Docosahexaenoic Acid

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1. Sarcopenia

One of the characteristic features of aging is the progressive loss of muscle mass, a nosological syndrome called sarcopenia. It is also a pathological risk factor for many clinically adverse outcomes in older adults. During the aging process, while slow-twitch muscle fibers (type I, which relies on aerobic respiration for muscle endurance) remain largely unchanged, the mass of fast-twitch fibers (type II, which determines muscle power) is significantly reduced via the progressive denervation and reinnervation processes [1]. In addition, the complex fiber-type transformation, which provides plasticity to muscles to adapt to developmental and environmental changes, requires tightly regulated proteolysis to remove the existing fibers, and this pathologic acceleration of proteolysis is implicated in sarcopenia, the age-related loss of muscle mass and function [2]. In sarcopenic muscle, type II fibers decrease much faster than type I. In 2019, European Working Group of Sarcopenia in Older People (EWGSOP2) classified sarcopenia into three stages: probable sarcopenia, confirmed sarcopenia, and severe sarcopenia [4]. However, despite its intuitive nosological definition, a consensus on the operational definition of sarcopenia has yet to be achieved.

Based on the meta-analysis, the overall prevalence of sarcopenia is approximately 10% in the population aged 60 years or older (without gender differences) [5]. Given this high prevalence and the fact that ~2.1 billion people are expected to be more than 60 years old by the year 2025 [6], sarcopenia will be a major healthcare issue for both patients and the society. Therefore, in addition to physical exercise, nutritional strategies are uniquely important as an effective preventive measure against sarcopenia, as well as the accompanying frailty and disabilities. The homeostatic imbalance between protein synthesis and degradation in the geriatric muscle probably originates from dysregulation of complex signaling pathways [7][8][9]. Therefore, understanding the mechanisms of sarcopenia is essential to identify the targets for pharmacological interventions to prevent or treat sarcopenia.

2. Treatment Approach for Sarcopenia

The primary treatment approach is resistance exercise. Previously, endurance training was considered not effective to improve muscle mass or strength, but it is now generally accepted that the ATP-producing endurance training and balance training, combining resistance and endurance trainings, are both preventive and therapeutic to age-induced sarcopenia of skeletal muscles [10]. Physical training can restore the aged muscle's sensitivity to protein intake, which subsequently produces anabolic stimuli to facilitate muscle protein synthesis. Potentially effective substances include anabolic steroids, myostatin (natural muscle growth antagonist) inhibitors, ghrelin agonists, and antioxidants. Several supplements have been suggested to produce beneficial muscle regenerative effects, for example, essential amino acids, such as leucine, creatine monohydrate, omega-3 polyunsaturated fatty acid (PUFA), vitamin D, vitamin B_6, folic acid, and magnesium [11][12]. De Spiegeleer et al. identified seven systematic reviews or meta-analyses, and found that vitamin D and testosterone can improve muscle mass, muscle strength and physical performance in subjects aged over 65 years [13].

3. Therapeutic Potentials of DHA in Sarcopenia by Modulating Muscle Protein Catabolism

Omega-3 PUFAs have been shown to reduce the development of sarcopenia in the older population by positively modulating intracellular metabolic signals [14][15]. However, how omega-3 PUFAs affect the cellular protein catabolism has not extensively studied yet on the molecular level. We previously reported that docosahexaenoic acid (DHA), a major dietary omega-3 PUFA, effectively delayed proteasomal degradation of muscle proteins in a cellular atrophy model [16].

The inhibitory effect of DHA on protein degradation might originate from the generation of excess proteasome substrates through oxidation, which suppresses cellular proteasome activity by accumulating the hard-to-degrade substrates. On the contrary, DHA appears to induce autophagy in many cancer cell lines via p53-mediated AMPK/mTOR signaling [17]. This phenomenon may reflect the negative feedback communication between the two catabolic systems, which are not independent, but are, in fact, connected by a highly regulated negative feedback crosstalk [18][19][20]. In this article, we review the mechanisms of sarcopenia development and progression in the context of protein homeostasis (proteostasis), focusing on DHA as a novel sarcopenia-targeting molecule. We address the recent understanding of muscle protein degradation via the ubiquitin–proteasome system (UPS) and the autophagy–lysosome system (ALS) during sarcopenia.

4. Conclusion and Future Perspectives

The skeletal muscle accounts for approximately 40% of total body weight [22]. In addition to providing locomotive power, muscle also serves as a reserve of readily available peptides and proteins. Recent progress in sarcopenia research clearly indicates that muscle homeostasis is the result of a precise balance between the anabolic and catabolic processes. A small decrease in synthesis or increase in degradation, if sustained, can lead to a devastating pathological condition. The term sarcopenia was introduced nearly 20 years ago; now, with the worldwide population rapidly aging, this disease is currently gaining more considerable research interest and public attention. Although muscle mass and muscle strength are not always correlated, it is possible that the suppression of muscle protein breakdown is critical for the prevention and treatment of sarcopenia. Understanding detailed mechanisms involved in control of age-related changes in muscle proteins might offer a new therapeutic strategy for patients with sarcopenia.

Omega-3 PUFA supplements might be an effective therapy to prevent or slow down sarcopenia. A number of studies based on rodents and humans have reported enhanced anabolic signaling in skeletal muscle [23]. Studies with C2C12 myotubes or fasted mice have demonstrated that treatment with EPA, but not DHA, significantly increased protein synthesis and decreased protein breakdown [24][25]. Many studies indicate EPA may effectively attenuate the UPS-mediated muscle protein degradation in cachexia murine models [25][26][27]. The mechanism of action mediating NF-κB inhibition appeared to be similar to the antitumor activity of bortezomib on multiple myeloma. Although the effects and mechanistic details of DHA on sarcopenia remain to be further elucidated, our current model suggests that DHA exerts its beneficial effects on muscle atrophy by decreasing proteasomal proteolytic activity by blocking it with oxidized proteins and excess proteasome substrates. However, the results regarding the effectiveness of DHA supplementation in attenuating muscle atrophy in humans are somewhat contradictory. In the RCTs performed by Smith et al., dietary supplementation with omega-3 fatty acids (containing 1.86 g EPA and 1.50 g DHA) significantly increased muscle protein synthesis delays the normal decline in muscle mass and function in older individuals [28][29] while a direct action of EPA and DHA on muscle protein synthesis or degradation was not investigated. Moreover, an 8-week administration of DHA preserved fasting (48 h)-induced muscle atrophy and proteolysis with upregulated autophagy [30]. The concentration, duration, and types of omega-3 PUFAs used in each experiment may directly affect the outcomes. Moreover, cells or organisms may have diverse and sometimes contradictory responses to DHA, which probably depend on the levels of oxidative stress induction.

Growing evidence suggests that the mTOR signaling pathway influences longevity and aging. Inhibition of mTOR signaling with rapamycin (or its derivative rapalogs) is currently the only reliable pharmacological treatment option known to increase longevity in mice, as well as in yeast, worms, and flies, and to prevent age-related conditions in rodents, dogs, nonhuman primates, and humans [31]. mTOR complexes are serine/threonine kinases that lie downstream of Akt in the PI3 kinase pathway and regulate not only protein synthesis but also protein degradation through autophagy [21][32]. Under normal conditions, the free amino acids, the products of proteolysis, stimulate mTOR and facilitate protein synthesis through the downstream effectors, such as ribosomal protein S6 kinase 1 (S6K1) and eukaryotic translation initiation factor 4E binding protein 1 (4EBP1). As rapamycin, rapalogs, and rapamycin metabolites, both endogenous and dietary DHA can target mTOR, altering of downstream effector activation and subsequent protein synthesis [33][34]. However, this also upregulates cellular autophagy (contributing to the anti-inflammaging effects) and subsequently inhibits the UPS, which is more critical for muscle protein degradation. Therefore, the processes involving mTOR probably create a complex crosstalk between the pathways involved in protein synthesis and degradation, although the detailed mechanisms remain to be identified. Dual inhibitory effects of DHA on mTOR signaling and protein catabolism could be a potentially promising strategy to slow aging and extend a healthy lifespan.

Currently, there is no pharmacological intervention method with a clear underlying molecular mechanism to prevent or treat sarcopenia. Considering the increasing recognition of individual and socioeconomic problems associated with sarcopenia, the potential of DHA as an anti-sarcopenic agent should be evaluated more thoroughly through global analysis of cellular oxidative stress and subsequent cellular proteome changes. Relatively newly instituted global

standards for the screening and diagnosis of sarcopenia (International Classification of Disease, ICD-10-CM code.M62.84) can be applicable in both prospective and retrospective clinical trials [35]. A small anti-sarcopenic property of DHA would have a big impact on health and quality of life for the older population.

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