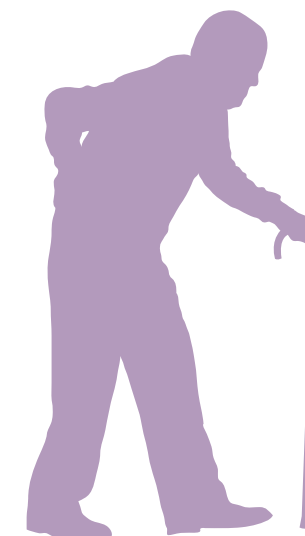
The effect of age on motor unit number

A **motor unit** (MU) consist of a motor neuron and the myofibers it innervates (8 to > 1000).¹

- Aging causes progressive **MUs loss**² and slower action potential.³
- By the age of 70, up to 40% of MUs in the limb muscles are lost.²
- MU loss and slower nerve signals³ cause **muscle shrinking, reduced strength**, and **poorer control of movement** in older adults.²



Differences on motor unit firing rate in young and older adults.³



1. Gustafsson T, et al. Aging Skeletal Muscles: What Are the Mechanisms of Age-Related Loss of Strength and Muscle Mass, and Can We Impede Its Development and Progression? Int J Mol Sci. 2024 Oct 11;25(20):10932.

2. Piasecki M, et al. Age-dependent motor unit remodelling in human limb muscles. Biogerontology. 2016 Jun;17(3):485-96.

3. Wages NP, et al. Reductions in Motor Unit Firing are Associated with Clinically Meaningful Leg Extensor Weakness in Older Adults. Calcif Tissue Int. 2024 Jan;114(1):9-23.

MOTOR UNIT DYSFUNCTION

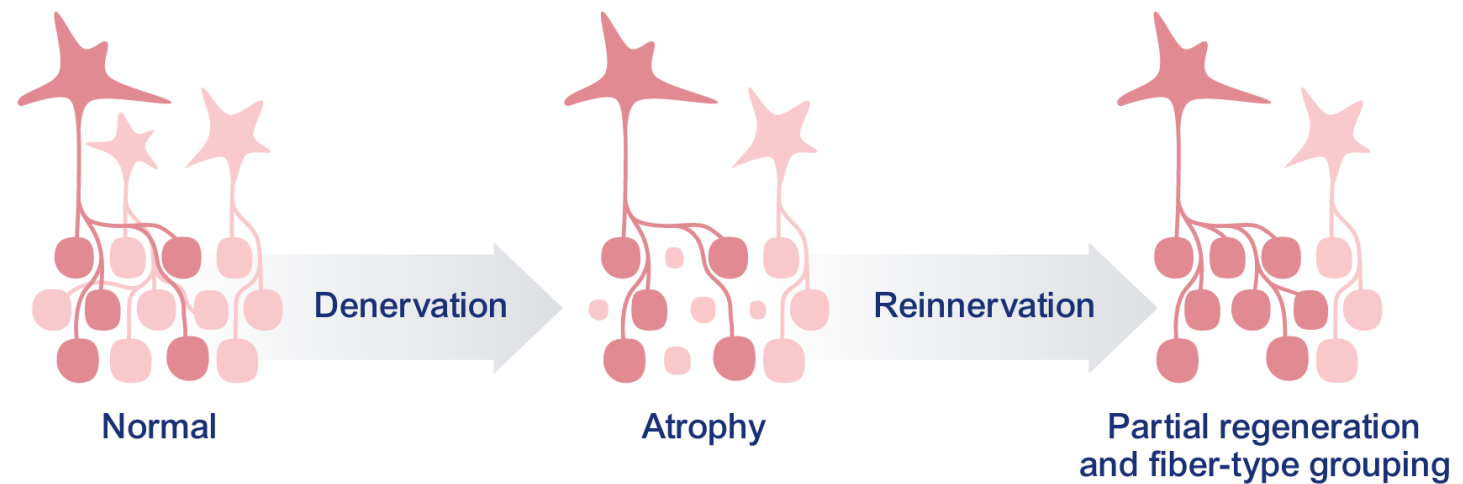
MU remodeling

Aging leads to the loss of MU.¹

Surviving motor neurons compensate by reinnervating denervated fibers, leading to enlarged motor units.¹

The capacity for reinnervation declines with age.¹

Remodeling is often incomplete and limited, contributing significantly to **muscle atrophy**, **reduced strength**, and **impaired motor control** in older adults.¹



Motor unit remodeling. Based on information from²

1. Piasecki M, et al. Failure to expand the motor unit size to compensate for declining motor unit numbers distinguishes sarcopenic from non-sarcopenic older men. J Physiol. 2018 May 1;596(9):1627-1637.
 2. Kirk B, et al. Motor Unit Remodeling. Sarcopenia. 2021;35-43.

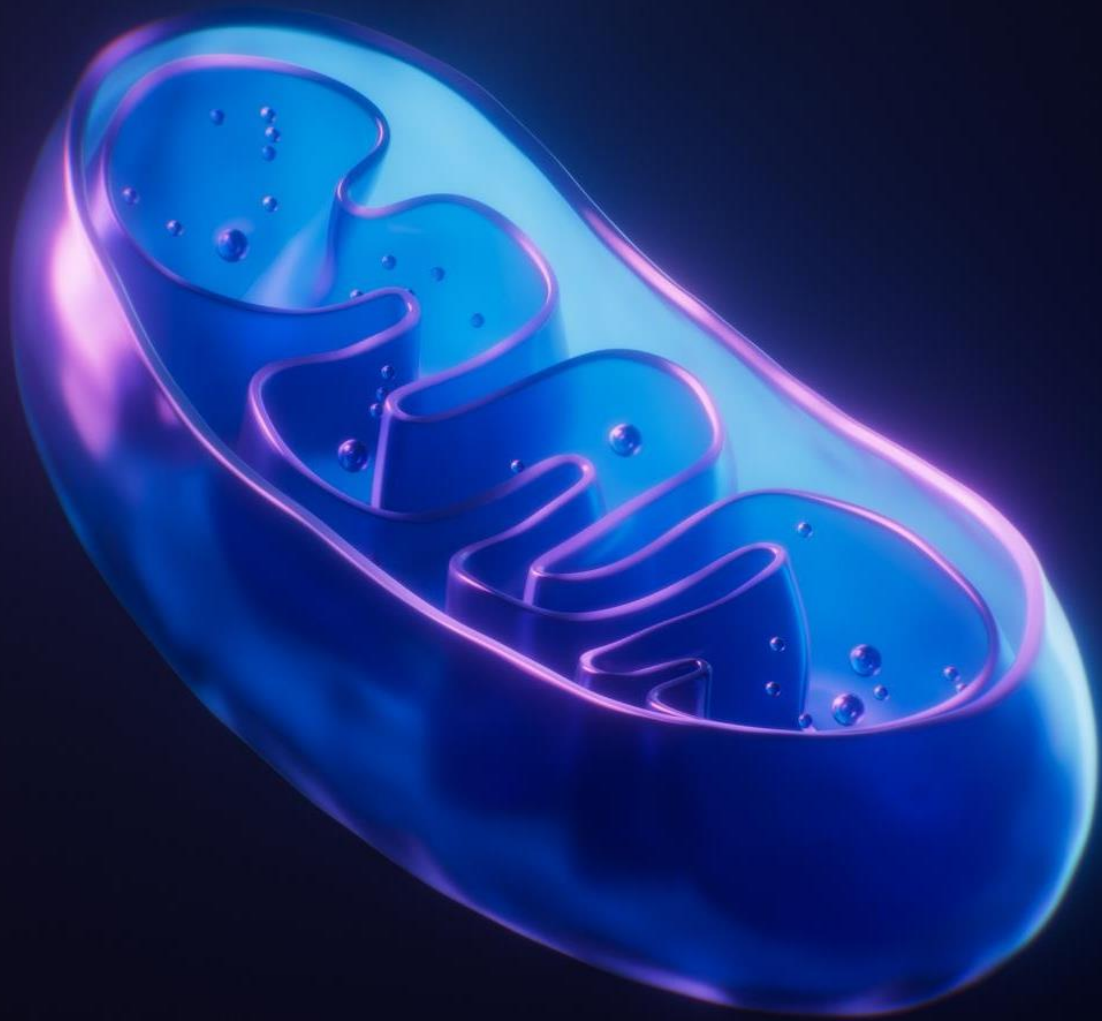


MOTOR UNIT DYSFUNCTION

Summary

- ✓ With aging, motor neurons are progressively lost, leading to muscle fiber denervation.
- ✓ Loss of motor units and slower nerve signals contribute to reduced strength and mobility.
- ✓ While some fibers are reinnervated, many are not—resulting in muscle atrophy, MU remodeling, and a decline in strength and function characteristic of sarcopenia.





MITOCHONDRIAL DYSFUNCTION

[6.1. How mitochondria support healthy skeletal muscle](#)

[6.2. Mitochondrial dysfunction in ageing](#)

[6.3. Mitochondrial dysfunction and muscle alteration](#)

[6.4. Summary](#)

MITOCHONDRIAL DYSFUNCTION

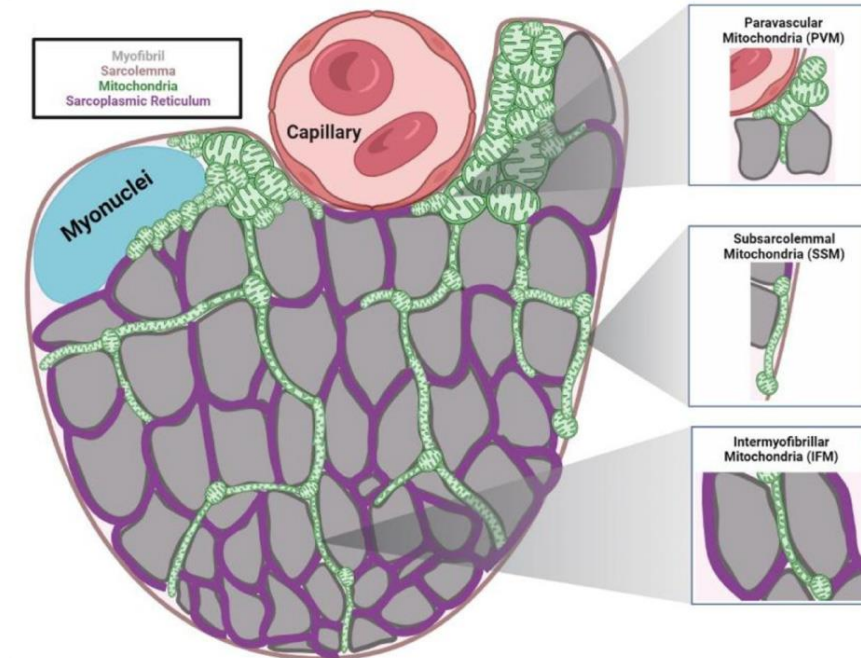
How mitochondria support healthy skeletal muscle (1/2)

Mitochondria are the 'powerhouse' of the cell, producing ATP required for cell metabolism by oxidative phosphorylation.¹

Mitochondria **regulate skeletal muscle metabolism**, and their structural and functional integrity is key to maintaining muscle health.²

Skeletal muscle fibers contain three distinct mitochondrial populations, each occupying a different subcellular location:³

- Paravascular mitochondria (PVM). Near capillaries. Larger and rounder. With greater electron transport chain activation, making them efficient in energy conversion
- Subsarcolemmal mitochondria (SSM). Beneath the cell membrane. Lower oxidative phosphorylation activation compared to PVM
- Intermyoibrillar mitochondria (IFM). Between myofibrils. Elongated. Specialized in fuel storage and Ca^{2+} regulation, but with the lowest oxidative phosphorylation activation of all three.



Location and shape differences between skeletal muscular mitochondria.³

1. Tilokani L, et al. Mitochondrial dynamics: overview of molecular mechanisms. Essays Biochem. 2018 Jul 20;62(3):341-360.

2. Chen X, et al. Mitochondrial dysfunction: roles in skeletal muscle atrophy. J Transl Med. 2023 Jul 26;21(1):503.

3. Parry HA, et al. Impact of capillary and sarcolemmal proximity on mitochondrial structure and energetic function in skeletal muscle. J Physiol. 2024 May;602(9):1967-1986.



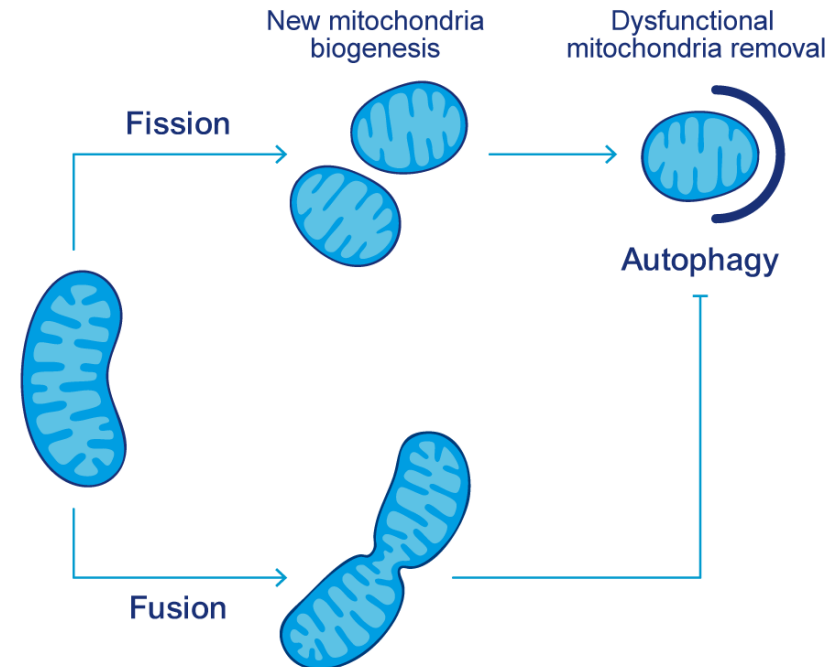
MITOCHONDRIAL DYSFUNCTION

How mitochondria support healthy skeletal muscle (2/2)

There are three important processes mitochondria undergo in order to maintain their optimal function:¹

1. Balanced fusion and fission regulate mitochondrial quality.
2. Biogenesis: Essential for maintaining mitochondrial quantity.
3. Mitophagy: Clearance of damaged mitochondria ensures mitochondrial health.

With ageing there is an imbalance in mitochondrial dynamics, which impairs their function contributing to muscle atrophy.¹



Mitochondrial dynamics. Based on information from ¹



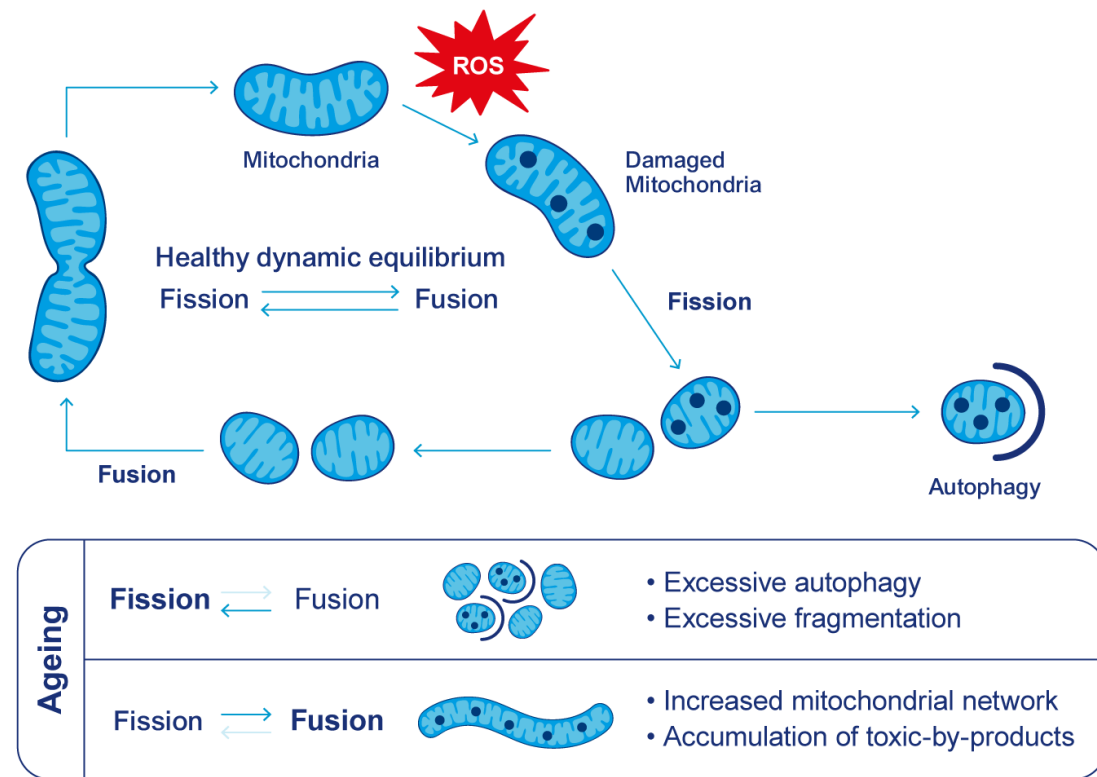
MITOCHONDRIAL DYSFUNCTION

Mitochondrial dysfunction in ageing

Mitochondrial dysfunction is a key driver of aging, and it is implicated in numerous age-related disorders.¹

Mitochondrial dysfunction in aging are caused by:

- Decline in mitochondrial proteolysis (accumulation of misfolded proteins)
- Disrupted mitochondrial dynamics (fusion and fission)
- Dysregulated mitochondrial unfolded protein response (UPR^{mt}) (refold misfolded and unfolded proteins)
- Unbalanced mitophagy



Disrupted mitochondrial dynamics in aging. Based on information from ¹

MITOCHONDRIAL DYSFUNCTION

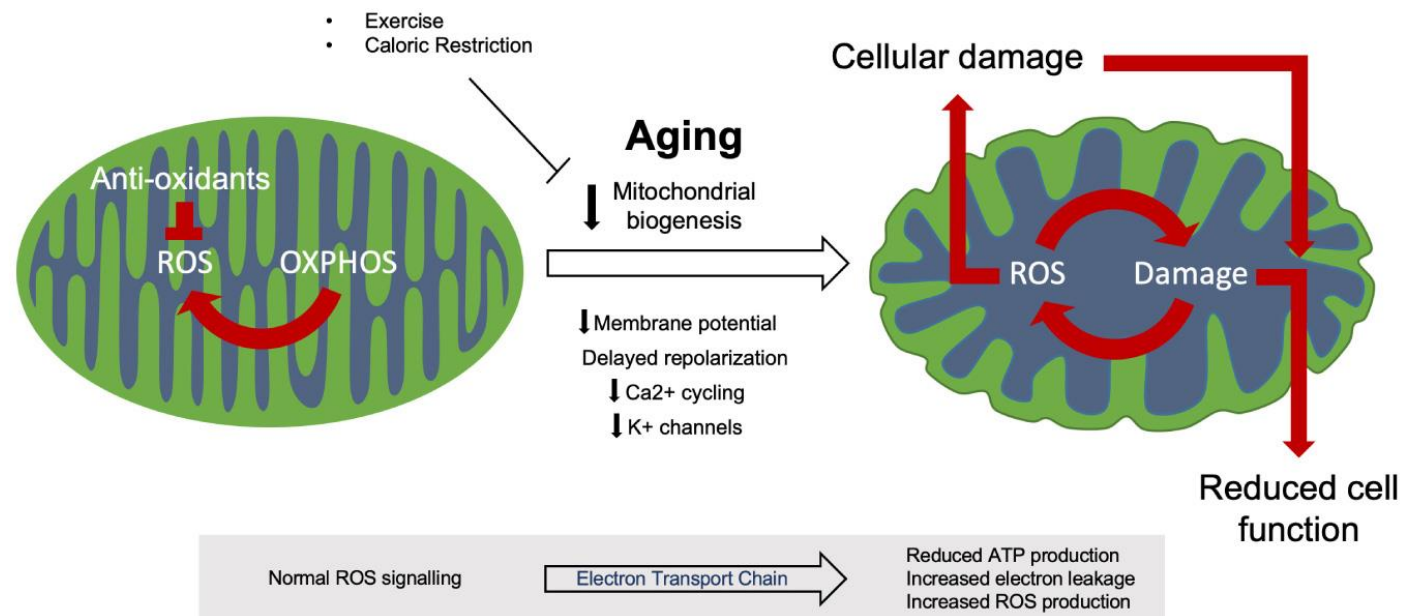
Mitochondrial dysfunction and muscle alteration

Sarcopenia

Sarcopenic patients have reduced mitochondrial oxidative capacity that leads to a higher production of ROS.¹

Aging²

- Reduction in mitochondrial biogenesis
- Reduction in mitochondrial quality
- Reduction in ATP production due to deficiencies in their electron transport chain
- Increased in ROS production



Mitochondrial impairment in a sarcopenic aged fiber muscle.²

1. Chen X, et al. Mitochondrial dysfunction: roles in skeletal muscle atrophy. J Transl Med. 2023 Jul 26;21(1):503.

2. Strickland M, et al. Relationships Between Ion Channels, Mitochondrial Functions and Inflammation in Human Aging. Front Physiol. 2019 Mar 1;10:158.

MITOCHONDRIAL DYSFUNCTION

Summary

- ✓ Mitochondria are the **power source of muscle cells**, producing the energy needed for strength and movement.
- ✓ **PVM have the highest oxidative phosphorylation activation**, while SSM function similarly to IFM, which have the lowest oxidative phosphorylation activation of all three.
- ✓ **Capillary proximity** influences mitochondrial structure and energy conversion, shaping their function within skeletal muscle.
- ✓ With aging and in sarcopenia, mitochondria become **less efficient** and their ability to produce energy declines, while harmful molecules like **ROS increase**.
- ✓ Mitochondrial dynamics imbalance leads to muscle weakness, damage, and contributes to the **progression of muscle loss**.





VASCULAR DYSFUNCTION AND MUSCLE LOSS

[7.1. Vascular perfusion of the muscle](#)

[7.2. Satellite cell-capillary relationship](#)

[7.3. The effect of age on capillarity structure](#)

[7.4. The effect of age on capillarity reduction](#)

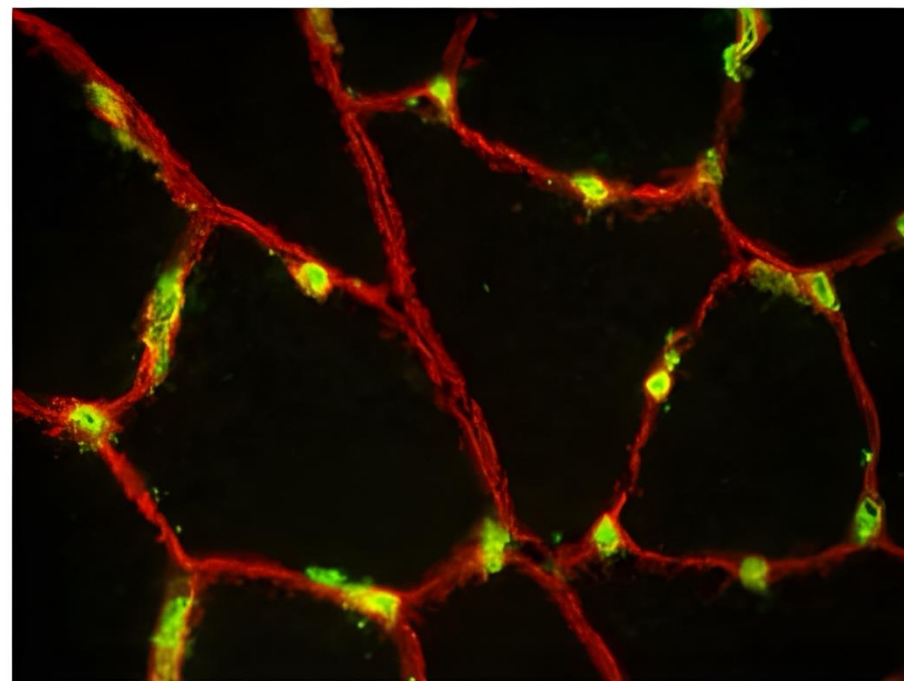
[7.5. Summary](#)

VASCULAR DYSFUNCTION AND MUSCLE LOSS

Vascular perfusion of the muscle

Proper muscle perfusion ensures the **delivery of nutrients, oxygen and hormones** to muscle fibers, while also facilitating the **removal of waste products**.^{1,2}

During skeletal muscle contraction capillary blood flow and O₂ flux may increase 100 times compared to resting levels.³



Cross-section of a muscle with embedded capillaries. Labeled with α -CD31.⁴



1. Moro T, et al. Low skeletal muscle capillarization limits muscle adaptation to resistance exercise training in older adults. *Exp Gerontol*. 2019 Nov;127:110723.
 2. Parise G, et al. Capillary facilitation of skeletal muscle function in health and disease. *Appl Physiol Nutr Metab*. 2020 May;45(5):453-462.
 3. Poole DC, et al. Skeletal muscle capillary function: contemporary observations and novel hypotheses. *Exp Physiol*. 2013 Dec;98(12):1645-58.
 4. Coudy-Gandilhon C, et al. A Single Bout of Ultra-Endurance Exercise Reveals Early Signs of Muscle Aging in Master Athletes. *Int J Mol Sci*. 2022 Mar 28;23(7):3713.

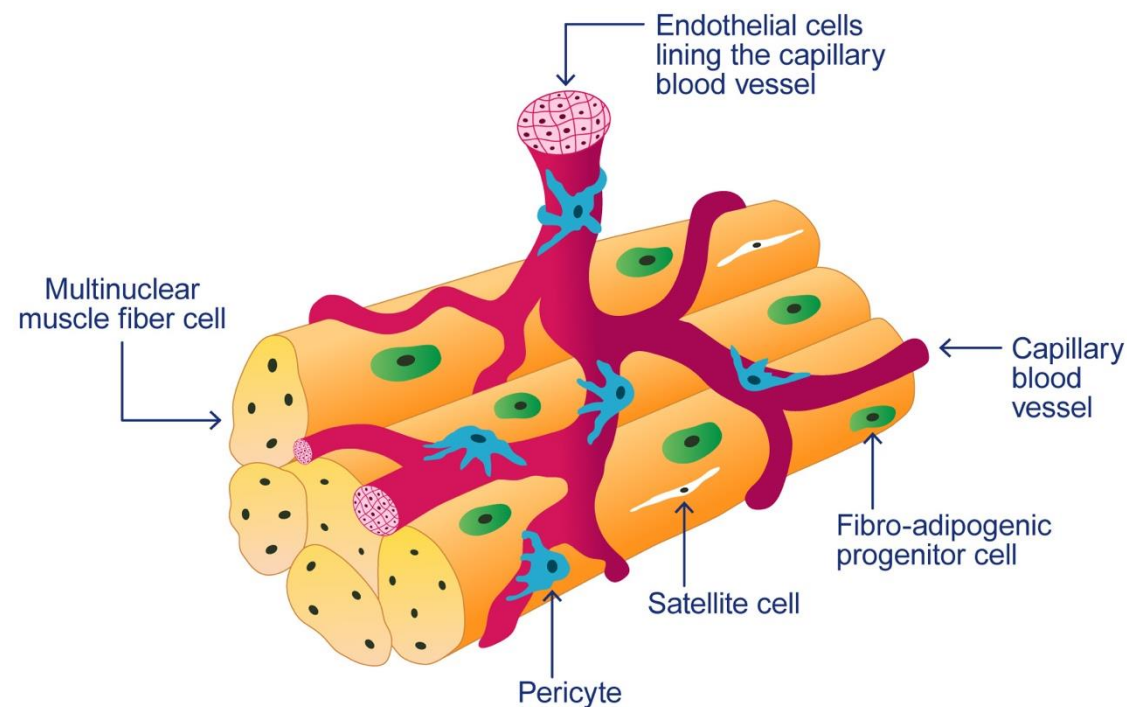
VASCULAR DYSFUNCTION AND MUSCLE LOSS

Satellite cell-capillary relationship

The microvascular system surrounding muscle fibers facilitates the distribution of signaling factors required for optimal satellite cell (SC) function in muscles.¹

Capillary proximity may regulate SC activation.

Activated SCs are positioned nearer to capillaries compared to their quiescent counterparts.¹



Fiber cell and associated capillaries.²



1. Parise G, et al. Capillary facilitation of skeletal muscle function in health and disease. Appl Physiol Nutr Metab. 2020 May;45(5):453-462.

2. Wikimedia. Multinuclear muscle fiber cells and some associated mononuclear cells. Available from: https://upload.wikimedia.org/wikipedia/commons/3/3c/Multinuclear_muscle_fiber_cells_and_some_associated_mononuclear_cells.jpg [Access 02-09-2025].

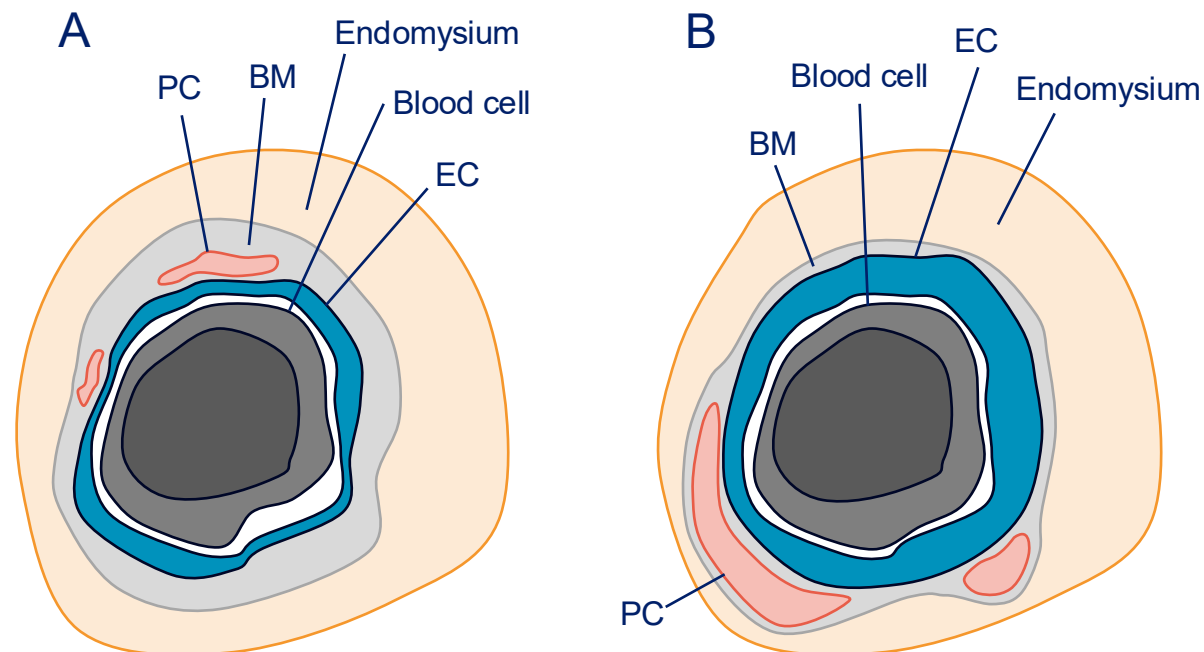
The effect of age on capillarity structure

Aging is associated with changes in the anatomical structure of capillaries:¹

- Increase in the basement membrane (BM) thickness
- Reduced pericyte (PC) and endothelial cell (EC) filipodia

Filopodia are involved in mechanical stabilization and communication between the ECs and PCs.

ECs and PCs interactions may regulate capillary function by modulating the luminal diameter in response to changes in blood flow.



Schematic illustration of the capillary structure within the muscle. A: old. B: young. BM: basal membrane, EC: endothelial cells, PC: pericyte. Based on information from ¹

The effect of age on capillarity reduction

Reduced capillarization in skeletal muscle contributes to muscle loss in older adults by limiting the delivery, oxygen, hormones, nutrients and other substrates.¹

The **distance** between SCs and capillaries is **greater** in older adults than in younger adults.² This might impair regulation of SCs thus negatively impacting muscle regeneration.

DID YOU KNOW?

Older adults with sarcopenia compared to their non sarcopenic counterparts have:

- 20% lower capillary-to-fiber ratio
- ~ 13%-15% lower VO_{2max}



1. Prior SJ, et al. Sarcopenia Is Associated With Lower Skeletal Muscle Capillarization and Exercise Capacity in Older Adults. J Gerontol A Biol Sci Med Sci. 2016 Aug;71(8):1096-101.
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Summary

- ✓ Muscular perfusion ensures delivery of oxygen, nutrients, and hormones, and remove waste.
- ✓ Capillary blood flow increases up to 100-fold during contraction.
- ✓ **Capillary proximity supports satellite cell (SC)** activation and function.
- ✓ Activated SCs are closer to capillaries than quiescent ones.
- ✓ **Aging reduces capillarization** and **alters capillary structure** which impacts muscle function.
- ✓ Greater SC–capillary distance in older adults may impair muscle regeneration.





CONCLUSIONS

CONCLUSIONS



- ✓ In aging muscle, **nutrient sensing** via mTOR becomes **impaired**.
- ✓ In aging skeletal muscle cells, **mTORC1** is **chronically overactivated**, leading to **suppressed autophagy**. However, this persistent activation does not translate into increased muscle protein synthesis.
- ✓ Aging **stiffens the muscle extracellular matrix**, reducing repair capacity and force transmission.
- ✓ **Satellite cell** number and function **decrease** with age, limiting regenerative capacity.
- ✓ With aging, motor neurons are progressively lost, leading to **muscle fiber denervation**.
- ✓ Older adults lose more muscle during inactivity and require longer to recover.
- ✓ Aging involves **mitochondrial dysfunction** and increase oxidative stress (ROS).
- ✓ Inflammaging suppresses muscle protein synthesis and increases muscle protein breakdown.
- ✓ Aging reduces capillarization and alters capillary structure which impacts muscle function.

This training material has been reviewed for scientific accuracy and relevance by Stuart Phillips – McMaster Experts. It is intended for educational purposes only and does not replace clinical judgment or institutional guidelines.



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Thank you!

