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Overlapping pathophysiological pathways between sarcopenia and chronic diseases

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Abstract

Sarcopenia and frailty are two geriatric syndromes that cause loss of muscle mass and function in addition to other various impairments. Sarcopenia is a specific phenotype of frailty where low grip strength, slow walking, and reduced muscle mass are observed. Since modern communities are aging more than ever, geriatric syndromes have become more prevalent and are linked to morbidity and disabilities. Several mechanisms are involved in the pathophysiology of sarcopenia, such as autophagy, protein synthesis and degradation, satellite cell activation damages, mitochondrial dysfunction, increased intracellular oxidative stress, and other factors like malnutrition, physical inactivity, and systemic inflammation that contribute to muscle weakness and degeneration. Modulating factors such as exosomes and transporters that can govern muscle loss and regeneration are involved in this pathogenetic pathway. The significance of these compounds is not theoretical since they provide a useful diagnostic tool as well as a potential treatment target. Thereby, the study of exosomes can explain the complex and intricate process of geriatric syndrome as an increasingly frequent complication of various diseases in the elderly. Therefore, this study explores the overlapping pathophysiological pathways between chronic diseases and sarcopenia by reviewing the current conception of exosome production and exosomal cargo in chronic diseases.

1. Introduction

Approximately 25% of the population will be older than 60 in 2050, and this demographic transition will lead to an increase in age-related diseases [1][2]. Besides the major chronic conditions (CCs) common in the elderly, such as cardiovascular disease, diabetes, strokes, cancer, chronic obstructive airway disease, musculoskeletal conditions, and dementia, geriatric syndromes (GS) should be considered since they accompany many of these medical conditions [3].

Frailty and sarcopenia are included in the category of GS. While frailty is defined as a considerable reduction in the performance of numerous organ systems, resulting in the individual's excessive sensitivity to endogenous and external stresses, sarcopenia is a subset of frailty characterized by progressive and extensive skeletal muscle impairments. Both situations increase the likelihood of faster functional decline and negative health consequences [4].

The incidence of GS can occur before or simultaneously with the clinical onset of the CC. However, there is the possibility that GSs can manifest themselves in the pathogenetic pathways of CCs as a related factor, especially in systemic diseases such as neurological, neoplastic, organ failure, arteriosclerosis, and diabetes [5]. Therefore, their presence determines a worsening of the health-related quality of life and clinical management of old patients [6]. Considering GSs as an inducing/worsening factor, their appearance can be linked to a pathophysiological mechanism shared with CCs.

In relation to the more prevalent CCs in the elderly, it was claimed that eliminating exposure to 12 recognized risk factors might postpone or even prevent up to 40% of CCs occurrences. Smoking, hearing issues, elevated blood pressure, diabetes, overweight, depression, lack of physical activity, social isolation, heavy drinking, brain injury, and

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air pollution are among these risk factors [7]. Thus, physical inactivity represents a fil rouge between CCs and GSs and can facilitate the development or worsen of the pathological state.

Various factors are considered when evaluating for frailty phenotype construct. These factors are weakness (assessed by the strength of the handgrip), sluggishness (assessed by movement speed), reduced physical activity, unintentional weight loss, and self-reported weariness [8][9]. The overlap between frailty and sarcopenia creates further uncertainties when analyzing patients who also manifest cachexia or malnutrition since all these cases appear to occur concurrently [10]. This overlapping complicates the understanding of the physiopathological pathway between GSs and CCs when simultaneously present. In particular, when there is a high overlap of diagnosis, it is necessary to focus on the patients, thus allowing to catch nuances that are more objective than subjective evaluations.

Recent statistics show increasing overlaps between GSs and CCs [11]. Furthermore, these numbers are expected to increase dramatically in the following 20-30 years [12]. Therefore, this article aims to analyze the current conception of physiopathological pathways between CCs and the appearance of sarcopenia.

2. Dementia and sarcopenia

The cognitive frailty (CF) was operationally defined when mild cognitive impairment (MCI) and physical frailty occur in the absence of dementia [13]. Despite having a possibly reversible loss in cognitive reserve, people with CF have a greater chance of acquiring dementia [14]. This places CF in between age-related cognitive impairments and neurodegenerative disorders [15].

An increased risk of frailty-malnutrition is observed in depressed patients as a consequence of dementia, and a high prevalence of sarcopenia can also be observed as the disease progresses [16]. Furthermore, an accelerated impairment of cognitive changes (a decline in memory, logic, social interaction, decision-making, and language-related abilities) is observed in the sarcopenia progression [17].

In dementia physiopathogenesis, neuroinflammation in response to pathogens or a number of pathophysiological processes (including excitotoxicity, mitochondrial dysfunction, and oxidative stress) results in stress or damage to neural, glial, and vascular endothelial cells. These stresses and injuries constitute the first occurrence of vascular dementia [18][19]. The cascade involvement of all these components leads to neuronal death, followed by the release of mitochondrial DNA (mtDNA) from the cells by extracellular vesicles (EVs). The circulating cell-free mtDNA molecules serve as damage-related molecular patterns (DAMPs), representing a functional connection between systemic inflammation and mitochondrial damage [20] (Fig. 1). This release can also occur when mitochondrial depolarization is insufficient. Cells may either postpone autophagy to remove slightly damaged organelles or switch from mitophagy to mitochondrial component extrusion within EVs [21]. The involvement of chronic cerebral hypoperfusion in the medial prefrontal area is associated with nutritional apathy [22] and represents a pathophysiological factor that decreases food intake, evolving into nutritional deficiency, which is worsened by the increase in anorexic cytokines [23][24]

Microglia activated by excitotoxicity release exosomes carrying the proinflammatory marker miR-21, which can be considered an exosomal biomarker of microglia activation [25]. Furthermore, proinflammatory stimuli (lipopolysaccharides, interleukin 4, and interleukin 10) result in exosome release increments and changes in exosome content [26][27][28]. The exosomes produced by neurons in major depressive disorder (MDD) were recently found to contain miR‑9‑5p, which polarizes microglia in M1 cells to induce inflammation [29]. This inflammatory inductor determines systemic inflammation that underlies sarcopenia of muscle loss in normal aging, where atrophy is caused by ubiquitin-proteasome system activation and NF–κB signaling [30]. This systemic inflammation plays an essential role in the development of sarcopenia. The chronic low-grade inflammation in dementia combined with the body composition changes linked to malnutrition can be interconnected phenomena that characterize the aging-disease process, leading to sarcopenia [31].

Sarcopenia was found to have a positive correlate with levels of Interleukin 6 (IL-6), Interleukin 10 (IL-10), and IL-6/IL-10 ratios, but a negative correlation with body mass index (BMI) [32][33]. The value of BMI in sarcopenic obesity, on the other hand, is negatively influenced by the development of proinflammatory cytokines by macrophage (IL-6) and C-RP by the liver. As a result, muscle mass loss is substantially associated with increasing fat mass rather than changes in BMI. Individuals with CF or moderate to severe depression were found to have higher levels of IL-6, which has been shown to have a deleterious influence on central dopaminergic function, resulting in weariness, motor skill difficulty, and cognitive decline [13][34].

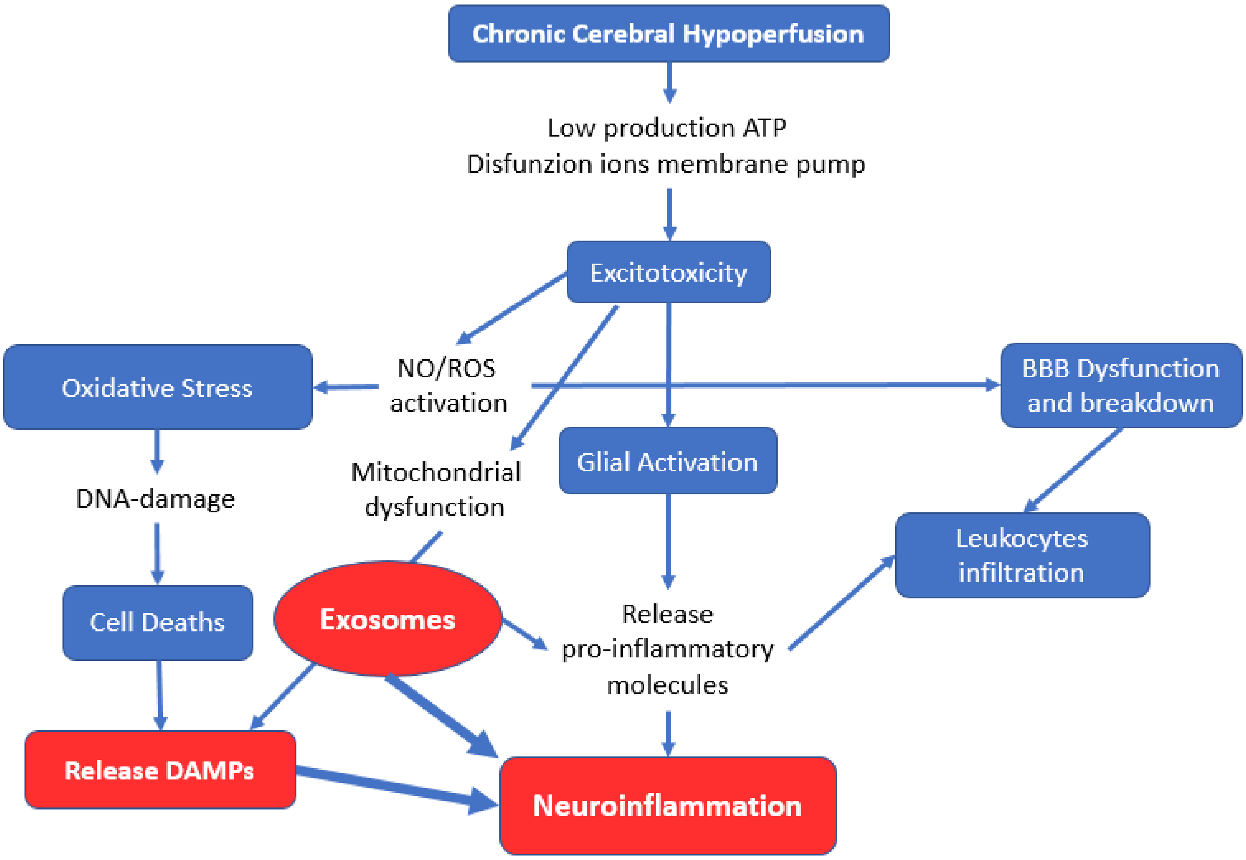

Figure 1. The potential physiopathological pathways of neuroinflammation involved in chronic cerebral hypoperfusion, which results in neuronal death and decreased production of angiogenesis regulators, leading to neurovascular unit uncoupling. These circumstances combine to induce chronic cerebral hypoperfusion, which lowers the amount of glucose and oxygen delivered to the brain, resulting in reduced ATP synthesis, bioenergetic impairment, and a number of pathogenic molecular and cellular processes. The function of the ATP-dependent transporters, such as the Na+/K+ ATPase, is initially affected, causing an ionic imbalance (i.e., Na+ and Ca2+ influx, and K+ efflux) across the plasma membrane, which causes anoxic depolarization within neurons and excitotoxicity in the form oxidative stress by activating a range of calcium-dependent ROS producing mechanisms in the mitochondria and cytoplasm. Thus, the DAMPs released by stressed or wounded cells bind to pattern recognition receptors (PRRs) to trigger an inflammatory response initiating the cascade process of neuroinflammation. Glial activation, BBB disruption, cell death, and demyelination are outcomes of these molecular pathways acting in concert with various cell types. White matter lesions, microinfarcts, and hippocampal atrophy are all examples of structural damage that is brought on by the these pathogenic processes. Each of the above anatomical alterations disrupts the functional connections and neural network, which eventually results in cognitive impairment.

The documented presence of a muscle-brain endocrine pathway controlled by myokines helps to explain how muscular deterioration can alter cognitive states [35]. These muscle-produced substances enhance memory and protect against neural damage [36]. Sarcopenia is also associated with a decrease in the regenerative ability of skeletal muscle stem cells, as well as an altered pace of tissue regeneration and differentiation, which may result in impaired myokine synthesis and secretion, with a deleterious impact on brain function [37]. Tumor necrosis factor-α (TNF-α), IL-10, and Interleukin-1 (IL-1) are inhibited by myokines generated during muscular contraction (Fig. 2). Irisin, myostatin, and Interleukin-15 work together to regulate muscle-adipose tissue communication [38]. During a contraction, muscle also secretes fibroblast growth factor 21 (FGF-21), Interleukin-8, leukaemia inhibitory factor (LIF), angiopoietin-like 4 (ANGPTL4), follistatin-like 1 (FSTL1), vascular endothelial growth factor (VEGF), and brain-derived neurotrophic factor (BDNF) [39]. High circulating BDNF levels have been linked to a lower incidence of dementia [40].

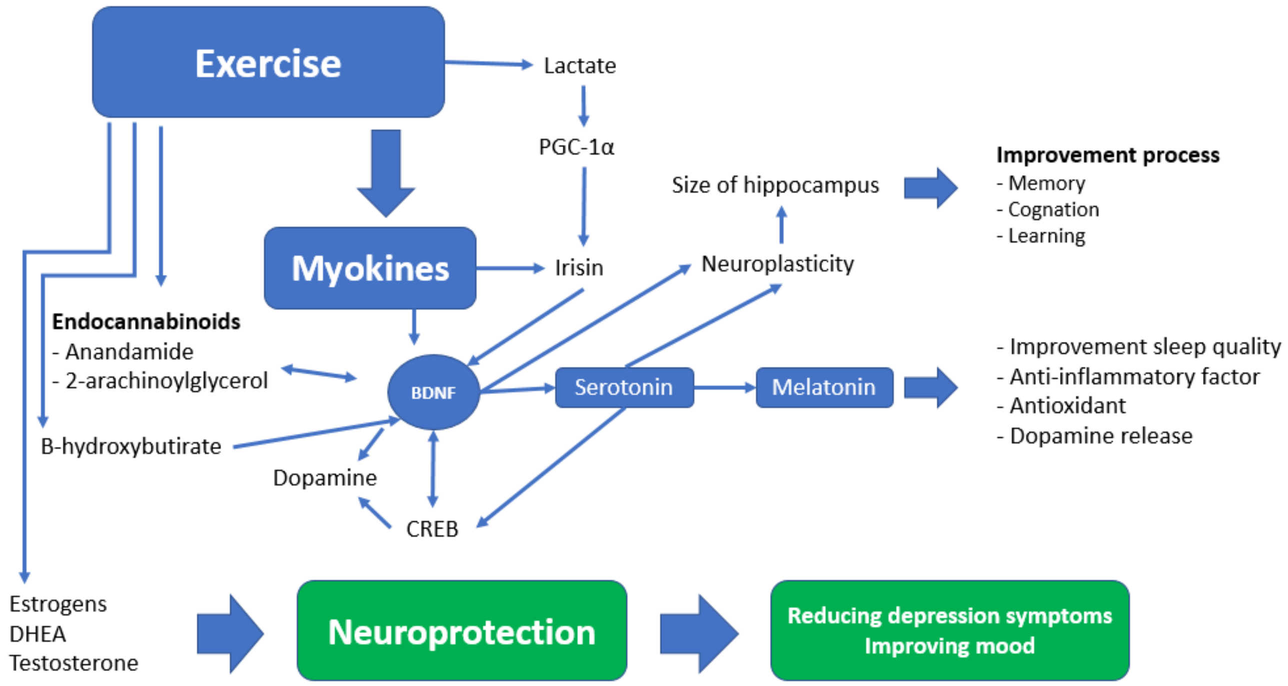

Figure 2. Protective neurological effects of muscle exercise. Myokines, which exert para-, auto-, and endocrine actions, are produced from skeletal muscle during exercise, supporting the crosstalk between skeletal muscle and other tissues, including the neurological system. Among these myokines, brain-derived neurotrophic factor (BDNF) expression and release are increased in response to exercise in both skeletal muscle and the brain, Then, BDNF contributes to synapse development and maintenance as well as the central nervous system capacity to repair and adapt to potential injury. When taking into account the biological indicators of depression, such as monoamines, tryptophan, endocannabinoids, inflammatory markers (oxidative stress and cytokines), stress, and sex hormones, the role of BDNF as a therapeutic agent with various nervous system disorders, including dementia, can be understood.

The molecular mechanisms that connect the loss of muscle mass with cognitive decline include a systemic inflammation determined through altered quality/quantity of brain myokine secretion by activated microglia, insulin resistance, anabolic resistance, oxidative stress, and mitochondrial dysfunction. In this pathway, nutrition should not be ignored since it is a vital element of the induction and recovery mechanism through the exosomes of food [41]. The production and secretion of myokines in grafted sarcopenia have negative consequences on the brain function, which can be called "neurogenic syndrome" [36][42]. This increased myokine production intensifies inflammation and worsens muscle glucose metabolism, potentially influencing insulin transportation throughout the blood-brain barrier and decreasing the prevalence of insulin receptors in the brain as we age. Poor mobility and decreased function of the lower limbs may occur years before the onset of dementia, resulting in a swift evolution towards prolonged bed rest which accelerates the sarcopenic process.

In dementia, cerebral hypoperfusion, accompanied by the consequent increase in free radicals and mitochondrial dysfunction, represent the primum movens of the chain of events leading to sarcopenia. The locosystemic progression of the disease is linked to the exosomes that perform a pivotal pathophysiological role in the development of neurodegenerative disorders and involve in skeletal muscle regeneration. Nevertheless, exosomes have shown the potential to carry therapeutic cargo, with promising future therapeutic and diagnostics applications in neurodegenerative disorders prior to the emergence of symptoms.

3. Cancer and sarcopenia

Cancer is largely related to older age since newly diagnosed cases, and deaths are usually observed in individuals over the age of 65 [44], and it is anticipated that by 2030, adults over the age of 65 will account for 70% of all newly diagnosed cases [45]. Similarly, sarcopenia in oncology is common in older persons and has been linked to chemotherapeutic toxicity and surgical complications [46]. Neoplasms with high sarcopenia prevalence (>50%) are Urothelial, oesophageal, colon, prostate, and thyroid cancers. Whereas the prevalence of sarcopenia varies between 35% and 50% in head and neck squamous cell carcinoma in addition to lung, pancreatic, and ovarian cancers. Lower prevalence (<35%) are observed in breast, gastric, colorectal, and hepatocellular cancers [47]. However, these outcomes still vary based on disease stage and even diagnosis method. For instance, 30-65 % of the patients with pancreatic cancer showed symptoms of sarcopenia [48]. The same study reported that when it is present, sarcopenia results in more severe outcomes such as physical disability, lengthy hospital stays, infections, poor tolerance to chemotherapy, and reduced survival [48].

Cancer-associated sarcopenia can be considered a complex metabolic syndrome in which distinctive pathophysiological elements are associated with the degradation of cellular components, producing an exceptional inflammatory secretome and a strong mitochondrial dysfunction [49]. In the early phase of pancreatic ductal adenocarcinoma (PDAC), the increased level of circulating branched-chain amino acids (BCAAs; isoleucine, leucine, and valine) and monocyte chemoattractant protein-1 (MCP-1) are early warnings of sarcopenia [50][51]. Cancer and the host immune system generate several inflammatory cytokines, including IL-1, IL-6, IL-8, and TNF-α. TNF-α promotes lipid metabolism, protein denaturation, insulin resistance, and muscular atrophy. When the effect of TNF-α is combined with IL-1, IL-6, and the oxidative stress-dependent product nuclear factor-kB (NF-kB), the ubiquitin-proteasome pathway is activated, resulting in the degradation of regulatory proteins [52]. When activated, NF-kB suppresses the production of myoblast determinant protein 1 (MyoD), a myoprotein involved in cell proliferation following muscle injury, hence impairing myocytes' capacity to repair themselves [53]. TNF-α is also linked to the IGF-1/PI3K/Akt signaling inhibition, which reduces muscle anabolic ability [54]. Increased IL-6 levels are associated with sarcopenia, extreme tiredness, and rapid weight loss. Additionally, IL-6 cooperates with TNF-α to stimulate the Janus kinase (JAK)-signal transducer and activator of transcription (STAT) pathway, which is implicated in inflammation, cancer development, and muscle mass atrophy [54]. Moreover, TNF-α and IL-6 both block myocyte development, resulting in ultrastructural myofiber degradation and the replacement of muscle mass with collagen and adipose tissue [54]. This pathway is also maintained by free fatty acids generated by lipolysis that stimulate the release of the ubiquitin ligases Atrogin-1 and MuRF1 [55].

The proinflammatory cytokines in pancreatic cancer, particularly IL-1, may also have a direct impact on the pathways underlying the central anorexia process by increasing the production of hypothalamic serotonin, which is necessary for the activation of proopiomelanocortin (POMC)/CART (cocaine- and amphetamine-regulated transcript) neurons [56]. Numerous miRNAs found in tumor-derived exosomes have been shown to exert effects on muscle cells and cause cancer-related muscle wasting by promoting inflammatory production, activating catabolism, and even regulating cellular breakdown pathways [57].

Exosomes are a class of extracellular vehicles (EVs) that are defined as membrane-bound nanovesicles of endocytic origin, with a diameter of 40–150 nm. These structures are composed of nucleic acids [DNA, mRNA, miRNA, and long and short non-coding RNAs], proteins [cytoskeletal proteins, transmembrane proteins, and heat shock proteins (HSPs)], and enzymes [GAPDH, ATPase, phosphoglycerate kinase 1 (pgk1), and RAB] [58]. For example, pancreatic cancer cells create exosomes that contain specifically miR-21. The production of miR-21 is increased by the production of TGF-β by M2 macrophage that invades the tumor inducing the death of muscle cells. This phenomenon takes place as a result of miR-21 ability to bind to and activate toll-like receptors promoting cell death through the activation of the c-Jun N-terminal kinase pathway (JNK) [57]. Recently, it was discovered that a zinc transporter known as ZIP4, which acts as a regulator of the growth of pancreatic tumours, plays a key role in the cachexia that is associated with pancreatic cancer. This transporter promotes the release of heat shock proteins 70 and 90 via EV activating toll-like receptor 4 (TLR4) and stimulating mitogen-activated protein kinase 14 (p38 MAPK)-mediated muscle breakdown [59]. According to the findings of the same study, knocking down ZIP4 boosted survival while reducing the loss of body weight and muscle mass. In fact, exosomes generated from the PDAC are capable of suppressing glucose intake and lipidosis (Fig. 3). Additionally, these exosomes have the ability to stimulate the movement of glucose transporter 4 protein (Glut4) from the cell surface to the plasma membrane. This movement facilitates the diffusion of circulating glucose across the concentration gradient into muscle and fat tissues [60].

It is possible to draw the conclusion that PDAC produced exomes and their content operate as the most important facilitator of intercellular communication. The fact that these molecules can target, control, program, and re-program their immediate microenvironment of organs and skeletal muscles provides a deeper understanding of the connection between cancer and sarcopenia.

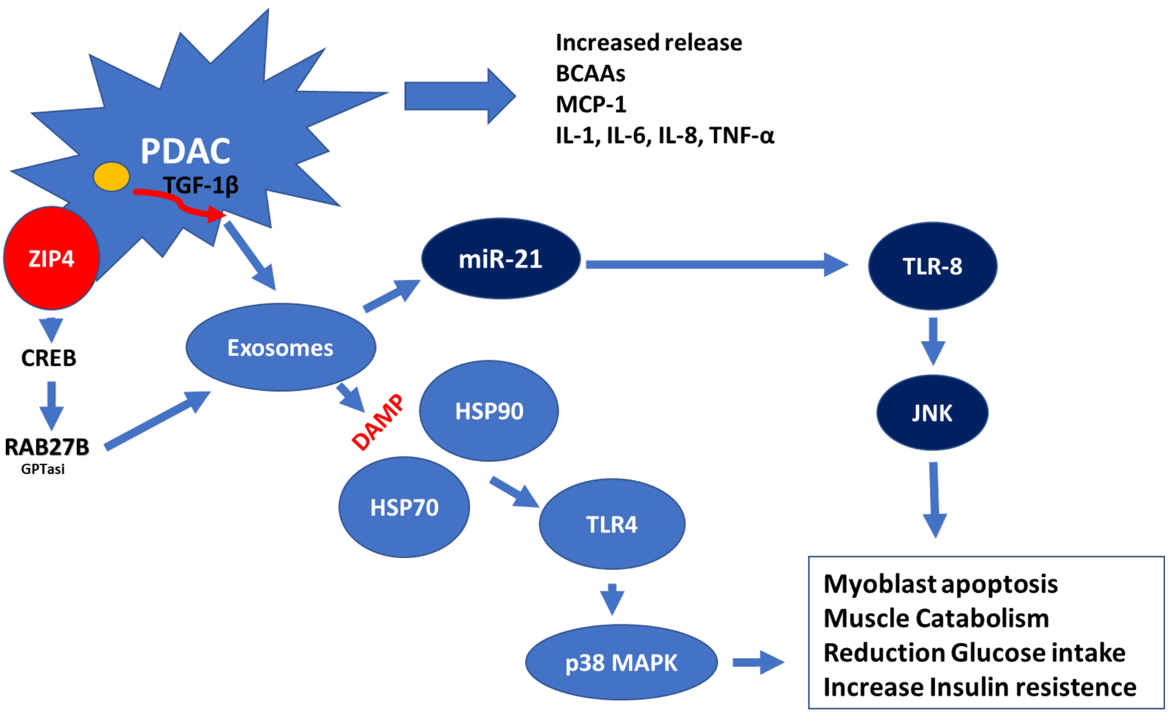

Figure 3. Pancreatic ductal adenocarcinoma pathophysiology pathway in the sarcopenia development. In pancreatic cancer extracellular vehicles are released under the influence of ZIP4 through zinc-sensitive transcription factor CREB followed by the up-regulation of RAB27B. HSP70- and HSP90-positive EVs are examples of the released damage-related molecular patterns released by pancreatic cancer cells. These DAMPs activate TLR4 in skeletal muscle tissues leading to p38 MAPK-mediated muscle protein degradation activation. Simultaneously, the release miRNA-21 containing EVs induces myoblast apoptosis via toll-like receptor 8 (TLR8) activation through the c-Jun N-terminal kinase (JNK) pathway.

4. Stroke and sarcopenia

Stroke is one of the world's leading causes of death and disability [61]. It is forecasted that stroke cases will triplicate in 2050 compared to 2010, with 1/3 of total cases in the >85 age group and almost 2/3 of stroke cases in those older than 75 [62]. Furthermore, stroke incidence in older people correlates with higher mortality and poorer outcome [63]. In fact, shortly after the onset of and up to 28 days after an ischemic stroke (IS) episode, neurons and glial cells in the involved area produce DAMPs activating astrocytes that secrete proinflammatory cytokines (IL-1β), chemokines, metalloproteinases and matrix metalloproteinases (MMPs) that contribute to the damage of the BBB [64]. If astrocytes polarize, they can uptake extracellular glutamate, changing their phenotype and secreting neurotrophic factors that protect the damaged brain tissue [65]. Likewise, quiescent microglial cells are activated a few minutes after IS onset through exosome release, which, when containing miR-21-5p, promotes polarization in M1 phenotypes. The latter secrete IL-1β, IL-6, MMP-9, and TNF-α/ROS that induce inflammation and neurotoxic substances that aggravate brain damage, leakage of BBB, and neuronal apoptosis [66]. On the other hand, In the presence of an exosome transporting, miR-124-3p polarizes M2 microglia, which is an anti-inflammatory phenotype that secretes anti-inflammatory cytokines (IL-4, IL-10, TGF-β) and activates T regulatory cells (CD4+ CD25+), which modulate immune reactions and reduce the inflammatory response, facilitating brain function recovery and improving the prognosis of stroke [67]. This polarization is oriented with the presence of several factors (IL-1, IL-6, IL-13, IFN-γ, IL-15, TXA2, and C1q) that promote microglia in M1 polarization or M2 microglia conversion to M1, while IL-4, IL-13, TGF-β, P2X4, and Nrf2 promote the conversion of both M2 and M1 microglia (Fig. 4 and Fig. 5) [67].

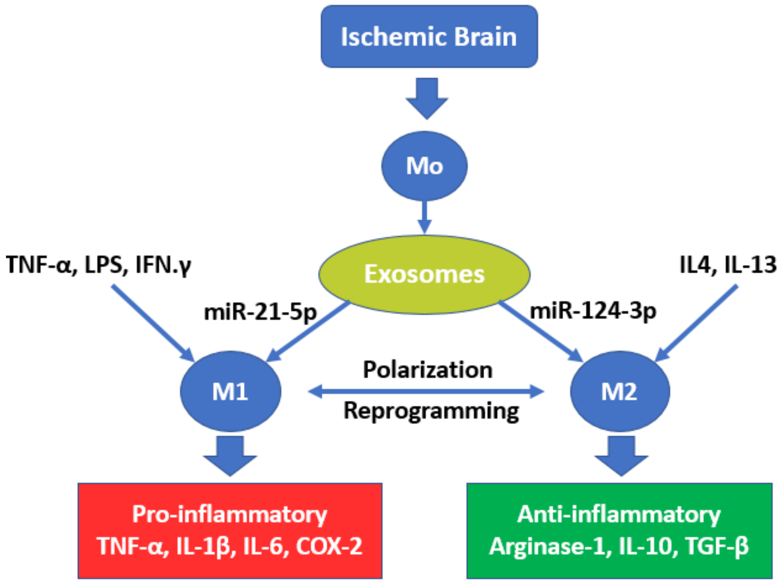

Figure 4. Microglia activation after stroke.

During the progression of cerebral ischemic stroke, there is an increase in the production of growth and trophic factors in addition to chemokines from the ischemic area [68]. These factors include the vascular endothelial growth factor (VEGF), fibroblast growth factor-2 (FGF-2), insulin-like growth factor-1 (IGF-1), brain-derived neurotrophic factor (BDNF), monocyte chemoattractant protein-1 (MCP-1), stromal cell-derived factor 1 (SDF1), endothelial nitric oxide synthase (eNOS), and angiopoietin-1/Tie2 (Ang1/Tie2) [68]. Some of these factors have many functions and encourage the development of new neurons, blood vessels, and oligodendrocytes [68]. The decreased trophic and regenerative EXOs and the motoneuronal damage that occurs during stroke negatively influence brain-muscle communication leading to the muscle becoming flaccid [69]. In fact, aging results in a natural gradual decline in communication between the central nervous system and skeletal muscle. This failure in communication leads to slow movement, weakness, increased falling tendency, and eventually a decline in function, a condition worsened by the ischemic event. This communication is bidirectional between the brain and skeletal muscle, and an important role is played by EVs, where the EXOs represent the essential components [70].

Upregulation of proinflammatory cytokine production that cross the blood brain barrier (BBB) leads the imbalanced secretion in the skeletal muscle of myokines and to muscle memory impairment. Lowering of the muscle myokine levels in blood, induced by sarcopenia, leads to reduce brain function through paracrine and autocrine manners. Failure of the brain-muscle axis is a direct result of ageing and this produces the major motor impairments which frequently accompany it. Many cytokines exhibit the pleiotropy (exert many different types of responses, often on different cell types) and redundancy (different cytokines can induce similar signals) phenomena, in which the circulating levels of cytokines make the difference. Cytokines not only can have overlapping actions but can also share receptor components (cytokine receptor pleiotropy and cytokine receptor redundancy). For example, modest levels of IL-6 may stimulate satellite cell activation and myotube regeneration, whereas chronically increased levels of IL-6 synthesis induce muscle tissue atrophy. These different effects may be explained by a cross-talk between the IL-6/IL-6 receptor and gp130 trans-signalling pathways, which counter the traditional IL-6 receptor signalling pathway's regenerative and anti-inflammatory properties. The exosomes released from the ischemic areas contain numerous molecules, including microRNAs (miRs), which can regulate the expression of genes involved in the fine regulation of numerous physiological processes, including muscle regeneration [71]. A number of studies have pointed to the significance of microRNAs, or miRs, in skeletal muscle functions and disorders. This is due to the fact that abnormal expression of miRs has been linked to a number of conditions affecting the skeletal muscle, including sarcopenia [72]. Expression of miRNAs such as miR-497, miRNA 21, and miR-99a in IS attenuates ischemic volumes and It prevents apoptosis in neuronal cells, which is essential for maintaining neurological processes, whereas overexpression of miR-let-7c-5p and miR-424 reduces the activation of microglia [73]. In this case, the extent of damage is correlated with the level of miRNAs expressed in the blood after IS and crossing BBB [74]. Up-regulation of miR-103, miR-103, miR-132, and miR-126 in intracerebral hemorrhage diminishes neurobehavioral and neuropathological alterations, which protects the integrity, attenuates neuroinflammation, and decreases neuronal apoptosis [75].

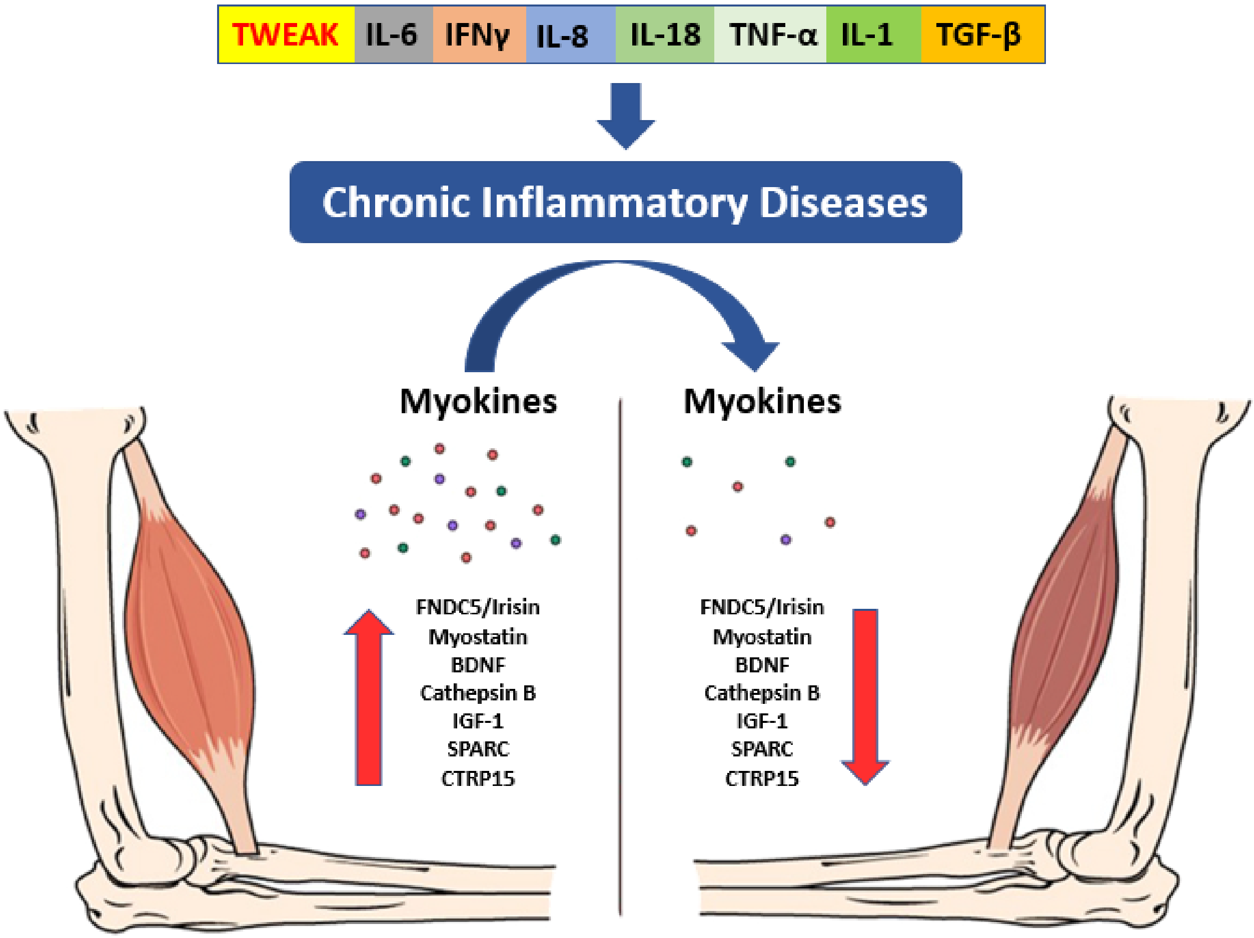

Figure 5. Cytokines released in ischemic stroke generate chronic inflammatory disease with a subsequent decrease of myokines secretion from skeletal muscle resulting in the development of sarcopenia. Upregulation of proinflammatory cytokine production crossing the blood brain barrier (BBB) leads to the imbalanced secretion of myokines in the skeletal muscles and muscle memory impairment. For instance, low IL-6 can activate satellite cells and the regeneration mechanism of myotube, while high IL-6 levels induce muscle tissue wasting through gp130 trans-signaling.

It is evident the exosomes released upon ischemia can play a vital role in post-stroke injury prevention or induction and development of geriatric syndromes such as sarcopenia. Therefore, these molecules can be considered valuable diagnostic and therapeutic tools in post-stroke rehabilitation.

5. Conclusion and future aspects

The malfunctioning of mitochondria and inflammation throughout the body are important contributors to the development of sarcopenia. On the other hand, our knowledge of the molecular factors that link the two systems is limited. Exosome-derived molecules have been shown to include cell-free mitochondrial DNA (mtDNA), which has been identified as one of the components that may behave as damage-associated molecular patterns (DAMPs).Among these molecules, non-coding miRNA represents the critical reunion point between mitochondrial dysfunction and chronic inflammation, with different types resulting in different outcomes. The importance of these molecules in the pathogenesis of chronic diseases discussed here represents only the tip of the iceberg of their participation in many, if not all, acute and chronic diseases. Thus, exosomes have acquired the pathophysiological audience nowadays as reliable biomarkers. The high heterogeneity of exosomes reflects the pathophysiological conditions of the cells from which they originate. Then, their cargo is a potential organ biomarker for diagnosis and clinical evaluation in the diagnostics of various diseases. For instance, a 100% accuracy in the diagnosis of PDAC was obtained using the CA19-9 marker in combination with miRNAs-21, -210 [76][77].

Furthermore, targeting the exosomal secretions is now considered for its therapeutic application not only to stop the evolution of sarcopenia [78] but also to treat various diseases, including those considered here. Integrating engineered exosomes as "Trojan Horses" can be applied in various human chronic and infectious diseases [79], rendering it a promising therapeutic method in the near future.

Conflict of interest statement

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