Mechanisms of Ageing and Development xxx (2013) xxx–xxx

Contents lists available at SciVerse ScienceDirect

Mechanisms of Ageing and Development

journal homepage: www.elsevier.com/locate/mechagedev

Review

Sarcopenia: The gliogenic perspective

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ARTICLE INFO

Article history:
Received 31 December 2012
Received in revised form 20 June 2013
Accepted 22 June 2013
Available online xxx

Keywords:
Sarcopenia
Aging
Muscle
Motor neuron
Glia
Schwann cells

ABSTRACT

It has been approximately 25 years since Dr. Rosenberg first brought attention to sarcopenia. To date, this aging-associated condition is recognized as a chronic loss of muscle mass and is usually accompanied by dynapenia. Despite its poly-etiological factors, sarcopenia has a strong neurogenic component underlying this chrono-degeneration of muscle mass, as shown in recent studies. As it seems plausible to explain the origin of sarcopenia through a motor neuron degeneration model, the focus of sarcopenia research should combine neuroscience with the study of the original myocyte and satellite cells. Although a complete mechanism underlying the development of sarcopenia has yet to be elucidated, we propose that the primary trigger of sarcopenia could be gliogenic in origin based on the close relationship between the glia, neurons and non-neural cells, for example, the motor unit and its associated glia in both the central nervous system (CNS) and the peripheral nervous system (PNS). In addition to muscle cells, both of the neural cells are affected by aging.

1. Introduction

Sarcopenia (Greek: *sarx* means "flesh", *penia* means "loss") is a chronic myo-degenerative syndrome. The term was first mentioned by Dr. Rosenberg at a meeting in 1988 where he described it as an age-associated decline in lean body mass that affects ambulation, mobility, energy intake, overall nutrient intake and status, independence and breathing (Rosenberg, 1997). Until now, exercise training, especially power training (but excluding endurance training) (Sanchis-Gomar et al., 2011; Freiberger et al., 2011), and proper nutrition (Volkert, 2011) seem to be the most effective ways for treating sarcopenia with the least amount of side effects. Thus, it is imperative to further study the mechanism or etiology of sarcopenia to develop more effective therapies for treating sarcopenia. So far, the characterization of sarcopenia differs in terms of the clinical features observed in the research studies. Some studies have only focused on muscle mass (Clark and Manini, 2008; Janssen, 2010; Visser and Schaap, 2011), while others focused on muscle strength and muscle function/quality (Lee et al., 2007a,b; Abellan van Kan, 2009). Recent findings suggest that the loss of muscle mass and the loss of muscle strength are two distinct processes with different pathophysiologies (Visser and Schaap, 2011). However, the chronic loss of both muscle mass and muscle strength holds a strong neurogenic component (Berger and Doherty, 2010; Kwan, 2013). In fact, the loss of motor neurons is one of the key features manifested in aging (Wang et al., 1999; Deschenes, 2004), along with other age-related neurodegenerative features. Although a complete mechanism underlying such age-associated degeneration has yet to be elucidated, it has been well documented that glia are important housekeepers for neuronal survival and function (Hanani, 2005; MacIntosh et al., 2006). Considering the pathogenic roles played by the glia in many neurological disorders (Schubert et al., 2001; Teismann et al., 2003; Calabresi, 2004; Holden, 2007; Howe and Barres, 2012), it is reasonable to suggest that glia serves as a possible factor in the pathogenesis of sarcopenia.

In this review, we aim to provide a new perspective on the etiology of sarcopenia and propose that this age-associated syndrome may be gliogenic in nature despite its muscle-related features. In the following sections, we will discuss some commonly accepted etiologies of sarcopenia before examining the close relationship between neurons and glia, its impact and an overview of physiological factors that contribute to our gliogenic hypothesis.

2. Etiology of sarcopenia

To date, the prevalence of sarcopenia has been affected by age, sex, race (Abellan van Kan, 2009; Tan et al., 2012; Lau et al., 2005; Lee et al., 2007a,b), morbidity (Muscaritoli et al., 2010; Lee et al., 2007a,b), nutrition (Volkert, 2011) and physical activity (Roubenoff, 2007; Freiberger et al., 2011). In other words, the body physiology and etiology of this syndrome are affected by, but

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0047-6374/$ – see front matter © 2013 Published by Elsevier Ireland Ltd.
http://dx.doi.org/10.1016/j.mad.2013.06.001

are not restricted, to five main clinical features: (1) aging, (2) genetics, (3) morbidity, (4) nutrition and (5) activity. Regardless of the poly-factorial etiology of sarcopenia, it is certain that the mass, strength, function and the quality of muscle are determined by the status of the motor unit by which its function is further determined by at least three cardinal physiological systems as described in previous works (Kwan, 2013). Clinical features such as genetic factors, neuro-degenerative diseases, hormonal dysregulatory diseases, auto-immune diseases, inflammation, malnutrition, physical injuries and inactivity (Muscaritoli et al., 2010; Tan et al., 2012; Garatachea and Lucía, 2013) could affect or alter these physiological systems at a certain level; therefore, all of these factors could account for the development of both dynapenia and sarcopenia. Because muscle functions rely on the status of the motor units and circulation factors, the pathology of sarcopenia may be deduced as neurogenic, musculogenic, synaptogenic and/or vasculogenic, as described in previous works (Kwan, 2013). Under the neurogenic model, the pathology of sarcopenia could be further deduced as gliogenic (caused by glia) and/or neuronogenic (caused by neurons). In the following sections, we will discuss the physiological factors that influence sarcopenia.

2.1. Common factors

According to most studies, the factors contributing to the loss of muscle mass in sarcopenia include the following: (1) mitochondrial dysfunction, (2) elevation of oxidative stress, (3) inflammaging, (4) altered rate of protein turnover, (5) decline in cellular trophic factors, (6) decline in intake of essential nutrients and (7) decline in physical activity. Interestingly, most of these pathological factors are not exclusive to the muscular system (Lee et al., 2007a,b; Dirks and Leeuwenburgh, 2005; Sanchis-Gomar et al., 2011; Roubenoff, 2007; Alway et al., 2003; Siu et al., 2008; Tan et al., 2012; Sriram et al., 2011; Hall et al., 2011; Garatachea and Lucía, 2013; Deschenes, 2004; Noren Hooten et al., 2010; Hamrick et al., 2010; Derbré et al., 2012; Braga et al., 2008) as they are also applicable to the nervous system for both neurons (Deschenes, 2004; Amadio et al., 2008; Ozdemir et al., 2012; Akundi et al., 2012; Tsai et al., 2012; Martin, 2011; Sanders et al., 2011; Nguyen et al., 2011; Ooishi et al., 2012; Li et al., 2011; Machado et al., 2011; Teismann et al., 2003) and glia (Paasche et al., 2000; Boumezbeur et al., 2010; Muntané et al., 2006; Dei et al., 2002; Gomez and Ferrer, 2010; Giunta et al., 2008; Sierra et al., 2007; Papadopoulos et al., 1998; Wyse and Sernia, 1997; Aberg et al., 2003; Yudkoff et al., 1996; Yudkoff, 1997; Li et al., 2005). Recent studies have also found that denervation could enhance cellular apoptotic potential by inducing an elevation of proapoptotic factors (e.g., caspase 8 and bax) in both young and aged rats (Alway et al., 2003). In particular, one animal study showed that the etiology of sarcopenia was more likely to be neurogenic when the gastrocnemius muscle cells of 6 month to 24 month old rats did not reveal any significant change in the proapoptotic factors (e.g., bax, cytochrome c and caspase 3 (Dirks and Leeuwenburgh, 2002)). Moreover, an increase in exercise activity could raise the production of neurotrophic factors in the CNS, including neurons of the hippocampus and the motor cortex of rodents (Whishaw and Kolb, 2005). This result is consistent with the fact that exercise may ameliorate the pathology of sarcopenia.

2.2. Neuronal factors

In terms of neurology, the loss of muscle power and muscle strength is associated with age-related changes in motor units and age-related changes in the degree of the coactivation of antagonist muscles, respectively (Deschenes, 2004). At the cellular level, aging is associated with a reduction in the motor axon conduction velocity and the number of myelinated axons. Aging is also associated with a reduction in the motor unit reinnervation after denervation and a reduction in the number of motor units and motor neurons specific to type II muscle fibers (Dirks and Leeuwenburgh, 2005; Deschenes, 2004). Because fast-twitch motor units determine the degree of power exerted by the underlying muscles, the loss of these units in aging contributes to the loss in muscle power (Deschenes, 2004). Under a normal aging process, a preferential denervation of type II muscle fibers occurs and these denervated fibers are then reinnervated by axonal sprouting from slow motor neurons in a process called motor unit remodeling. However, if the denervation outpaces the reinnervation, a population of denervated fibers will then undergo atrophy and degeneration (Jang and Van Remmen, 2011) as a result of the loss of trophic factors (Schiaffino et al., 1999). This process leads to a loss of muscle mass, which is at least partially occurs through apoptosis (Alway et al., 2003). At the molecular level, rat studies revealed that progressive denervation during aging have disrupted the precise overlapping between the pre-synaptic nerve terminal and the post-synaptic acetylcholine receptor (AChR) clusters at the neuromuscular junction (NMJ) (Kulakowski et al., 2011). Denervated muscles have also elevated the expression of proapoptotic/atrophic factors, which include bax; caspases 3, 7, 8 and 10, (Alway et al., 2003); and a reduction in the trophic factor signals, which include TrkB signaling via BDNF as well as NT-4/5 (Kulakowski et al., 2011) and ErbB/PI3K signaling via neuregulin (Mantilla and Sieck, 2008). These factors increase the apoptotic potential of myocytes. It seems that denervation could be a primary trigger for muscle loss and such supposition is consistent with the findings from recent studies (Power et al., 2012; Aagaard et al., 2010).

2.3. Glial factors

While neurons are commonly considered as basic neural units involved in information processing, glia, as non-excitable cells, are commonly regarded as the housekeeper for maintaining an optimal physiological environment for neuronal survival and functions. Glia, in particular astrocytes (which exist at approximately 8 times more than neurons in the brain) (Alexei and Arthur, 2007a), function primarily as supportive cells by providing the mass structure for the brain, neuronal insulation, developmental guidance, environmental homeostasis, neuroenergetics regulation, neuronal nourishment and even immune functions. (Alexei and Arthur, 2007a; Kettenmann and Ransom, 2005). There is a great variety of glia (Fig. 1) throughout the human body (e.g., myelinating glia, non-myelinating glia, developmental radial glia and immunological microglia, etc.). Both glia and neurons are capable of expressing practically every type of neurotransmitter receptor known so far. Supported by findings that glia could communicate with neurons through gliotransmitters (e.g., glutamate, ATP and D-serine) (Alexei and Arthur, 2007a), both glia and neurons are mutually integrated into highly effective information processing units to form a functional neuronal-glial unit by wiring transmission and volume transmission (Alexei and Arthur, 2007b). Due to its dynamic interaction with neurons and blood vessels (Alexei and Arthur, 2007c; Takano et al., 2006; Kettenmann and Ransom, 2005), the malfunction of glia could directly affect neural functions. The most representative examples would be demyelination in multiple sclerosis (MS) and Charcot–Marie–Tooth disease (CMT). Recent studies have also suggested the causative role played by glia in common neurodegenerative diseases, including Parkinson's disease, Alzheimer's disease, amyotrophic lateral sclerosis and ischemic stroke (Schubert et al., 2001; Holden, 2007; Teismann et al., 2003; Jackson et al., 1999; Seifert et al., 2006; Filosa et al., 2006; Takano et al., 2006; Rao and Weiss, 2004; Kettenmann and Ransom, 2005). Regarding the etiology of

Please cite this article in press as: Kwan, P., Ng, G., Sarcopenia: The gliogenic perspective. Mech. Ageing Dev. (2013), http://dx.doi.org/10.1016/j.mad.2013.06.001