Current Concept of Sarcopenia and its Neurogenic Model

Ping KWAN

Department of Rehabilitation Sciences
The Hong Kong Polytechnic University, Hong Kong (SAR) of China
1 Introduction

The commonly accepted concept of aging is considered as a natural feature/process of change in the properties of the subject of interest with respect to time. This process of change can occur spontaneously and/or non-spontaneously, while the subject of interest could be a living, non-living, tangible or intangible. In regard to the living organisms including human, aging is commonly defined as a time-associated physiological integrity decline which eventually leading to functional impairment and increased vulnerability to death [López-Otín et al., 2013]. As one of the health concerns, aging attracts community attentions that gradually become greater with respect to the growing aging population, especially in the more developed countries or societies. While Alzheimer’s disease (since 1907) [Alzheimer, 1907; Alzheimer et al., 1995] and Parkinson’s disease (since 1817) [Parkinson, 2002] are classic themes of aging research in the nervous system, osteoporosis (since 1835) [Lobstein, 1835] and sarcopenia (1988) [Rosenberg, 1997; Kwan, 2013a] are themes of aging research in the musculoskeletal system. Among these aging research themes, it is important to note that although sarcopenia (Greek: sarx means “flesh”, penia means “loss”) is a new term proposed by Rosenberg in the 1988 Albuquerque (New Mexico, USA) meeting [Morley & Cruz-Jentoft, 2012; Rosenberg, 1997; Kwan, 2013a; Kwan, 2013b], the phenomenon of aging-associated loss of muscle strength and muscle mass was already documented in 1931 by Critchley [Rosenberg, 2011; Critchley, 1931], and the aging-associated loss of muscle fibers (also known as myocytes) was documented in 1983 by Lexell and colleagues [Rosenberg, 2011; Lexell et al., 1983].

Dr. Irwin H. Rosenberg (1988) [Rosenberg, 1997; Kwan, 2013a]: “...no decline with age is as dramatic or potentially more significant than the decline in lean body mass. In fact, there may be no single feature of age-related decline more striking than the decline in lean body mass in affecting ambulation, mobility, energy intake, overall nutrient intake and status, independence and breathing.”

The Greek term sarcopenia is originally created for a better recognition of and attention to the concept of involuntary aging-associated loss of skeletal muscle mass and consequently of strength by the scientific community [Morley & Cruz-Jentoft, 2012; Rosenberg, 1997; Kwan, 2013a; Kwan, 2013b; Rosenberg, 2011; Janssen, 2010]. Remarkably, the United States (US) National Institute on Aging had emanated a call for research proposals on sarcopenia within a year of the publication of the first sarcopenia leading report [Rosenberg, 2011]. However, maybe partly due to the fact that the verbal definition and the etiologic definition of sarcopenia have not been matched by a consensus on which measurements need to be used in defining and diagnosing sarcopenia in the clinical setting, the diagnosis and treatment of sarcopenia is not yet a standard part of the geriatric care repertoire in the US [Rosenberg, 2011]. Additionally, the prevalence data of sarcopenia varies among different prevalence studies due to the difference in study sample, definition of sarcopenia, and the assessment tool used [Kwan, 2013a; Abellan van Kan, 2009]. In order to clarify and promote the concept of sarcopenia, this book chapter will provide an up-to-date overview of this aging-associated condition. Additionally, the current concept of the mechanism of human locomotion and the relationship between muscle mass and strength will also be discussed.
2 Current Consensus Definitions of Sarcopenia

Recently, three international consensus definitions of sarcopenia have been promulgated and supported by different groups of scientific communities among which there are some common scholars/authors [Morley & Cruz-Jentoft, 2012; Fielding et al., 2011]. The first definition was promulgated in November 2009, when a group of geriatricians and scientists from academia and industry met in Rome for the purpose of reaching a consensus definition of sarcopenia [Rosenberg, 2011; Fielding et al., 2011].

**International Working Group on Sarcopenia (IWGS)** [Rosenberg, 2011; Fielding et al., 2011]: “Sarcopenia is the age-associated loss of skeletal muscle mass and function. Sarcopenia is a complex syndrome that is associated with muscle mass loss alone or in conjunction with increased fat mass. The causes of sarcopenia are multi-factorial and can include disuse, changing endocrine function, chronic diseases, inflammation, insulin resistance, and nutritional deficiencies. While cachexia may be a component of sarcopenia, the two conditions are not the same.”

Several months later, the second definition was published by the **European Working Group on Sarcopenia in Older People (EWGSOP)** in July 2010 [Morley & Cruz-Jentoft, 2012; Cruz-Jentoft et al., 2010]. This scientific community included representatives from four endorsing participant organizations which are the European Union Geriatric Medicine Society (EUGMS), the European Society for Clinical Nutrition and Metabolism (also known as ESPEN), the International Association of Gerontology and Geriatrics-European Region (IAGG-ER) and the International Association of Nutrition and Aging (IANA) [Morley & Cruz-Jentoft, 2012; Cruz-Jentoft et al., 2010].

**EWGSOP** [Morley & Cruz-Jentoft, 2012; Cruz-Jentoft et al., 2010]: “Sarcopenia is a syndrome characterized by progressive and generalized loss of skeletal muscle mass and strength with a risk of adverse outcomes, such as physical disability, poor quality of life, and death.”

In addition to the recommendation of using both low muscle mass and low muscle function (strength/physical performance) for the diagnosis of sarcopenia, EWGSOP proposed that dividing sarcopenia into categories (primary and secondary) and stages (presarcopenia, sarcopenia and severe sarcopenia) may be helpful in clinical practice/management [Morley & Cruz-Jentoft, 2012; Cruz-Jentoft et al., 2010]. In this proposal: primary sarcopenia is solely caused by aging, while secondary sarcopenia is caused by non-aging-associated factors (e.g. genetic disorders, neurodegenerative diseases, hormonal dysregulations, autoimmune diseases, inflammation, malnutrition, physical injuries, and inactivity) [Morley & Cruz-Jentoft, 2012; Tan et al., 2012; Garatachea & Lucía, 2013; Muscaritoli et al., 2010].

One year later, the third definition was published by the **Society of Sarcopenia, Cachexia and Wasting Disorders (SSCWD)** in July 2011 concluding that “sarcopenia, ie, reduced muscle mass, with limited mobility” should be considered an important clinical entity and that most older persons should be screened for this condition [Morley & Cruz-Jentoft, 2012; Morley et al., 2011].

**SSCWD** [Morley et al., 2011]: “Sarcopenia with limited mobility is defined as a person with muscle loss whose walking speed is equal to or less than 1 m/s or who walks less than 400 m during a 6-minute walk, and who has a lean appendicular mass corrected for height squared of 2 standard devia-
tions or more below the mean of healthy persons between 20 and 30 years of age of the same ethnic
group. The limitation in mobility should not clearly be a result of otherwise defined specific diseases of
muscle, peripheral vascular disease with intermittent claudication, central and peripheral nervous sys-
tem disorders, or cachexia. Clinically significant interventions are defined as an increase in the 6-minute
walk of at least 50 meters or an increase of walking speed of at least 0.1 m/s.”

Although all of these consensus definitions of sarcopenia differ from each other (e.g. while the
SSCWD definition excludes cachectic individuals from the definition of sarcopenia, the IWGS definition
accepts that cachexia is one part of sarcopenia) [Morley & Cruz-Jentoft, 2012; Fielding et al., 2011; Mor-
ley et al., 2011], they all clearly refer to the phenomenon of aging-associated loss of muscle mass [Mor-
ley & Cruz-Jentoft, 2012; Fielding et al., 2011; Cruz-Jentoft et al., 2010; Morley et al., 2011]. However,
if sarcopenia is defined solely as a process of aging-associated muscle mass decline, it may not be appr-opriate as suggested by some studies [Morley & Cruz-Jentoft, 2012]. The main reasons are but not limited
to: 1) the phenomenon referred by Rosenberg is the aging-associated muscle mass decline that results in
physiological/functional impairments and physical disabilities [Rosenberg, 1997; Kwan, 2013a; Rosen-
berg, 2011]; 2) aging-associated loss of muscle mass does not necessarily lead to physical disabilities
[Kwan, 2013a]; 3) the association between muscle mass, muscle function (strength and power), physical
performance and other downstream outcomes is not linear [Morley & Cruz-Jentoft, 2012]; and 4) the
regulatory agencies have failed to accept that restoration of muscle mass is, of itself, a sufficient reason
to allow a drug to be approved for use [Morley & Cruz-Jentoft, 2012].

Therefore, it is reasonable to see these three consensus definitions having a function-related por-
tion in addition to the aging-associated muscle mass decline (the first definition included the muscle
function, the second definition included the muscle strength while the third definition included the lim-
ited mobility). According to these cases, it seems evident that clinical consequences of muscle wasting
have to be considered if sarcopenia wants to have a place in clinical practice [Morley & Cruz-Jentoft,
2012]. Interestingly, it is worth noting that there are studies in 2008 defining sarcopenia solely as the ag-
ing-associated loss of muscle mass while the aging-associated loss of muscle strength is considered as
another condition and coined with a new term “dynapenia” [Clark & Manini, 2008; Manini et al., 2012;
Janssen, 2010; Visser & Schaap, 2011] although this term has been reused in the 2011 SSCWD publica-
tion as the loss of power (where the loss of force/strength is coined as Kratopenia) [Morley et al., 2011].
The reasons underlying such considerations are mainly due to the difference in pathophysiology between
aging-associated loss of muscle mass and muscle strength (figure 1) [Clark & Manini, 2008; Visser &
Schaap, 2011].
Additionally, the correlations between change in muscle mass and change in muscle strength in older adults are inconsistent and not very robust [Morley et al., 2011; Visser & Schaap, 2011]. Although measurement of muscle mass is straight and amenable to be used in big epidemiological studies [Morley & Cruz-Jentoft, 2012], Visser M and colleagues have indicated that the impact of poor muscle functioning was stronger and more consistent throughout different studies compared with the impact of low muscle mass [Visser & Schaap, 2011]. Regarding the commonly used measurement techniques for muscle mass and other relevant properties, please refer to table 1 and table 2, respectively.
<table>
<thead>
<tr>
<th>Method</th>
<th>DEXA</th>
<th>CT</th>
<th>MRI</th>
<th>Ultrasound</th>
<th>BIA</th>
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<tbody>
<tr>
<td></td>
<td>Measures attenuation of free muscle mass</td>
<td>Density of muscle area</td>
<td>Density of muscle area</td>
<td>Visualization of cross-sectional area</td>
<td>Indirect measure of muscle mass</td>
</tr>
<tr>
<td>Precision</td>
<td>1%-4%</td>
<td>1%-3%</td>
<td>1%-3%</td>
<td>2%</td>
<td>2%-4%</td>
</tr>
<tr>
<td>Radiation exposure</td>
<td>1 mrem (10 μSv)</td>
<td>15 mrem (150 μSv)</td>
<td></td>
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<tr>
<td>Availability</td>
<td>++</td>
<td>++</td>
<td>++</td>
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<td>+</td>
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<tr>
<td>Cost</td>
<td>+</td>
<td>+++</td>
<td>+</td>
<td>+</td>
<td></td>
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<tr>
<td>Technical difficulty</td>
<td>+ (needs standardization)</td>
<td>++</td>
<td>+++</td>
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<td>+</td>
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</tbody>
</table>

| Reference examples | ♂ < 7.26 kg/m² | ♂ < 55 cm²/m²† | ♂ < 176 cm³ | ♂ < 11 mm‡ | ♂ < 14.6 kg/m²# |
|                   | ♀ < 5.45 kg/m² | ♀ < 39 cm²/m²† | ♀ < 93 cm³ | ♀ < 10 mm‡ | ♀ < 11.4 kg/m²# |

Table 1: Methods available to assess muscle mass for sarcopenia: DEXA = Dual Energy X-ray Absorptiometry; CT = Computed Tomography; MRI = Magnetic Resonance Imagery; Ultrasound; and BIA = Bioelectrical Impedance. It is important to recognize that the "examples of references" are limited studies often only in one ethnic group and are given purely as examples. +++ indicates high (cost and difficulty) or more readily available while + indicates low (cost and difficulty) or less readily available. † = lumbar skeletal mass index; ‡ = musculo-tendon torque for gastrocnemius medialis; # = fat-free mass index without bone. [Morley et al., 2011]

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Appropriate Measurements</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loss of muscle mass</td>
<td>DEXA, MRI, CT, mean arm muscle circumference/calf circumference, Ultrasound, BIA, 13C-creatine dilution†</td>
</tr>
<tr>
<td>Loss of muscle strength (force)</td>
<td>Dynamometry (isometric), isotonic or isokinetic strength tests</td>
</tr>
<tr>
<td>Loss of muscle power (force x velocity)</td>
<td>Walking speed, walking distance, stair climbing</td>
</tr>
<tr>
<td>Loss of function (disability)</td>
<td>Instrumental activities of daily living, activities of daily living, Barthel index, functional index measure</td>
</tr>
</tbody>
</table>
| Frailty (increased risk of disability when stressed) | • CHS criteria: unintentionial weight loss, poor grip strength, reduced energy level, slow walking speed, low level of physical activity  
• SOF criteria: weight loss, inability to raise from a chair 5 times without using arms, reduced energy level  
• IANA criteria: weight loss, fatigue, resistance (climb 1 flight of stairs), aerobic (walk 1 block), illnesses (>5) |

Table 2: Methods available to assess different aspects of muscle or physical properties for sarcopenia. DEXA = Dual Energy X-ray Absorptiometry; CT = Computed Tomography; MRI = Magnetic Resonance Imagery; BIA = Bioelectrical Impedance; CHS = cardiovascular health study; SOF = study of osteoporotic fractures; IANA = international academy on nutrition and aging; † = other epidemiologically valid serum measurements of muscle mass are being explored. [Morley et al., 2011]
Current Etiological Concepts of Sarcopenia

As body physiology is regulated by a myriad of molecular factors (extracellular and intracellular) that weave together as different molecular cascades working in an interlacing fashion [Kwan, 2013a], one pathological condition may be a result of aberrant changes in one or more of these factors and/or their associated molecular cascade(s). In other words, one pathological condition may be resulted from more than one pathophysiological factor independently or synergistically (e.g. amyotrophic lateral sclerosis has several subtypes and each of which is associated with a different gene or protein). Similarly, one physiological factor may relate to several pathological conditions (e.g. inflammation is involved in both Alzheimer’s disease and Parkinson’s disease) [Kwan, 2013a].

To this date, sarcopenia is commonly recognized as a multi-etiological geriatric syndrome that is common, complex, and costly among older individuals [Morley & Cruz-Jentoft, 2012; Kwan, 2013a; Kwan, 2013b]. Such consideration of sarcopenia (as a syndrome) is mainly due to the incompletely understood interactions of disease and age on multiple systems through which a constellation of signs and symptoms is produced [Morley & Cruz-Jentoft, 2012; Kwan, 2013a; Kwan, 2013b]. This consideration mandates a multidimensional approach to understand its pathophysiology, to investigate its etiology in affected individuals, to improve its consensus definition, to define the molecular targets for intervention, and probably to successfully treat it [Morley & Cruz-Jentoft, 2012].

As a basis for development of therapeutic interventions, etiological studies of sarcopenia facilitate the understanding of this aging-associated condition which in turn contributes to its better management. To this day, many studies have a different description about the etiological factors of sarcopenia [Rosenberg, 2011; Morley et al., 2011; Tan et al., 2012; Garatachea & Lucía, 2013; Deschenes, 2004; Boirie, 2009; Saini et al., 2009; Lee et al., 2007; Muscaritoli et al., 2010; Rasmussen & Volpi, 2012]. For example, Rosenberg and his colleagues have proposed a schema for considering the causes of sarcopenia in 2011 as a list of interacting factors which are: 1) inactivity; 2) increased muscle fat; 3) insulin resistance; 4) loss of α-motor neurons; 5) decreased dieting intake (of protein?); 6) increased interleukin-6; 7) loss of estrogen or androgen; and 8) decreased growth hormone secretion [Rosenberg, 2011]. Interestingly, SSCWD has indicated in their publication that factors involved in the pathophysiology of sarcopenia are: 1) inactivity and bed rest; 2) collagen infiltration, fat infiltration and insulin resistance; 3) decreased motor units; 4) decreased calorie and protein intake; 5) cytokine excess; 6) decreased hormones; 7) decreased capillary blood flow; and 8) genetic, epigenetic and mitochondrial abnormalities [Morley et al., 2011].

Due to the similarity between these etiological descriptions for sarcopenia, the current etiological concept of sarcopenia is summarized as figure 2.
Figure 2: Current concept of etiology of sarcopenia. Blue line = positive regulators/reinforcements; red line = negative regulators/suppression; solid line = dash line. [Rosenberg, 2011; Morley et al., 2011; Tan et al., 2012; Garatachea & Lucia, 2013; Deschenes, 2004; Rasmussen & Volpi, 2012]

4 Physiological Pathways of Skeletal Muscle Motor Actions

As sarcopenia is a muscle tissue aging condition and is related to the locomotor capability, investigations into different parts of the motor unit (notably the lower motor neuron and its innervating muscle fibers) as well as its physiologically associated bodily parts are important. Prior to the discussion on the pathophysiology of sarcopenia, an introduction on the human motor physiological pathways is provided in this section.

In human, all voluntary and involuntary motor actions are regulated by various neural circuits orchestrating in the brain and spinal cord [Tortora & Derrickson, 2009b; Tortora & Derrickson, 2009d]. Regardless of the influence by the sensory and other functional pathways, all excitatory and inhibitory signals are ultimately converge on the motor neurons (also known as motoneurons) which then generate and propagate the efferent action potentials or nerve impulses along the motor pathways down to their effectors, the corresponding skeletal muscles (figure 3) [Tortora & Derrickson, 2009b; Tortora & Der-
Figure 3: An overview of the human motor pathways. 1) brain level; 2) brain stem + spinal cord level; 3) neuromuscular junction level; 4) excitation-contraction coupling; 5) sliding filament theory. Red line = motor; blue line = sensory; orange circle with black contour = lower motor neurons. [Tortora & Derrickson, 2009b; Tortora & Derrickson, 2009d; Tortora & Derrickson, 2009c; Haggard, 2008; Shokur et al., 2013; Jones et al., 2004c; Manuel & Zytnicki, 2011]

4.1 Voluntary Motor Actions

As directly related to the physical activities, voluntary motor actions are mainly regulated by a complex and delicate network of interactions among different neural circuits and the downstream muscle fibers. As a major control region for the execution of motor commands, the primary motor cortex (M1) receives mainly two broad classes of key inputs: 1) pre-supplementary motor area (preSMA); and 2) lateral part of the premotor cortex [Tortora & Derrickson, 2009d; Haggard, 2008]. The preSMA receives
inputs mainly from the basal ganglia and the prefrontal cortex, and conveys these inputs directly and indirectly (through supplementary motor area, SMA) to M1 [Haggard, 2008]. The lateral part of the premotor cortex receives inputs mainly from the intermediate-level representations in the parietal cortex, which in turn receive inputs from the early sensory cortices (e.g. primary somatosensory cortex, S1), and conveys these inputs directly to M1 [Haggard, 2008]. It is worth to note that the parietal-premotor pathway guides objects-oriented actions but also contributes to some aspects of voluntary behavior [Haggard, 2008].

Upon execution of the motor commands/programs, the upper motor neurons in M1 convey the motor signals down to the lower motor neurons in the brain stem and spinal cord (commonly seen in ventral horn) through direct contacts (direct motor pathways) and indirectly through motor centers in the brain stem (indirect motor pathways) [Tortora & Derrickson, 2009d; Haggard, 2008]. Direct motor pathways (pyramidal motor pathway) include: 1) lateral corticospinal tract (approximately 90% M1-to-spinal-cord axons, decussate at medulla), which controls skeletal muscles in distal parts of the contralateral limbs by spinal nerves; 2) anterior corticospinal tract (approximately 10% M1-to-spinal-cord axons, do not decussate at medulla), which controls skeletal muscles in proximal parts of the limbs and trunk on the contralateral side by spinal nerves; and 3) corticobulbar tract (M1-to-brain-stem axons, with and without decussations), which controls skeletal muscles of the head and neck by cranial nerves [Tortora & Derrickson, 2009d]. Indirect motor pathways (extra-pyramidal motor pathway) include: 1) rubrospinal tract (receives inputs from the cerebral cortex and cerebellum), which controls skeletal muscles in distal parts of the contralateral upper limbs by red nucleus; 2) vestibulospinal tract (receives inputs from the inner ear), which controls skeletal muscles in proximal parts of the limbs and trunk on the ipsilateral side by vestibular nucleus; 3) tectospinal tract, which controls skeletal muscles in the head, eyes and trunk on the contralateral side by superior colliculus; and 4) medial and lateral reticulospinal tract, which controls skeletal muscles in proximal parts of the limbs and trunk on the ipsilateral side by reticular formation [Tortora & Derrickson, 2009d].

Additionally, the conveyance of motor signals from the upper motor neurons is influenced by the neurons in the basal ganglia and cerebellum [Tortora & Derrickson, 2009d]. As part of the inputs to the M1 upper motor neurons, basal ganglia play important roles in: 1) initiation and termination of movements; 2) suppression of unwanted movements; 3) regulation of muscle tone; and 4) regulation of sensory, limbic, cognitive and linguistic functions [Tortora & Derrickson, 2009d]. On the other hand, cerebellum is important to both learning and performing rapid, coordinated, highly skilled movements by comparing the motor command signals (intentions for movement) with the sensory information (actual movement performed) and sending out corrective feedbacks to the upper motor neurons when necessary [Tortora & Derrickson, 2009d].

### 4.2 Involuntary Skeletal Muscle Related Reflexes

As part of the protective mechanisms, involuntary reflexes are fast, automatic, unplanned sequence of actions that occurs in response to a particular stimulus [Tortora & Derrickson, 2009c]. In regard to the skeletal muscles, somatic reflexes will be briefly introduced [Tortora & Derrickson, 2009c]. Different from voluntary motor actions, the motor signals in these reflexes do not derive from M1 [Tortora & Derrickson, 2009c].

One of the most representative somatic reflexes is the withdrawal reflex, which moves the stimulated body part away from the stimulus by contracting the corresponding skeletal muscles [Tortora &
In this reflex, the motor signals are derived from the corresponding sensory neurons which are excited upon stimulation of their associated sensory receptors [Tortora & Derrickson, 2009c]. These excited sensory neurons then generate nerve impulses propagating toward the integrating center (brain stem and/or spinal cord) where these nerve impulses activate the corresponding interneurons which in turn activate the corresponding lower motor neurons for muscle contraction [Tortora & Derrickson, 2009c]. In addition to the withdrawal reflex, the crossed extensor reflex also works in the same way but with an additional effect on the contralateral antagonistic skeletal muscles (i.e. ipsilateral flexor plus contralateral extensor, or ipsilateral extensor plus contralateral flexor) due to the pattern of interneuron-to-motor-neuron connections [Tortora & Derrickson, 2009c].

Another representative somatic reflex is the tendon reflex, which relieves excess muscle tensions imposed on the tendons by relaxing the connecting skeletal muscles while contracting their antagonistic muscles in the same body part [Tortora & Derrickson, 2009c]. Although working similarly to the aforementioned reflexes, tendon reflex uses Golgi tendon organs as the sensory receptors, and the reflex arc/pathway controlling muscle relaxation uses inhibitory interneurons for the relaxing muscles while the one controlling antagonistic muscle contraction uses excitatory interneurons for the contracting muscles [Tortora & Derrickson, 2009c; Keynes et al., 2011c]. Similar to this reflex is the stretch reflex (e.g. knee jerk), which relieves stretching of the skeletal muscles by contracting them while relaxing their antagonistic muscles in the same body part [Tortora & Derrickson, 2009c]. Instead of the Golgi tendon organs, muscle spindles are used as the sensory receptors [Tortora & Derrickson, 2009c; Keynes et al., 2011c]. In this reflex, contraction of the stretched skeletal muscle is directly regulated by the sensory neurons [Tortora & Derrickson, 2009c]. In other words, the lower motor neurons are excited/activated directly by the sensory neurons in the integrating center [Tortora & Derrickson, 2009c]. However, the reflex arc/pathway controlling muscle relaxation still uses inhibitory interneurons for the relaxing muscles [Tortora & Derrickson, 2009c].

### 4.3 Final Common Pathway

Regardless of whether the motor action is a voluntary locomotion or involuntary reflex, all excitatory motor signals conveyed from the upper motor neurons and/or the local circuit interneurons converge on the lower motor neurons (also known as somatic motor neurons) [Tortora & Derrickson, 2009a; Tortora & Derrickson, 2009d; Manuel & Zytnicki, 2011]. As the lower motor neurons innervate (form chemical synapse with) and control directly the skeletal muscles, the pathway connecting the lower motor neuron and its associated skeletal muscle fibers is coined as the final common pathway (the pathway directly associated with the effector, skeletal muscle fibers in this case) [Manini et al., 2012; Tortora & Derrickson, 2009b; Tortora & Derrickson, 2009d; Manuel & Zytnicki, 2011].

In this final common pathway (activation/behavior of motor unit), the lower motor neuron is excited/activated by the neurotransmitters released from the upstream neurons [Tortora & Derrickson, 2009b; Tortora & Derrickson, 2009d; Tortora & Derrickson, 2009c]. This excited lower motor neuron then generates a nerve action potential propagating toward its axon terminals which innervate a particular population of muscle fibers in a particular muscle [Tortora & Derrickson, 2009a; Tortora & Derrickson, 2009b; Tortora & Derrickson, 2009c; Lieber, 1992b; Keynes et al., 2011c; Jones et al., 2004c]. Upon arrival at the axon terminal, the nerve action potential activates/opens the voltage-sensitive calcium (Ca^{2+}) channels which cause the influx of Ca^{2+} ions into the axonal terminal leading to the fusion of synaptic vesicles with the presynaptic axonal membrane and thus the release of neurotransmitters into the synaptic
cleft (an approximately 50nm wide gap separating the axonal terminal from the muscle fiber) [Tortora & Derrickson, 2009a; Tortora & Derrickson, 2009b; Keynes et al., 2011a; Jones et al., 2004b]. It is worth noting that such neurotransmitter release can be depressed by high magnesium concentrations [Jones et al., 2004b].

The chemical synapse formed by the lower motor neuron with the muscle fiber is known as the **neuromuscular junction (NMJ)** in which the presynaptic axon terminal is called the synaptic bouton/end bulb while the postsynaptic terminal on the muscle fiber plasma membrane (sarcolemma; Greek: lemma means “sheath”) is called the motor end plate [Tortora & Derrickson, 2009a; Lieber, 1992a; Keynes et al., 2011a; Keynes et al., 2011b; Jones et al., 2004a]. In skeletal muscles, NMJs are usually cholinergic in which the presynaptic neurotransmitters are **acetylcholines (ACh)** while the postsynaptic receptors are **acetylcholine receptors (AChR)** [Tortora & Derrickson, 2009a; Tortora & Derrickson, 2009c; Lieber, 1992a; Keynes et al., 2011a; Jones et al., 2004b].

Binding of ACh (by diffusion in the synaptic cleft) to the AChR (at the crests of the motor end plate invaginations) causes a depolarization of the sarcolemma [Tortora & Derrickson, 2009a; Jones et al., 2004b]. If the depolarization is sufficiently large (depends on the number of activated/opened AChR), an action potential will be generated and propagated along the sarcolemma (outward in all directions) and into the **transverse tubular system** (also known as T tubule system) of the postsynaptic muscle fiber [Tortora & Derrickson, 2009a; Lieber, 1992b; Jones et al., 2004b]. Once the action potential reached the transverse tubular system, the excitation-contraction coupling process (the conversion of neural signals for muscle activation into muscle contraction) initiates: The propagating muscle action potential activates the voltage-sensitive **dihydropyridine (DHP) receptors (DHPR)** on the membrane of the transverse tubule, which (DHPRs) in turn activate/open their coupled **ryanodine receptors (RyR; Ca\(^{2+}\)-release channels) on the sarcoplasmic reticulum (SR; an intracellular Ca\(^{2+}\) store) leading to the release of Ca\(^{2+}\) ions from the SR into the sarcoplasm [Manini et al., 2012; Tortora & Derrickson, 2009a; Keynes et al., 2011c]. In addition to this voltage-induced Ca\(^{2+}\) release (VICR) mechanism, the skeletal muscles have also adapted a Ca\(^{2+}\)-induced Ca\(^{2+}\) release (CICR) mechanism which predominates in cardiac muscle [Manini et al., 2012; Endo, 2009]. In this skeletal muscle version of CICR, Ca\(^{2+}\) may activate/open RyRs and thus may amplify the effects of VICR [Manini et al., 2012; Endo, 2009].

The released Ca\(^{2+}\) then diffuses to the thin filaments (composed of actin, tropomyosin and troponin in a molecular ratio of 7:1:1, respectively) where it binds (to the C subunit) and changes the shape of **troponin** (a globular protein associates with a fibrous protein tropomyosin which covers the myosin head binding site on the actin monomers) leading to the exposure of binding sites for myosins (constituents of the thick filaments) by moving the **tropomyosin**, and this process ultimately results in **cross-bridge cycling** (i.e. mechanisms mentioned in the sliding-filament theory) [Tortora & Derrickson, 2009a; Lieber, 1992b; Keynes et al., 2011b; Jones et al., 2004a].

Once the motor unit returned to the resting state, the AChs in the synaptic cleft are broken down (into choline and acetic acid) by acetylcholinesterases while the sarcoplasmic Ca\(^{2+}\) ions are actively transported back (2 Ca\(^{2+}\) ions at the expense of 1 ATP hydrolysis) to the SR by the Ca\(^{2+}\)-activated ATPases (sarcoplasmic/endoplasmic reticulum Ca\(^{2+}\) ATPase, SERCA), facilitated by the store-operated Ca\(^{2+}\) channels (SOCC) and sequestered by calsequestrin (has an approximately 1:45 binding ratio for Ca\(^{2+}\), and enhances the capability of Ca\(^{2+}\) reuptake into the SR) [Manini et al., 2012; Tortora & Derrickson, 2009a; Keynes et al., 2011c; Keynes et al., 2011a].
Diversity of Motor Units

To this point, it is important to note that muscular tissues have a great diversity as reflected by the 3 commonly seen types (skeletal, cardiac and smooth) [Tortora & Derrickson, 2009a]. Although all these 3 types of muscles manifested aging-associated reduction in contractile performance, it seems that only the striated muscles (namely, skeletal and cardiac) would manifest the aging-associated reduction in muscle mass (smooth muscles manifested an aging-associated increase in cell mass) [Korhonen et al., 2006; Lin et al., 2008; Bitar & Patil, 2004; Jones & Ravid, 2004]. As is more extensively studied and is more relevant to the aforementioned consensus definitions of sarcopenia, skeletal muscles will remain as the focus in the following discussions while cardiac and smooth muscles will not be discussed further.

While similar enough to be recognized as the same muscle type (skeletal muscle) but different enough to be further divided into subclasses, skeletal muscles in the early 1800s have been found heterogeneous according to their gross appearance which color ranged from pale white to deep red [Lieber, 1992b]. Due to the advancement in experimental techniques, more physiological characteristics have been recognized despite many of them do not correlate with one another, for example the speed of contraction and the type of metabolism [Lieber, 1992b; Manuel & Zytnicki, 2011]. More recently, skeletal muscles are classified according to the type of composing muscle fibers which anatomists identified as type I and type II while physiologists identified as “slow twitch” and “fast twitch”, respectively [Lieber, 1992b]. To this day, these skeletal muscle fibers are identified/characterized by mainly but not limited to 3 physiological features: 1) type of metabolism (oxidative and/or glycolytic); 2) activity of myosin ATPases; and 3) presence of the myosin heavy chain (MHC) isoforms [Korhonen et al., 2006; Lieber, 1992b; Jones et al., 2004c; Manuel & Zytnicki, 2011; Verdijk et al., 2007]. Since the classification by Brooke and Kaiser in 1970, skeletal muscle fibers are now commonly recognized as three main types (table 3): type I, type IIA and type IIX (formerly known as type IIB; as the human MHC 2b is not homologous with the rodent MHC 2b but the rodent MHC 2x, the nomenclature “type IIX” is adopted in more recent literatures) [Korhonen et al., 2006; Lieber, 1992b; Jones et al., 2004c; Manuel & Zytnicki, 2011; Tan et al., 2012].
<table>
<thead>
<tr>
<th>Structural Characteristics</th>
<th>Type I fiber</th>
<th>Type IIA fiber</th>
<th>Type IIX fiber</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary MHC isoform</td>
<td>I</td>
<td>Iia</td>
<td>Iix</td>
</tr>
<tr>
<td>Myoglobin content</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Creatine kinase content</td>
<td>+</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>Glycogen stores</td>
<td>+</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>Mitochondria</td>
<td>+++</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Capillaries</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Color</td>
<td>Red</td>
<td>Red-pink</td>
<td>White (pale)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Functional Characteristics</th>
<th>Type I fiber</th>
<th>Type IIA fiber</th>
<th>Type IIX fiber</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATP generation capacity</td>
<td>+++</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Respiration</td>
<td>Oxidative (Aerobic)</td>
<td>Oxidative (Aerobic) and Glycolytic (Anaerobic)</td>
<td>Glycolytic (Anaerobic)</td>
</tr>
<tr>
<td>Rate of ATP hydrolysis by myosin ATPase</td>
<td>+</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Contraction velocity</td>
<td>+</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>Fatigue resistance</td>
<td>+++</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Order of recruitment</td>
<td>First</td>
<td>Second</td>
<td>Third</td>
</tr>
<tr>
<td>Abundant location</td>
<td>Postural muscles</td>
<td>Lower limb muscles</td>
<td>Upper limb muscles</td>
</tr>
<tr>
<td>Primary functions</td>
<td>Aerobic endurance activities (e.g. postural maintenance)</td>
<td>Walking and sprinting</td>
<td>Rapid and intense movements of short duration</td>
</tr>
</tbody>
</table>

Table 3: Comparison between the major muscle fiber types. MHC = myosin heavy chain; ATP = adenosine triphosphate. +++ indicates high or fast while + indicates low or slow. [Tortora & Derrickson, 2009a; Korhonen et al., 2006; Doria et al., 2012; Lieber, 1992b; Jones et al., 2004c]

It is important to note that: 1) the **activity of myosin ATPase** is directly proportional to the **maximum shortening velocity** of the corresponding muscle; 2) different myosin isoforms are associated with different levels of ATP consumption in the order of type I < type IIA < type IIX < type IIB; 3) the **faster myosins** tend to be more stable at alkaline pH and labile in acidic pH while the **slower myosins** tend to be the other way round; 3) unlike actin which seems to be quite uniform across muscle fibers, myosin (in particular the MHC) isoforms are frequently differentially expressed depending on the demand/activity of the corresponding muscle fiber; and 4) more importantly, **hybrid fibers** containing different myofibrillar protein isoforms (i.e. type I/IIA and type IIA/X) are quite frequent [Manini et al., 2012; Korhonen et al., 2006; Jones et al., 2004c]. A brief summary of the commonly used biomarkers for muscle fiber identification is provided in table 4.
Table 4: Commonly used biomarkers for histochemical analysis of skeletal muscle fibers. * = only present in rodents; SDH = succinate dehydrogenase; α-GPDH = α-glycerol phosphate dehydrogenase; NADH-TR = NADH tetrazolium reductase. +++ indicates intensely stained while + indicates lightly stained. [Lieber, 1992b; Jones et al., 2004c]

As part of the motor unit, the lower motor neurons also manifested a considerable diversity as the skeletal muscle fibers they innervate. Since their discovery in the late 19th century, motor neurons have been eventually recognized as a very heterogeneous class of neurons as they differ by their function (the muscle fibers they innervate), their intrinsic electrical properties, the pathways that control them, their molecular properties, and their susceptibility to degeneration [Manuel & Zytnicki, 2011]. To this day, there are 3 main classes of lower motor neurons have been identified (table 5): 1) α-motor neuron; 2) γ-motor neuron; and 3) β-motor neuron [Tortora & Derrickson, 2009d; Keynes et al., 2011c; Manuel & Zytnicki, 2011].

Table 5: Comparison between different classes of motor neurons. FF = fast fatigable; FR = fast fatigue-resistant; S = slow; * = in terms of soma size, axon diameter and number of axonal branches. [Tortora & Derrickson, 2009d; Keynes et al., 2011c; Jones et al., 2004c; Manuel & Zytnicki, 2011]
It is interesting to note that the names of the α-motor neuron subtypes are indeed the names of the motor units which provide information about the speed of contraction and fatigability [Lieber, 1992b; Jones et al., 2004c; Manuel & Zytnicki, 2011]. A brief summary of the properties of different motor units is provided in table 6.

<table>
<thead>
<tr>
<th>Technique</th>
<th>Description</th>
<th>Motor unit type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Electrophysiology (intracellular microelectrodes) and histochemistry</td>
<td>Type of motor neuron</td>
<td>S</td>
</tr>
<tr>
<td></td>
<td>Type of muscle fibers</td>
<td>I</td>
</tr>
<tr>
<td></td>
<td>Number of innervated muscle fibers</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>Size of motor neuron</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>Contractile speed</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>Fatigue resistance</td>
<td>+++</td>
</tr>
</tbody>
</table>

Table 6: Comparison of various properties between different motor units, and the techniques used in these assessments. +++ indicates many/fast/high while + indicates few/slow/low. [Lieber, 1992b; Jones et al., 2004c; Manuel & Zytnicki, 2011]

Finally, it should be aware that although the faster motor units tend to include more muscle fibers, there could be a quite remarkable difference between different body positions. For example, muscles controlling eye movements may have 10 to 20 muscle fibers per motor unit while biceps brachii (arm) and gastrocnemius (calf) may have 2000-3000 muscle fibers per motor unit [Tortora & Derrickson, 2009a; Jones et al., 2004c]. In regard to the motor unit recruitment, it is well known that the smaller diameter neurons being recruited first due to a biophysical basis that the smaller surface area with fewer parallel ion channels would create a higher overall resistance and ultimately causing a greater change in membrane potential based on Ohm’s Law [Manini et al., 2012]. Interestingly, it may be explained by larger/faster motor neurons tend to have a relatively sparse afferent innervation and consequently receive relatively less excitatory input from spindles leading to a slower recruitment or a higher recruitment order (table 3) [Jones et al., 2004c].

To this point, it is reasonable to expect that any pathophysiological changes occurred within these motor pathways would affect body locomotor capabilities.

6 Dynapenia, the Aging-Associated Decline in Muscle Strength

As one of the major factors which impairment could lead to physical disabilities, muscle (or more appropriate: neuromuscular) strength is related to sarcopenia either as a clinical consequence or as one of the considerations in the common consensus definitions of sarcopenia [Manini et al., 2012]. In human, both sexes manifested an aging-associated sequential loss of muscle power, muscle strength and muscle mass (both upper and lower limbs) beginning since the age of 40 years, 30 years and 24 years, respectively [Deschenes, 2004]. While the aging-associated loss of muscle power is more rapid than the loss of muscle strength, the strength in turn is more rapid than the loss of muscle mass [Garatachea & Lucía,
Thus, it is worth looking at the etiology of dynapenia prior to the aging-associated loss of muscle mass.

As mentioned previously, voluntary motor actions are regulated by the complex motor pathways ultimately connecting cortices of the brain and the effector muscles. Due to the effect of aging, anatomical and functional changes occur in the frontal cortex, white matter fiber tracts, dopaminergic system and all the systems that contribute to motor neuron excitation. Together with the aging-associated slowing of peripheral nerves, degradation of the NMJ and changes in the muscle contractile properties, aging results in the dysfunction of muscle and possibly also the progressive muscle atrophy that characterizes sarcopenia. In summary, the etiology of dynapenia may associate with but not limited to the following [Bhanushali et al., 2012]:

1) Motivation and dopaminergic signals
2) Generation of the motor program
3) Sensory inputs and their integration with the motor program
4) Execution of the motor program through the spinal cord and associated nerves
5) Muscular factors and excitation-contraction uncoupling

### 6.1 Motivation and Dopaminergic Signals

As part of the human motivation system, dopaminergic system manifested aging-associated reduction in levels of dopamine, presynaptic dopamine transporters and postsynaptic dopamine receptors [Bhanushali et al., 2012; Volkow et al., 1998]. This down regulation of the dopamine signaling results in attenuated reward signals and/or increased cost signals and altered dynamics upon which decision making is based, thus the motivation for movement is decreased [Bhanushali et al., 2012]. Additionally, the dopamine transporters decline after the fifth decade of life also contributes to slow motor performance, deficits in response selection and motor adjustments [Bhanushali et al., 2012]. For example, lower striatal dopamine transporter levels are associated with reductions in speed, cadence, single and double support durations, thereby contributing to impaired gait [Bhanushali et al., 2012]. Further, presynaptic dopaminergic denervation in the anteroventral striatum contributed 20-25% of the variability in antero-posterior body sway magnitude [Bhanushali et al., 2012]. In addition to the dopaminergic system, other neurotransmission systems including serotonergic [Bigham & Lidow, 1995], cholinergic [Schliebs & Arendt, 2011], adrenergic [Bigham & Lidow, 1995], GABAergic [Mora et al., 2008] and glutamatergic [Segovia et al., 2001] systems are also impaired with aging and this is responsible for at least some age-related behavioural abnormalities [Manini et al., 2012].

### 6.2 Generation of the Motor Program

Prefrontal area is a brain region regulates: 1) movement preparation and execution; 2) switching between complex coordinated movements; and 3) direction and extent of movement [Bhanushali et al., 2012]. Frontal area is a brain region regulates automaticity for certain movements [Bhanushali et al., 2012]. According to the MRI and diffusion tensor imaging (DTI) studies, both of these areas have manifested the most severe aging-associated decline in volume (both grey and white matter) [Bhanushali et al., 2012]. Additionally, aging substantially declines connectivity of the prefrontal structures while selectively impairs the efficiency of the function of frontal networks [Bhanushali et al., 2012]. Further, aging also impairs cortical plasticity which may influence new motor learning [Manini et al., 2012; Bhanushali et al., 2012]. One of the evidences of such impairment is the negative correlation between the increase in am-
plitude of motor-evoked potentials by paired associative stimulation and the advancing age [Manini et al., 2012; Fathi et al., 2010]. In addition to the cortical plasticity, cortical excitability is also impaired with aging as evidenced by the more intracortical inhibition while intracortical facilitation is less in the older adults (50 to 60 years of age) compared with younger adults (20 years of age) [Manini et al., 2012].

Interestingly, albeit the reduction in neurotrophic factors/molecules (e.g. BDNF) [Manini et al., 2012; Hayashi et al., 1997], M1 (the major region of motor program generation) does not appear to have actual decrease in cortical neurons as suggested by animal studies despite human studies provided a different picture [Manini et al., 2012; Peters, 2002; Tigges et al., 1990; Peinado et al., 1997]. However, the nearby premotor cortex has manifested a 43% volume reduction in the neuronal cell body size in the older adults (>65 years of age) compared with younger adults (<45 years of age) [Manini et al., 2012]. Additionally, several areas near the precentral gyrus showed marked atrophy and cortical thinning has been observed before middle age [Manini et al., 2012].

Aging also disrupts the integrity of white matter and the marked loss of the myelinated nerve fibers (primarily the thinner fibers) with age may explain some of the functional decline seen in older adults [Manini et al., 2012; Marner et al., 2003]. One of the commonly seen features affected by aging, velocity of movement has been observed to decrease for 30%-70% in older adults compared with younger adults [Bhanushali et al., 2012]. This may be partly explained by the aging effect on white matters, which associated with the speed and coordination of movement, and balance [Bhanushali et al., 2012]. For example, finger movement speed was associated with the integrity of white matter fiber tracts in the cerebellar hemispheric fiber bundles, internal and external capsules [Bhanushali et al., 2012].

In addition to the velocity of movement, quality of the motor programs is also affected by aging [Bhanushali et al., 2012]. This is reflected by the aging-associated increase in neuromuscular noises in older adults [Bhanushali et al., 2012]. Such an increase may shorten the primary movement while increasing the role of corrective sub-movements to improve motion precision in older adults [Bhanushali et al., 2012].

### 6.3 Sensory Inputs and Their Integration with the Motor Program

Both the motor and somatosensory regions of the brain are subjected to an increased vulnerability to aging-associated atrophy [Bhanushali et al., 2012]. As a result of the sensory decline, in addition to increased reliability on visual feedback for motor performance, lower limb proprioceptive acuity also decreases while this shows a positive correlation with falls in previous 12 months [Bhanushali et al., 2012]. On the muscle side, muscle spindles have manifested an aging-associated reduction in density with fewer intrafusal fibers and smaller spindle diameter [Bhanushali et al., 2012]. Additionally, cutaneous and joint mechanoreceptors also show reduced number and mean density of receptors with aging [Bhanushali et al., 2012].

Slower reaction times and worse recognition of stimuli are usually associated with old adults [Bhanushali et al., 2012]. This aging-associated slowing in reaction time maybe related to attention as when distracted, older people tend to devote their exclusive attention to one stimulus while ignoring another stimulus more completely than younger people [Bhanushali et al., 2012]. Interestingly, when the older adults tested for their upright stance during a concurrent ‘n-back’ working memory task (with vision and a fixed support surface), their postural sway increased when their attention was divided [Bhanushali et al., 2012].
Finally, subcortical structures important for motor performance and coordination including cerebellum and the caudate nucleus manifested aging-accelerated decrease in volume [Bhanushali et al., 2012].

6.4 Execution of the Motor Program through the Spinal Cord and Associated Nerves

Similar to the cortical excitability, aging also impairs spinal excitability by decreasing both the maximum soleus H-reflex (*H-max*, a measure of global spinal excitability) and maximum soleus M-wave (*M-max*, also known as the compound muscle action potential) with the H-max being more pronounced [Manini et al., 2012]. Additionally, heteronymous facilitation and oligosynaptic reflexes are also decreased with aging [Manini et al., 2012].

As the final common pathway, motor units in the older adults (63-81 years of age) are approximately one half of those in the younger adults (20-40 years of age) [Manini et al., 2012; Bhanushali et al., 2012]. This reduction of motor neurons is partially compensated by increasing the size of the motor units (by increased sprouting) and thus results in progressively less but larger motor units [Manini et al., 2012; Deschenes, 2004; Bhanushali et al., 2012]. As the pattern of motor unit recruitment changes with aging in which the recruitment in older adults becomes more transient, a fluctuation in force production is observed in the older adults [Bhanushali et al., 2012]. Together with the more variable rate of motor unit discharges seen in older adults, the resulting greater fluctuations in force production impair the ability of the older adults to move their limbs accurately to a desired target as well as to maintain steady forces [Manini et al., 2012; Bhanushali et al., 2012]. It is interesting to note that there is an aging-associated decline in maximal and mean motor unit discharge frequency (firing rate) which limits the performance of fast voluntary contractions in addition to the slowing of muscle contractile properties [Manini et al., 2012; Bhanushali et al., 2012]. Additionally, the motor unit doublet discharges is lower in older adults [Manini et al., 2012].

Further down the nerves, both sensory afferent axons and efferent motor axons are affected by aging while the sensory axons are more affected [Bhanushali et al., 2012]. One of the main aging effects on nerve fibers is the shortening of the total length of myelinated nerve fibers [Manini et al., 2012; Marner et al., 2003]. Additionally, it has been observed that the peripheral nerve has a slow linear decline in the conduction velocity beginning after 30 to 40 years of age (by 60 to 80 years of age, the difference is normally less than 10 m/s) [Bhanushali et al., 2012]. This decline in conduction velocity is at least in part due to the drop outs of the largest axonal fibers as well as the reduced myelinations [Bhanushali et al., 2012]. Additionally, the amplitude of the compound muscle action potentials and the sensory nerve action potentials also declines progressively with age [Bhanushali et al., 2012].

Due to the aging associated loss of synaptic input at the NMJs, the remain-intacted axons at these NMJs respond by sprouting to reinnervate the surrounding denervated motor end plates [Bhanushali et al., 2012]. During this reinnervation process, perisynaptic Schwann cells (discuss in later sections) at the NMJs play an essential role in guiding the axonal sprouts to their target motor end plates [Bhanushali et al., 2012]. However, the capacity for axonal and motor endplate sprouting is relatively limited with aging [Bhanushali et al., 2012]. Additionally, aging also associated with other physiological and morphological changes at the NMJ including but not limited to: 1) increased quantal contents; 2) widening of synaptic clefts; 3) degeneration of junctional folds at the motor end plates; 4) increased neural cell adhesion molecule (NCAM) expression; 5) increased number of perijunctional AChR; and 6) increased smaller conglomerates of AChR [Manini et al., 2012; Deschenes, 2004; Bhanushali et al., 2012].
6.5 Muscular Factors and Excitation-Contraction Uncoupling

On the muscle side, both actin (of thin filament) and myosin (of thick filament) are the predominant proteins in the skeletal muscles. Similarly, aging-associated loss of these proteins is observed [Manini et al., 2012]. Interestingly, an aging-associated decline in the myosin vs actin ratio in the rat muscle semimembranosus has been observed but only in very old animals and not in muscle soleus or old animals [Manini et al., 2012]. Additionally, studies using electron paramagnetic resonance demonstrated that aging has reduced the number of strongly bound crossbridges in maximally-activated aged-rat muscle fibers [Manini et al., 2012]. Proteomic studies suggested that increased age is related to the reduced expression of muscle thin filament proteins (namely, tropomyosin and troponin) and increased post-translational modifications (e.g. nitration) through which the muscle quality is impaired [Manini et al., 2012]. Finally, the role of cytoskeletal proteins in muscle quality remains controversial as increased specific force in mice muscle has been observed after desmin knocking out despite other knockout animal studies suggested that loss of desmin is associated with reduced muscle quality [Manini et al., 2012; Balogh et al., 2003].

Another worth mentioning aging-associated features on the muscle side is the excitation-contraction uncoupling as manifested by the reduced number and expression of DHPRs (particularly the α-1s subunit), mitsugumin 29 (MG29; associated with store-operated Ca$^{2+}$ entry) and junctophilin 45 (JP45; junctional face membrane protein of the SR) with aging [Kwan, 2013a; Manini et al., 2012; Bhanushali et al., 2012; Delbono et al., 1995]. Such uncoupling results in altered protein-protein interaction and disrupted VICR thus leading to deficits in Ca$^{2+}$ supply to the contractile proteins and ultimately results in a reduced contractile force of the skeletal muscle (affecting both muscle power and strength) [Kwan, 2013a; Manini et al., 2012; Bhanushali et al., 2012; Delbono et al., 1995]. Additionally, older muscles manifest a reduced RyR-FKBP binding which associated with a reduced muscle quality and impaired Ca$^{2+}$ release [Manini et al., 2012]. Further, aging may impair SR Ca$^{2+}$ release in a DHPR-independent manner [Manini et al., 2012].

In regard to the muscle filaments, aging-associated structural changes of myosin further contribute to the contractile force reduction by changing the kinetics of the cross-bridge cycle [Bhanushali et al., 2012]. Finally, it is worth noting that: 1) there is a significant increase in the time to peak tension and time to relaxation following evoked twitches of the skeletal muscles in the older adults; and 2) maximal rate of torque development during fast contractions is lower in the older adults [Bhanushali et al., 2012]. As a consequence, the slowing of muscle contraction, peripheral nerve conduction velocity and rate of torque development reduces the capacity for rapid force production in physical activities including protective reflexes [Bhanushali et al., 2012]. Interestingly, dynapenia is also associated with the aging-associated changes in the coactivation degree of antagonist muscles [Deschenes, 2004].

7 Sarcopenia, the Aging-Associated Decline in Muscle Mass

Aging is a symplectic (“sym”: together; “plektos”: braid) natural process of matters and contributes significantly to various physiological declines as seen in previous sections about dynapenia. As sarcopenia is associated with muscle mass decline, pathophysiology underlying the aged muscle fiber atrophy and even cell death will be the focus of this section.
Aged subjects are commonly associated with a **reduction in the number of both type I and type II skeletal muscle fibers** and a **more prominent atrophy of the type II fibers** (more prominent in type IIX fibers than type IIA fibers) [Kwan, 2013a; Garatachea & Lucía, 2013; Deschenes, 2004; Sato et al., 1984; Lexell et al., 1988]. Although the underlying mechanisms leading to such condition are likely numerous, the ultimate consequence will be the altered trophic balance within the skeletal muscle fibers. Unlike single-nucleated cells (e.g., neurons), skeletal muscle fibers are multinucleated cells (syncytium) in which apoptosis of one single nucleus (of the muscle fiber) may not necessarily result in cell death [Dupont-Versteegden, 2006; Daubenmire, 1936; Dirks & Leeuwenburgh, 2005]. Thus, it is reasonable to assume that muscle fibers may have a greater potential to resist apoptotic cell death than neurons (as being multinuclei). This phenomenon is related to the concept of nuclear domains within the skeletal muscle fibers (initially proposed by Hall and Ralston in 1989) with a premise that each myonucleus is responsible for the maintenance of a particular given area within the sarcoplasm of the muscle fiber [Deschenes, 2004; Dupont-Versteegden, 2006; Hall & Ralston, 1989]. This concept suggests that due to a constant **sarcoplasm vs nuclei ratio** within the muscle fiber, there would be more myonuclei added to the corresponding muscle fibers during hypertrophy (presumably new nuclear domains have been added to the enlarged muscle fiber) while the number of myonuclei would be decreased during atrophy (e.g., in the case of unloading/disuse) [Deschenes, 2004]. As studies suggested that the atrophy detected among the aged muscle fibers is also reflected by a decreased number of myonuclei, the decreased cross-sectional areas (CSA) noted in the senescent/aged muscle fibers may be the consequence of a decrease of nuclear domain number but not its size [Deschenes, 2004].

As the loss of myonuclei by apoptosis (a highly regulated programmed cell death; figure 4) occurs during muscle fiber loss and atrophy [Dupont-Versteegden, 2006; Dirks & Leeuwenburgh, 2005; Glantz et al., 2006; Dirks & Leeuwenburgh, 2002], signaling pathways that influence/interact with apoptosis would be potential targets of therapeutic interventions for sarcopenia. For more details regarding this degradation pathway, please refer to the following suggested review articles:

Figure 4: Mitochondrial, ER (endoplasmic reticulum) stress, and death-receptor pathways each converge on caspase-3 activation. The mitochondrial pathway can be activated by pro-apoptotic stimuli (e.g. glutamate, free radicals, calcium). Upstream, activation is controlled by interactions of bcl-2 family gene products in the mitochondrial membrane, including pro-apoptotic (e.g. BAX, BID) and anti-apoptotic (e.g. Bcl-2, Bcl-XL) proteins. Bcl-2 family protein levels are controlled in part by potent regulatory genes including p53 and par-4. Higher BAX/Bcl-2 and BAX/Bcl-XL ratios promote mitochondrial cytochrome c release and vice versa. Once released, cytochrome c binds with Apaf-1 and procaspase-9 to form the apoptosome complex. This, in turn, activates caspase-3 and other downstream caspases. Inhibitor-of-apoptosis (IAP) proteins serve as downstream inhibitors of caspase-9 and caspase-3. IAPs are themselves inhibited by the mitochondrial factor Smac/Diablo.

In the ER stress pathway, procaspase-12 is cleaved to form activated caspase-12 that can activate caspase-9 and caspase-3. In the death-receptor pathway, Fas ligand (FasL) binds the TNF death-receptor and causes recruitment of Fas-associated death domain protein (FADD). FADD recruits procaspase-8 which is autocatalytically cleaved and activates cytoplasmic caspase-3. FADD also activates JNK which can activate nuclear caspase-3 and caspase-7. The death-receptor pathway interacts with the mitochondrial pathway via pro-apoptotic Bid protein. Downstream, activated caspase-3 begins proteolytic cleavage of key structural and functional proteins, including DFF (DNA fragmentation factor) and PARP (poly(ADP-ribose) polymerase) in the nucleus, contributing to DNA fragmentation. Reprinted with permission from Glantz and colleagues 2006. [Glantz et al., 2006]
Among these signaling pathways, mTOR is the most representative due not only to its inhibitory effects on apoptosis but also its importance in cell survival as well as other cellular events that are vital to normal cell/tissue functions [Kwan & Tse, 2013; Tse & Kwan, 2013; Maiese et al., 2013].

7.1 Satellite Cells, the Myogenic Precursors and Tissue Regeneration

Tissue growth/regeneration through stem cells is an important mechanism for maintaining proper tissue functions by tissue growth/replacement/repair. In skeletal muscles, satellite cells (also known as myoblasts; discovered by Mauro in 1961) are situated beneath the basal lamina surrounding each muscle fiber and are served as myogenic stem cells for muscle growth/replacement/repair [Lee et al., 2007; Collins et al., 2005]. The entire process of muscle repair can be divided into 4 phases after tissue damage: 1) inflammation; 2) degeneration; 3) regeneration; and 4) fibrosis [Saini et al., 2009].

During inflammation, a variety of immune cells enter the damaged tissue resulting in phagocytosis [Saini et al., 2009]. It has been proposed that muscle injury is capable of activating the dormant satellite cells, which in turn signal for invasion by macrophages [Saini et al., 2009; Lee et al., 2007]. Upon activation, the satellite cells then undergo proliferation, migration, differentiation, and eventually fusing to either one another to form new muscle fibers (also known as myotubes) or to existing damaged muscle fibers to repair them [Saini et al., 2009; Lee et al., 2007]. After repairing, no further cell proliferation takes place while some active satellite cells returned to the dormant state and await activation by further damage, thus replenishing the quiescent satellite cell pool [Saini et al., 2009]. A brief summary of these processes is provided in figure 5.
Satellite cell activation is not restricted to the local site of damage as satellite cells can influx from areas of the fiber that are distant to the regeneration site [Lee et al., 2007]. The newly regenerated muscle fiber is characterized by the centrally located myonuclei, which in time migrate to the periphery as a marker of aging [Lee et al., 2007]. With advancing age, satellite cells manifested an aging-associated decrease in number/density (commonly seen in type II fibers but not in type I fibers) and in proliferative capacity [Deschenes, 2004; Lee et al., 2007; Verdijk et al., 2007; Dreyer et al., 2006; Gibson & Schultz, 1983; Shefer et al., 2006]. The diminished satellite cell proliferative capacity (also known as replicative senescence) may associate with but not limited to: 1) shortening of telomeres; and 2) aging-associated decrease of mechano growth factor (MGF) expression [Deschenes, 2004; Lee et al., 2007; Verdijk et al., 2007; Renault et al., 2002; Shefer et al., 2006; López-Otín et al., 2013]. MGF is a specific splice variant/isoform of insulin-like growth factor (IGF)-1 but locally synthesized within muscle tissues and regulates satellite cell activity in vivo [Deschenes, 2004; Saini et al., 2009; Hameed et al., 2003]. Although MGF overexpression and amplification have been demonstrated to prevent the loss of both muscle mass and strength, the role of MGF in muscle injury remains controversial [Deschenes, 2004]. In addition to the MGF, non-human studies suggested that fibroblast growth factor (FGF) and hepatocyte growth factor (HGF) may regulate satellite cell proliferation and recruitment in both younger and older subjects while HGF may also up-regulate FGF receptors [Shefer et al., 2006].

To this point, it is worth noting that some studies suggested that the failure of skeletal muscle maintenance and repair in aged animals may be due more to an age-related decline in environmental cues than an age-related decline of stem cell function or potential [Lee et al., 2007]. Indeed, this view is supported by several other studies [Lee et al., 2007; Dreyer et al., 2006; Hameed et al., 2003; López-Otín et al., 2013; Edström & Ulfhake, 2005; Carlson & Faulkner, 1989; Conboy et al., 2005]. Among the environmental cues (e.g. heat shock proteins, redox environment and proinflammatory cytokines) [Lee et al., 2007], the role of both growth hormone (GH) and IGF system in the maintenance of skeletal muscle have received a great deal of interest and are generally well supported [Saini et al., 2009]. IGF-1 signaling is commonly recognized as an important mediator of a number of cellular events such as cell proliferation, differentiation, survival, growth, apoptosis and regeneration [Saini et al., 2009]. As a major signaling pathway downstream of IGF-1, mTOR signaling pathway is introduced in the next section.

7.2 The mTOR Signaling Pathway

Mammalian target of rapamycin (mTOR) is a central regulatory nexus integrating different physiological signals from various intracellular pathways (including those elicited by the nutrient, hormonal and exercise stimuli), its signaling also regulates many intracellular events (including cell growth, survival, differentiation, translation control, immune response, synaptic plasticity and memory reconsolidation)
As centered to cellular development, tissue regeneration and repair, mTOR signaling associates not only with stem cell development and quiescence but also with cell death (during apoptosis or autophagy) [Maiese et al., 2013]. In fact, mTOR itself is ubiquitously expressed throughout the body (including the nervous system, vascular system, and immune system) and is a core protein through which its associated adapter proteins form complexes with it [Kwan & Tse, 2013; Tse & Kwan, 2013; Maiese et al., 2013]. mTOR exert its signaling effect by 2 associated protein complexes: mTORC1 and mTORC2 [Rasmussen & Volpi, 2012; Kwan & Tse, 2013; Tse & Kwan, 2013]. Although mTORC1 has been extensively studied, mTORC2 is relatively less known [Kwan & Tse, 2013]. To this day, mTORC1 signaling is identified as an essential pathway regulating the rate of muscle protein synthesis in humans in response to hormones, muscle contraction and nutrition [Rasmussen & Volpi, 2012]. Additionally, the importance of mTORC1 signaling in the control of in vivo muscle hypertrophy has been demonstrated through: 1) positive correlation between the acute phosphorylation of S6K1 (downstream effector of mTORC1) and the increase in muscle mass over 6 weeks of electrical stimulation in rodent hind limb muscles; 2) such positive correlation has also been demonstrated in human subjects after 12 weeks of resistance exercise training; and 3) inhibiting mTORC1 signaling by rapamycin blocks muscle hypertrophy following functional overload in rodents [Rasmussen & Volpi, 2012].

It is important to note that other signaling pathways may also involve in the regulation of cellular hypertrophy in a mTOR-signaling-dependent/independent manner, for example: 1) extracellular signal-regulated kinase 1/2 (ERK1/2) pathway interacts with mTORC1 signaling through direct interaction with tuberous sclerosis complex 2 (TSC2) or indirectly by phosphorylation of p90RSK (ERK1/2 downstream effector); and 2) ERK1/2 is capable of enhancing protein synthesis independent of mTORC1 signaling through mitogen-activated protein kinase (MAPK)-interacting kinase 1 (MNK1) signaling to eIF4E [Rasmussen & Volpi, 2012; Wang et al., 2007]. As a brief summary, an overview of mTOR signaling is provided in figure 6. For more details regarding this hypertrophic pathway, please refer to the following suggested review articles:

Figure 6: An overview of mTOR signaling pathways. Colored arrow-ended line (all colors other than red): stimulation/activation; red circle-ended line: inhibition; dash line: MAPK signaling; long dash dot line: degradation control (ubiquitin-proteosomal and autophagic lysosomal degradations). Reprinted with permission from Kwan and Tse 2013. [Kwan & Tse, 2013]

Although mTOR signaling is commonly considered to be important for cellular hypertrophy, chronic hyperactivity of mTOR signaling may not necessarily result in cellular hypertrophy. Animal studies indicated that hyperactivation of the mTOR signaling pathways (which originally expected to promote growth and regulate protein translation) does not reverse the atrophy observed in obese muscles (may due to insulin resistances) while the application of adenosine monophosphate-activated protein kinase (AMPK)-agonists (mTOR signaling inhibitors) increased the translation capacity and mass of obese muscles [Williamson, 2011]. Although not completely understood, hyperactivity of mTOR signaling may lead to a secondary resistance to the growth stimuli probably due to the negative feedback of a homeostatic effect [Hall et al., 2011]. In fact, recent studies have indicated that hyperactivation of mTOR signaling can diminish the ability of Akt (PKB) to function properly in fat-fed obese rats [Haran et al., 2012].

Finally, it is interesting to note that some human studies reported that the muscle mass of obese older adults was higher than their less obese counterparts [Park et al., 2006; You et al., 2004]. As the un-
derlying reasons are not clear yet, more studies are required to clarify these issues. One guess of the reasons may be due to a decreased level of sex hormone binding globulins (SHBG) and thus the increased level of circulating androgens may facilitate muscle growth [You et al., 2004; Clarke & Khosla, 2010].

7.3 Decreased Trophic Factors and Proteins that Maintain Proper Cellular Functions

As part of the contributors to cellular hypertrophy, trophic factors (particularly hormones and growth factors) and proteins that maintain proper cellular functions are worth taking a look. Aging is associated with a decrease of sex hormones, including androgens (testosterone and DHEA) and estrogens, in both male and female [Lee et al., 2007]. In the nervous system, such decrease of sex hormones may affect brain functions as circulating sex hormones are capable of penetrating the blood-brain barrier [Ooishi et al., 2012]. Additionally, aging is also associated with a decrease of growth factors and their relevant regulators which affect both muscle cells and neurons, for example: 1) GH, which regulates the synthesis of IGF-1 [Deschenes, 2004] and the survival of neurons [Sanders et al., 2011]; 2) IGFs, which stimulate amino acid and glucose transport and are important trophic factors to both muscle cells [Tan et al., 2012; Garatachea & Lucía, 2013] and neurons [Ozdemir et al., 2012; Akundi et al., 2012; Tsai et al., 2012]. IGF-1 regulates growth, differentiation and regeneration of muscle cells [Garatachea & Lucía, 2013] by inducing hypertrophic signaling (e.g. PI3K and MAPK pathways) [Tan et al., 2012] while IGF-2 is associated with the proliferative actions in adult muscles [Garatachea & Lucía, 2013]; and 3) ciliary neurotrophic factor (CNTF), which is an important hypertrophic factor for both muscle cells and neurons [Garatachea & Lucía, 2013; Guillet et al., 1999], and is believed to play an important role in the re-innervation of muscle fibers by motor neurons after muscle and nerve injury [Tan et al., 2012]. Additionally, aging is associated with a decrease of stress-induced expression of heat shock proteins (HSP; normally functioned as chaperones and antioxidants; expressed by both muscle cells and neurons) [Doria et al., 2012; Lee et al., 2007; Dirks & Leeuwenburgh, 2005]. HSP70 reduces the apoptotic potential of a cell by inhibiting the formation of apoptosome and functioning as an antagonist of AIF [Dirks & Leeuwenburgh, 2005]. In summary, the aging-associated decline in these candidates may have a serious consequence on both the muscular and nervous systems.

7.4 Commonly Accepted Contributors to the Etiology of Sarcopenia

In regard to the multi-etiological concept of sarcopenia, there are several pathophysiological factors particularly worth noting: 1) mitochondrial dysfunction; 2) elevation of oxidative stress; 3) inflammation; 4) altered rate of metabolic balance and protein turnover; 5) malnutrition; and 7) physical inactivity [Kwan, 2013a; Kwan, 2013b; Tan et al., 2012; Garatachea & Lucía, 2013; Deschenes, 2004; Dirks & Leeuwenburgh, 2005].

7.4.1 Mitochondrial Dysfunction

Mitochondria are the major sites for aerobic ATP generation (uses molecular oxygen) in which a significant fraction (approximately 2%) of oxygen are converted to the reactive oxygen species (ROS) in and around mitochondria [Inoue et al., 2003]. During aging, mitochondrial function can be disrupted by: 1) mitochondrial DNA (mtDNA) mutations; 2) reduced mitochondrial biogenesis; 3) destabilization of electron transport chain (ETC) complexes; 4) altered mitochondrial dynamics; and/or 5) defective quality control by mitophagy [López-Otín et al., 2013; Sanchis-Gomar et al., 2011; Derbré et al., 2012]. Together with
the consequent increased ROS production, these pathophysiologival factors further lead to an increase in mtDNA damage by oxidative stress, changes in the mitochondrial respiratory chain enzymes, and changes in the mitochondrial proapoptotic proteins [Kwan, 2013a]. Mitochondrial dysfunction results in an impaired mitochondrial oxidative function and energy production, which in turn affect cell viability through necrosis and/or apoptosis of both muscle fibers and neurons [Dirks & Leeuwenburgh, 2005; López-Otín et al., 2013; Martin, 2011].

7.4.2 Elevation of Oxidative Stress

Progressive cellular oxidation (e.g., nitration) and accumulation of reactive species including advanced age glycation end-products (AGE) and lipoxidation end-products (ALE), lead to aging-associated elevation of oxidative stress which is commonly seen in aged animal cells and is characterized by an increase in oxidative species (e.g., H$_2$O$_2$ species, malondialdehyde, 4-hydroxyalkenals, nitrotyrosine, catalase [Siu et al., 2008], iNOS [Hall et al., 2011]) and a decrease in antioxidative species (e.g., manganese superoxide dismutase/superoxide dismutase 2 [Inoue et al., 2003; Siu et al., 2008], glucose-6-phosphate dehydrogenase [Braga et al., 2008]) [Dirks & Leeuwenburgh, 2005; Miyata et al., 2000; Fanzani et al., 2012]. In addition to the activity impairment of both extracellular and intracellular proteins (e.g. myosin) mediated by AGE and/or ALE, the consequence of an elevated oxidative stress in muscles is the down-regulation of a set of myogenic proteins including muscle creatine kinase (CKM) and MyoD (mediated by, e.g. iNOS) [Dirks & Leeuwenburgh, 2005; Hall et al., 2011], and the inhibition of general protein translation by both the phosphorylation of eIF2α and the inhibition of mTOR signaling (mediated by, e.g. nitric oxide) [Hall et al., 2011]. Additionally, aging-associated up-regulation of inducible nitric oxide synthase (iNOS) correlates with an increase in caspase 2 and c-Jun N-terminal kinase (JNK) signaling activities (suggests an involvement of JNK-mediated apoptotic signaling) [Braga et al., 2008; Siu, 2009]. Further, oxidative stress may also lead to an alteration in the balance between mitochondrial fission and fusion as well as an activation of the apoptotic pathway as seen in neurons [Nguyen et al., 2011].

7.4.3 Inflammaging (Aging-Associated Chronic Inflammation)

Inflammation is intimately associated with oxidative stress and manifested an elevation of the baseline level of proinflammatory markers and cytokines (e.g., TNF-α, IL-6, CRP) with aging [Roubenoff, 2007]. The most representative cytokines are tumour necrosis factor (TNF)-α and interleukin (IL)-6. TNF-α is capable of inducing apoptosis through: 1) direct interaction with the death domain receptors which in turn leads to the activation of procaspase 8 [Dirks & Leeuwenburgh, 2005; Always et al., 2003]; and indirectly through 2) activation of its downstream effectors (e.g. NF-κB, which activity is also elevated by aging) [Hall et al., 2011].

Activated nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) up-regulates myostatin (MSTN; also known as GDF8) [Sriram et al., 2011; O’Neil et al., 2011], iNOS and muscle RING finger (MuRF)-1 [Fanzani et al., 2012; Hall et al., 2011], which play a negative role in the trophic state of muscle fibers and satellite cells [Langley et al., 2002]. Additionally, IL-6 also negatively regulates cellular trophic state by down-regulating IGF-1 [Lee et al., 2007]. Due to inflammaging, the anabolic potential of muscle cells (including satellite cells) is impaired due mainly but not limited to: 1) decreased expression of proteins involved in myogenesis and other relevant muscle growth processes (e.g. myogenin and MyoD) [Hall et al., 2011; Always et al., 2003; Bera & Ray, 2009; Szalay et al., 1997]; and 2) elevated expression of MSTN which exerts its effect on muscle growth by regulating the Activin re-
ceceptor-mediated pathway, MAPK pathway, and Akt (PKB) pathway (Akt/mTORC1/S6K) [Tan et al., 2012]. Additionally, MSTN induces ROS production via nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and TNF-α [Kwan, 2013a; Sriram et al., 2011]. The elevated TNF-α then in turn induces further MSTN production while the higher levels of MSTN promote proteasome-mediated catabolism of intracellular proteins [Kwan, 2013a; Sriram et al., 2011]. In addition to the muscular system, both oxidative stress and inflammation considerably affect the nervous system and significantly contribute to the progression of neurodegenerative diseases [Kwan, 2013a; Kwan, 2013b; Nguyen et al., 2011; Machado et al., 2011].

### 7.4.4 Altered Rate of Metabolic Balance and Protein Turnover

At least partly affected by oxidative stress and inflammation, aged cells manifested altered metabolic balance and protein turnover influencing cellular functions. In muscle cells, there is an aging-associated change in expression of hypotrophic/dystrophic/atrophic factors (e.g. Id1, Id2 and Id3) [Dirks & Leeuwenburgh, 2005; Always et al., 2003] and trophic factors (e.g. MGF) [Deschenes, 2004; Saini et al., 2009]. Similarly in neurons, the expression profile of hypotrophic/proapoptotic factors (e.g. BAX and procaspase 3) [Robinson et al., 2002] and trophic factors (e.g. CNTF) [Deschenes, 2004; Guillet et al., 1999] are also altered by aging.

It is commonly believed that animal cell fate is affected by the **metabolic balance between hypertrophy and hypotrophy/dystrophy/atrophy** which are positively correlated to the activity of hypertrophic signaling (e.g. growth-factor-mediated pathways) and hypotrophic/dystrophic/atrophic signaling (e.g. proapoptotic-factor-mediated pathways), respectively. In other words, when the activity of hypertrophic metabolism exceeds the activity of hypotrophic metabolism, the cell will undergo atrophy and eventually death by apoptosis [Kwan, 2013a]. Although the complete mechanism is not clear, the loss of myonuclei in aged muscle fibers is suggested to be a result of apoptosis regulated by apoptosis inducing factor (AIF)-mediated DNA fragmentation (caspase independent) [Dirks & Leeuwenburgh, 2005]. Unlike single-nucleated neurons, apoptosis of one single nucleus of the muscle fiber may not result in cell death [Dirks & Leeuwenburgh, 2005]. Instead, it will undergo atrophy due to the decrease of nuclear domains (maintaining the sarcoplasm vs nuclei ratio) [Deschenes, 2004]. Together with the “use it or lose it” perspective (discuss in later sections), this may explain (at least in part) the more remarkable changes in type II muscle fibers compared to the type I muscle fibers in aged subjects. Recently, studies have implicated that the altered response of muscle to previously well-established anabolic stimuli (i.e. anabolic resistance) may be the major cause of the deranged metabolic equilibrium seen in aged subjects [Haran et al., 2012]. Anabolic resistances have been observed to arise in response to aging, obesity, high-fat feeding, inflammation and lipotoxicity [Haran et al., 2012]. According to recent studies, the ability of insulin and branched-chain amino acids (discuss in later sections) to foster muscle protein synthesis is hampered with aging and such observed decline in muscle protein synthesis is believed to be the result of diminished mTOR signaling (AMPK activation and concentration are elevated in aged skeletal muscles) [Haran et al., 2012]. In the condition of diet-induced obesity (which often implicated in insulin resistance), muscle protein synthesis is also reduced in response to nutrient intake [Haran et al., 2012].

The contribution of **lipotoxicity** to anabolic resistance can be but not limited to the following: 1) accumulation of lipids is associated with macrophage infiltration (in muscle and intermuscular adipose tissue) and activation of proinflammatory mediators; 2) actions of ceramides which diminish intracellular amino acid availability and reduce phosphorylation of translational regulators downstream of mTOR sig-
naling (through activation of protein phosphatase 2A); and 3) actions of triglycerides which intramuscular infiltration is associated with an increase in several lipogenic regulators (including sterol regulatory element binding protein, fatty acid synthase, acetyl CoA carboxylase, and stearoyl CoA desaturase) [Haran et al., 2012].

At the epigenetic level, microRNAs (miRNA) may also contribute to the aging-associated alteration in protein turnover as they are capable of regulating protein expression at the transcription level. Many miRNA candidates altered their expression level during aging in both muscle fibers and neurons [Li et al., 2011; Noren Hooten et al., 2010; Hamrick et al., 2010]. As for referencing, a list of miRNAs associated with muscle physiology is provided as table 7.

<table>
<thead>
<tr>
<th>miR</th>
<th>Target(s)</th>
<th>Proposed Function(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>miR-1</td>
<td>Hand2, HDAC4</td>
<td>Myogenesis, Skeletal muscle hypertrophy</td>
</tr>
<tr>
<td>miR-26a</td>
<td>HMT, Ezh2</td>
<td>Myogenesis</td>
</tr>
<tr>
<td>miR-27a</td>
<td>Pax3, MSTN</td>
<td>Myogenesis</td>
</tr>
<tr>
<td>miR-27b</td>
<td>MSTN</td>
<td>Myogenesis</td>
</tr>
<tr>
<td>miR-29</td>
<td>YY1</td>
<td>Myogenesis and rhabdomyosarcoma</td>
</tr>
<tr>
<td>miR-133</td>
<td>SRF</td>
<td>Myogenesis, skeletal muscle hypertrophy</td>
</tr>
<tr>
<td>miR-146a</td>
<td>Numb</td>
<td>Muscle differentiation and proliferation</td>
</tr>
<tr>
<td>miR-181</td>
<td>Hox-A11</td>
<td>Myogenesis and regeneration</td>
</tr>
<tr>
<td>miR-206</td>
<td>Cx43, Fstl1, Pola1, Utrn</td>
<td>Myogenesis</td>
</tr>
<tr>
<td>miR-221</td>
<td>p27</td>
<td>Muscle cell differentiation and mature</td>
</tr>
<tr>
<td>miR-222</td>
<td>p27</td>
<td>Muscle cell differentiation and mature</td>
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</tbody>
</table>

Table 7: Muscle-physiology-associated miRNAs. Shaded/colored area indicates muscle-specific expression. Cx43 = connexin 43; Ezh2 = Enhancer of Zeste homolog 2; Fstl1 = follistatin-like 1; Hand2 = heart and neural crest derivatives expressed 2; HDAC4 = histone deacetylase 4; HMT = histone methyltransferase; Hox-A11 = homeobox A11; Numb = Notch-1 inhibitor; Pola1 = DNA polymerase alpha 1; SRF = serum response factor; Utrn = utrophin; YY1 = Ying Yang 1. [Tan et al., 2012]

7.4.5 Malnutrition

As a resource for replenishment and normal cell functions (including energy, growth and recovery), nutrients as well as their intake and utilization are especially important to health. Therefore, lacking nutrients may alter the body metabolism (including protein turnover) and thus contribute to the development of sarcopenia [Muscaritoli et al., 2010]. Muscle accounts for 60% of the body's protein stores and is rapidly mobilized in order to provide the immune system, liver and gut with amino acids (especially glutamine), during metabolic stress situations [Muscaritoli et al., 2010]. Anorexia and reduced food intake are frequently underdiagnosed and may significantly contribute to the nutritional deterioration of muscle wasting (e.g. cachexia) [Muscaritoli et al., 2010]. Interestingly, recent studies indicated that the blunted vasodilatory response of older muscle to insulin may play a role in nutrient deficiency and unavailability [Haran et al., 2012]. Insulin acts to prime the muscle for protein synthesis while the branched-chain amino acids (BCAA) stimulate muscle protein synthesis in a dose-dependent manner [Haran et al., 2012].
The current recommended daily nutrition intake for the prevention of sarcopenia and frailty is 24–36 kcal energy and 0.8–1.2 g high quality protein per kg body weight [Volkert, 2011]. **Essential amino acids** (EAA), in particular the BCAA especially **Leucine**, are potent anabolic signals for protein accretion (which requires ~0.7 kcal energy for the synthesis of each gram of muscle protein) [Fujita & Volpi, 2006; Koopman & van Loon, 2009]. Such protein accretion is due mainly to the Leucine-induced activation of mTORC1 signaling which stimulates translation initiation in the skeletal muscle cells by increasing the phosphorylation of several signaling proteins including S6K1 and 4E-BP1 [Rasmussen & Volpi, 2012; Kwan & Tse, 2013].

Aging is commonly associated with not only anorexia but also a decline in the ability to utilize exogenous amino acids [Soenen & Chapman, 2013; Fujita & Volpi, 2006]. For example, a 7 g EAA bolus containing 26% (1.7 g) of leucine may stimulate muscle protein synthesis in younger adults, but in older adults only an EAA bolus with 41% leucine was able to effectively increase protein synthesis [Rasmussen & Volpi, 2012]. Additionally, the older adults manifested a significantly less muscle protein accretion than the younger adults following the ingestion of a 7 g EAA bolus [Rasmussen & Volpi, 2012]. Interestingly, excess amounts of EAA seem to exert similar effects in younger and older adults [Rasmussen & Volpi, 2012]. Although not completely understood, the underlying causes may due mainly but not limited to: 1) decrease of transmembrane amino acid transport for protein synthesis; 2) alterations in the whole body amino acid turnover which results in a reduced availability of substrates for protein synthesis; 3) alterations in the endogenous hormonal response; and/or 4) alterations in the response of muscle to the hormonal stimuli after meal intake [Fujita & Volpi, 2006]. In addition to EAAs, studies have shown that aging is associated with an inability of insulin to stimulate muscle protein synthesis and net amino acid uptake in healthy, glucose tolerant persons which is associated with reduced mTORC1 signaling and endothelial dysfunction [Rasmussen & Volpi, 2012].

Finally, it is interestingly to note that caloric restriction (CR; in the premise of not being malnutrition) may have a positive impact on cells [Williamson, 2011]. Animal studies shown that caloric restriction attenuates the progressive functional decline of organs [Dirks & Leeuwenburgh, 2005]. At the cellular level, caloric restriction is associated with a decreased damage of peripheral nerve during aging (due to the increased expression of chaperones and autophagic machineries [Jang & Van Remmen, 2011]. Additionally, CR has been shown to ameliorate the loss of muscle mass, decrease abnormalities in the ETC and diminish apoptotic potential in skeletal muscles [Dirks & Leeuwenburgh, 2005]. Further, it is associated with neuronal protection against degeneration in animal CNS [Manzanero et al., 2011]. Although CR has been suggested to be salubrious, more ongoing investigations in humans are still required to determine its efficacy in reality.

### 7.4.6 Physical Inactivity (Disuse Atrophy)

Inactivity as a contributor to the physiological decline is commonly seen in various physiological systems (including muscular, skeletal and nervous systems) [Siu et al., 2008; McEachern & Shaw, 1999; Lau & Guo, 2011]. Physical inactivity (induced by either sedentary lifestyle or immobility due to illness/injury) is also a trigger for muscle wasting commonly recognized as **disuse atrophy** [Kwan, 2013a; Saini et al., 2009], which is associated with the inhibition of hypertrophic IGF-1 signaling and the increase of hypertrophic/dystrophic/atrophic **ubiquitin-proteasomal** and **lysosomal (autophagy)** signaling via FOXO proteins (which normally inhibited by the IGF-1/Akt signaling) [Saini et al., 2009; Zhang et al., 2007; Mammucari et al., 2007]. Thus, the decreased trophic state of muscle cells leads to their atrophy.
In contrast, increased physical activity (particularly, exercises) is associated with an increase of satellite cells and MGF [Dreyer et al., 2006; Hameed et al., 2003]. Additionally, resistance training enhances the skeletal muscle mass, strength, power and balance (ameliorate the signs/pathology of sarcopenia which in turn decrease the risk of physical limitation and/or the onset of frailty) [Korhonen et al., 2006; Dirks & Leeuwenburgh, 2005; Dreyer et al., 2006; Hameed et al., 2003; Koopman & van Loon, 2009; Freiberger et al., 2011]. The effect of exercise training has been shown dose dependent (i.e. the higher the intensity involved in the training, the better the yield of the effect) [Mayer et al., 2011]. Training at 60%–85% of the individual maximum voluntary strength can increase the skeletal muscle mass while more than 85% can also increase the rate of force development [Mayer et al., 2011]. Further, the addition of a sensorimotor component to the exercise training program may also improve the postural control in older adults [Mayer et al., 2011].

In addition to the muscular system, the positive influences of exercise training on the nervous system is also well documented (including the improvement of: motor unit recruitment and firing patterns; neuromotor excitability; reaction of large and small muscles; sensory organization and balance control) [Sale, 1988; Fong et al., 2012; Chung & Ng, 2012]. Moreover, it is well known that exercise activities could raise the production of neurotrophic factors in the CNS (at least in rodents; including neurons of the hippocampus and the motor cortex) [Whishaw & Kolb, 2005].

Interestingly, exercise trainings do not prevent the aging-associated impairment of skeletal muscle features (mass, strength and power) as indicated by studies that both the muscle size and function were impaired in aged sprint-trained athletes (type II fibers were more impaired than type I fibers) [Korhonen et al., 2006]. In summary, the subjects may commonly arrange in the following order in terms of their skeletal muscle features (from best to worst): Younger (trained) > Older (trained) > Younger (untrained) > Older (untrained) [Korhonen et al., 2006].

8 Activity-Dependent Pattern of Sarcopenia

According to the current observations, the effect of activity (positive by exercise; negative by disuse) on skeletal muscle features (mass, strength and power) provided an association between sarcopenia and physical activity. Physical inactivity may reflect inactivity of the motor units. Unused or rarely used neurons are capable of undergoing disuse degeneration, causing further disuse degeneration of its synthetically connected cells [McEachern & Shaw, 1999]. Thus, aging-associated progressive denervation and loss of muscle fibers could be a result of disuse atrophy and degeneration of the NMJs and/or motor neurons. In reference to the “use it or loss it” doctrine, it is reasonable to explain the more prominent type II motor unit atrophy and degeneration compared to the type I motor unit, and a higher susceptibility to sarcopenia of the sedentary individuals. As sedentary individuals have limited fast and/or explosive actions, the frequency of usage of the fast motor unit (type II fibers) would be lower than that of the slow motor unit (type I fibers; which frequently engaged in antigravity functions/postural maintenance). As a consequence, the potential for disuse atrophy and degeneration of the type II fibers would be higher.

In fact, aging-associated denervations, loss of motor units and motor neurons are all observed more prominent in those associated with type II fibers compared to those associated with type I fibers [Deschenes, 2004; Wang et al., 1999]. This view is further supported by the space flight studies reporting that the loss of muscle mass, strength and power associated with the type I fibers are more prominent
than those associated with the type II fibers under microgravity [Fitts et al., 2010]. When gravity is decreased in space, the usage of slow motor units becomes less than that of the fast motor units (at least less antigravity actions), leading to a higher potential for disuse atrophy and degeneration of the type I fibers compared to the type II fibers. It is important to note that the number of type II fibers was also decreased after the space flight compared to the pre-flight data. As the decreased gravity results in a lesser resistance force for activity, type II motor units would then consume lesser strength, energy or power for the same task as if it was conducted on earth. Thus, the type II fibers are also susceptible to the disuse issue but to a lesser extent.

9 Choreography of Body Physiology

To this day, there are nine hallmarks of cellular aging have been proposed by the Spanish group in 2013: 1) genomic instability; 2) telomere attrition; 3) epigenetic alterations; 4) loss of proteostasis; 5) deregulated nutrient sensing; 6) mitochondrial dysfunction; 7) cellular senescence; 8) stem cell exhaustion; and 9) altered intercellular communication [López-Otín et al., 2013]. Similar to these hallmarks, most of the pathophysiological (etiological) factors mentioned previously are also conserved among various cell types, in particular the muscle cells [Tan et al., 2012; Garatachea & Lucía, 2013; Deschênes, 2004; Lee et al., 2007; Dirks & Leeuwenburgh, 2005; Derbré et al., 2012; Siu et al., 2008; Braga et al., 2008; Hall et al., 2011; Roubenoff, 2007; Always et al., 2003; Sriram et al., 2011; Noren Hooten et al., 2010; Hamrick et al., 2010; Sanchis-Gomar et al., 2011] and neural cells (both neuron [Deschênes, 2004; Martin, 2011; Nguyen et al., 2011; Machado et al., 2011; Li et al., 2011; Ooishi et al., 2012; Sanders et al., 2011; Ozdemir et al., 2012; Akundi et al., 2012; Tsai et al., 2012; Amadio et al., 2008; Teismann et al., 2003] and glia [Paasche et al., 2000; Boumezbeur et al., 2010; Muntané et al., 2006; Dei et al., 2002; Gomez & Ferrer, 2010; Giunta et al., 2008; Sierra et al., 2007; Papadopoulos et al., 1998; Wyse & Sernia, 1997; Aberg et al., 2003; Yudkoff et al., 1996; Yudkoff, 1997; Li et al., 2005]).

Due to the multi-etiological nature, sarcopenia is apparently the result/consequence/adaptation of a delicate interplay/interaction between various networks of molecular (both intra and extracellular) and cellular factors. Thus, except genetic defects, the origin of sarcopenia may not be necessarily in the muscle tissue. In other words, it is possible that these conserved factors may serve only to exacerbate the progression/development of the pathological condition by lowering the threshold of the pathogenic trigger (i.e. allowing an easier trigger for the pathological condition). Once the correct pathogenic factor(s) encounter(s), the pathological condition could quickly develops. Due to the inspiration of the old concept that “force is useless without control”, the etiological considerations for sarcopenia should not be simply focused on muscle cells alone. As the nervous system and the muscular system are intimately linked, sarcopenia may originate from the following regions: 1) muscle fibers per se (musculogenic), subsequently causing denervation and the loss of motor neurons; 2) synapses (synaptogenic), which atrophy and degeneration at the NMJ causing subsequent muscle pathologies; 3) motor neurons (neuronogenic), which atrophy and degeneration lead to subsequent synaptogenic muscle pathologies; 4) glia (gliogenic), which impaired trophic support/maintenance function during aging may lead to subsequent synaptogenic/neurogenic muscle pathologies; and 5) blood supply (vasculogenic).

In regard to the blood circulation (vital element to mammalian physiology), aging is associated with changes in: 1) microcirculation; 2) ultrastructure of the vascular endothelium; 3) decline in
vascular endothelial functions; and 4) decrease of exercise-induced blood flow which may be partly resulted from: a) aging-associated decrease of vasodilatory capacity; and b) capillarization [Degens, 1998; Burton et al., 2011]. The decreased blood flow in turn limits the exchange of oxygen, energy sources, metabolites, and heat between blood and the body cells, which ultimately results in a less trophic cellular environment [Degens, 1998]. As dynamic partners with blood vessels [Kettenmann & Ransom, 2005; Takano et al., 2006], glia may contribute to the development of sarcopenia through their regulation on blood vessels [Haydon & Carmignoto, 2006]. Aged astrocytes (becoming reactive) have been demonstrated to produce more endothelin (potent vasoconstrictor) [Latimer et al., 2011]. Additionally, reactive astrocytes also increase the permeability of blood vessels [Farrall & Wardlaw, 2009; Abbott et al., 2006; Argaw et al., 2012]. Prior to further discussions, an introduction on glia is provided in the next subsection.

9.1 Glia, the Potent Contributors

Glia (also known as neuroglia) are commonly regarded as the housekeeper for maintaining an optimal physiological environment for neuronal survival and functions. These cells, in particular astrocytes (which are approximately 8 times more than neurons in the brain) [Verkhratsky & Butt, 2007a], are essential to brain functions by providing the mass structure for the brain, neuronal insulation, developmental guidance, environmental homeostasis, neuroenergetics regulation, neuronal nourishment and even immune functions. [Verkhratsky & Butt, 2007a; Kettenmann & Ransom, 2005]. There is a great diversity of glia throughout the human body (table 8; including myelinating glia, non-myelinating glia, developmental radial glia and immunological microglia).

<table>
<thead>
<tr>
<th>Brain (100%)</th>
<th>Neurones (~10%)</th>
<th>Glia (~90%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Macroglia (~85-90%)</td>
<td>Microglia (~10-15%)</td>
</tr>
<tr>
<td></td>
<td>Astrocytes (~80%)</td>
<td>Oligodendrocytes (~5%)</td>
</tr>
</tbody>
</table>

Table 8: Neural cell populations in the human brain (in percentage). [Verkhratsky & Butt, 2007a]

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 (particularly: glutamate, ATP and d-serine) [Verkhratsky & Butt, 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 [Verkhratsky & Butt, 2007b]. Due to its dynamic interaction with neurons and blood vessels [Verkhratsky & Butt, 2007c; Kettenmann & Ransom, 2005; Takano et al., 2006], glia malfunctioning 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 (ALS) and
ischemic stroke [Teismann et al., 2003; Kettenmann & Ransom, 2005; Takano et al., 2006; Schubert et al., 2001; Holden, 2007; Jackson et al., 1999; Seifert et al., 2006; Filosa et al., 2006; Rao & Weiss, 2004].

In regard to sarcopenia, Schwann cells (which are a subtype of PNS glia) may play an important pathogenic role as these major peripheral glial elements insulate and nourish motor neuron axons and NMJs. During aging, Schwann cells manifested number decrease and the nodes of Ranvier became widened [Jang & Van Remmen, 2011]. A number of mouse studies also demonstrated that young adult Schwann cells were well structured, “plump” and could cover the entire motor endplate, while aged Schwann cells were found to be disorganized, thinner and only partially covered the motor endplate [Chai et al., 2011]. At the molecular level, there is an aging-associated decrease of major myelin protein expression (e.g. P0, PMP22 and MBP) [Jang & Van Remmen, 2011], while the CNS glia (e.g. oligodendrocytes and astrocytes) of the motor cortex and/or the spinal cord may contribute to the proper function of motor neurons. Thus, the pathophysiological contributions of glia should not be overlooked.

10 Neurogenic Model of Sarcopenia

Recent studies have demonstrated that denervation could enhance the cellular apoptotic potential by elevating the proapoptotic factors (e.g. caspase 8 and BAX) in both younger and aged rats [Always et al., 2003]. Additionally, another animal studies demonstrated the insignificant change with age of the pro-apoptotic factors (BAX, cytochrome c and caspase 3) in the rat gastrocnemius muscle cells (6 months vs 24 months) [Dirks & Leeuwenburgh, 2002]. More importantly, studies indicated that certain myogenic factors (e.g. myogenin) are strongly regulated by electrical activity while the muscle fiber phenotype is affected by the motor axon activities (mainly mediated by the Ras-MAPK pathway) [Schiaffino et al., 1999]. These evidences suggested that the etiology of sarcopenia is more likely to be neurogenic or neurogenic in origin, at least the animal studies have demonstrated that neuronal activity in the mediobasal hypothalamus (MBH) is associated with the muscle endurance and quadriceps muscle fiber size in a NF-κB-dependent manner [Zhang et al., 2013].

To further analyze this issue, the following evidences should be considered: Aging is associated with decreased number of type II-fiber-associated motor units (determinant of the degree of muscle power) and lower motor neurons (α type; in spinal cord) [Deschenes, 2004; Dirks & Leeuwenburgh, 2005; Tomlinson & Irving, 1977]. In addition to the decreased number of myelinated neuronal axons in the muscle [Deschenes, 2004], aging is also associated with an impaired denervation-reinnervation cycle (motor unit remodeling) [Deschenes, 2004; Jang & Van Remmen, 2011] in which the net effect of denervation (outpaces reinnervation) induces the remain-denervated population of muscle fibers to undergo atrophy and degeneration (at least partly by apoptosis) [Always et al., 2003; Jang & Van Remmen, 2011] due to the loss of trophic factors (e.g. BDNF, NT-4/5) [Schiaffino et al., 1999; Kulakowski et al., 2011]. Such aging-associated increase of denervation is partly evidenced by the aging-associated increase of NCAM concentration at the aged NMJs [Deschenes, 2004]. Additionally, there is a preferential denervation of the type II fibers and reinnervation by the slow motor neurons leads to a conversion of muscle fibers from type II to type I [Jang & Van Remmen, 2011]. This is consistent with most of the studies that observed a more remarkable atrophy occurred in type II fibers of the aged skeletal muscles [Korhonen et al., 2006; Deschenes, 2004; Dirks & Leeuwenburgh, 2005].
At the NMJ, rat studies have shown that aging-associated progressive denervation has disrupted the precise overlapping between the presynaptic axon terminal and the postsynaptic AChR clusters [Kulakowski et al., 2011]. Additionally, denervated skeletal muscles increased the expression of proapoptotic/atrophic factors (including BAX, caspase 3, 7, 8, and 10) [Always et al., 2003] while decreased trophic factor signaling (including TrkB signaling via BDNF and NT-4/5 [Kulakowski et al., 2011]; and ErbB/P13K signaling via neuregulin [Mantilla & Sieck, 2008]). Studies also indicated that: 1) a number of trophic factors (e.g. NT-4/5 and TrkB) are innervation dependent [Kulakowski et al., 2011]; 2) pathophysiological change in the presynaptic terminal is more remarkable than that in the postsynaptic terminal in aged animals [Kulakowski et al., 2011]; and 3) neurotrypsin-dependent NMJ degeneration results in a full sarcopenia phenotype in younger adult mice [Bü tikofer et al., 2011].

Thus, denervation may be the primary trigger for muscle fiber loss despite the hypotrophy of muscle fibers may also be a cause of denervation. This view is further supported by the previous studies: 1) indicated that the loss of motor units occur in a regressive manner, with the denervation of muscle preceding the loss of motor axons and eventual motor neuron death [Power et al., 2012]; and 2) suggested that axon impairment during aging may start as a distal process, causing a partial denervation of muscle fibers within a motor unit [Aagaard et al., 2010].

To this point, it is important to note that the aging-associated loss of muscle mass starts as early as 24 years of age while the onset of aging-associated denervation is at a later age (around 60 years) [Deschenes, 2004], this implies that either: 1) sarcopenia is not neurogenic in origin; or 2) such early onset of sarcopenia is caused by a hidden mechanism (other yet discovered factors) similar to the impact of hypothalamus on the muscular system mentioned earlier. Interestingly, the aging-associated loss of muscle strength and muscle mass (despite different onset times) are both well maintained or only decline slowly before the age of 60 years when a more rapid rate of decline commences [Deschenes, 2004]. This suggested that even sarcopenia may not be neurogenic in origin (at least in some secondary causes), the nervous system may still serve as a strong amplifier for the pathological development of sarcopenia.

Finally, when considering: 1) NMJs are maintained/regulated by glia (particularly, the perisynaptic Schwann cells) [Chung & Barres, 2012; Barres, 2008]; and 2) aging-associated denervation at the NMJ correlates better with Schwann cells than that of the motor neurons [Chai et al., 2011], it seems that glia may be a more appropriate target in this neurogenic model of sarcopenia.

10.1 Perisynaptic Schwann Cells and Sarcopenia

Schwann cells were first recognized by Louis Antoine Ranvier in 1871. All neurons in the PNS are intimately associated with Schwann cells, which serve diverse functions including insulation of PNS axons by their associated myelin sheaths [Kettenmann & Ransom, 2005; Mathey & Armati, 2007]. In addition to the satellite Schwann cells found in the DRG associating directly with neuronal cell bodies [Mathey & Armati, 2007], several other types of Schwann cells have been identified in the PNS including: 1) myelinating Schwann cells; 2) non-myelinating Schwann cells; 3) perisynaptic Schwann cells; and 4) terminal Schwann-like cells of sensory neurites [Verkhratsky & Butt, 2007c].

It is important to note that recent studies indicated that: 1) the loss of motor unit occurs in a regressive manner that begins with the denervation of muscle, followed by motor axon degeneration and eventually the loss of α-motor neurons [Power et al., 2012]; 2) aging muscles may not be in a state of poor adaptive responsiveness per se while the impaired capacity of axonal reinnervation of denervated muscle fibers may be responsible for the net loss of muscle mass during senescence [Aagaard et al., 2010]; 3)
glia are crucial in the formation and maintenance of functional neural circuits in the CNS, PNS and NMJs [Chung & Barres, 2012]; and 4) an aging-associated increase in the percentage change of fully denervated NMJs is associated with the deterioration of Schwann cells [Chai et al., 2011].

Among the 5 types of Schwann cells, perisynaptic Schwann cells (covered by the basal lamina that fuses with that of the muscle fiber and motor endplate) may be more relevant to sarcopenia as this subtype of Schwann cells ensheath the terminal axonal branches and synaptic boutons at the NMJs [Verkhratsky & Butt, 2007d]. Additionally, perisynaptic Schwann cells play many roles in the NMJs including: 1) synaptic function modulation; 2) maturation and extension of the motor endplate; 3) NMJ stabilization; 4) modulation of presynaptic ions and Ca$^{2+}$ concentration; 5) modulation of postsynaptic acetylcholine receptor aggregation; and most importantly 6) growth guidance of regenerating presynaptic nerve terminals of adult NMJs [Verkhratsky & Butt, 2007d]. Finally, it is important to note that trophic factor CNTF (nourishes both the nervous system and muscular system) is abundantly synthesized by Schwann cells in adult peripheral nerves [Guillet et al., 1999].

In summary, the aging-associated dysfunction of Schwann cells and possibly with other glia may explain the origin of sarcopenia (at least an important contributor to its etiology). However, more studies are still required to verify this neurogenic/gliogenic model and to bring further insights into the field of aging muscle researches.

11 Conclusion

To this day, although the consensus definition for sarcopenia is still open for improvement, the concept of sarcopenia is more or less settled – a multi-etiological muscle aging condition associated with at least the chronic loss of muscle mass. Although the nervous system plays a crucial role in the motor unit physiology and the pathogenesis of sarcopenia, it is still not clear whether the pathogenic origin lies in the nervous system and thus demanding further investigations into the issue. After all, due to the burgeoning evidences suggesting the important role played by the nervous system (both CNS and PNS) and the importance of glia (as either a physiological regulator or a pathophysiological factor), the future sarcopenia research shall take these fractions into account.

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Appendix

The author declares that he has no conflict of interest. For any queries/comments/criticisms, please feel free to contact the author by: pkwan@connect.polyu.hk / scienstein@msn.com.
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