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Review

The regulation of stem cell aging by Wnt signaling

Shin Fujimaki[1,2], Tamami Wakabayashi[1], Tohru Takemasa[2], Makoto Asashima[1] and Tomoko Kuwabara[1]

[1]Stem Cell Engineering Research Group, Biotechnology Research Institute for Drug Discovery, Department of Life Science and Biotechnology, National Institute of Advanced Industrial Science and Technology (AIST), Tsukuba Science City, Ibaraki and [2]Physical Education, Health and Sport Sciences, Graduate School of Comprehensive Human Sciences, University of Tsukuba, Tsukuba Science City, Ibaraki, Japan

Summary. Aging is an inevitable physiological process that leads to the dysfunction of various tissues, and these changes may contribute to certain diseases, and ultimately death. Recent research has discovered biological pathways that promote aging. This review focuses on Wnt signaling, Wnt is a highly conserved secreted signaling molecule that plays an essential role in the development and function of various tissues, and is a notable factor that regulates aging. Although Wnt signaling influences aging in various tissues, its effects are particularly prominent in neuronal tissue and skeletal muscle. In neuronal tissue, neurogenesis is attenuated by the downregulation of Wnt signaling with aging. Skeletal muscle can also become weaker with aging, in a process known as sarcopenia. A notable cause of sarcopenia is the myogenic-to-fibrogenic trans-differentiation of satellite cells by excessive upregulation of Wnt signaling with aging, resulting in the impaired regenerative capacity of aged skeletal muscle. However, exercise is very useful for preventing the age-related alterations in neuronal tissue and skeletal muscle. Upregulation of Wnt signaling is implicated in the positive effects of exercise, resulting in the activation of neurogenesis in adult neuronal tissue and myogenesis in mature skeletal muscle. Although more investigations are required to thoroughly understand age-related changes and their biological mechanisms in a variety of tissues, this review proposes exercise as a useful therapy for the elderly, to prevent the negative effects of aging and maintain their quality of life.

Key words: Wnt, Aging, Neural stem cells, Satellite cells, Exercise

Offprint requests to: Tomoko Kuwabara, Stem Cell Engineering Research Group, Biotechnology Research Institute for Drug Discovery, Department of Life Science and Biothecnology, National Institute of Advanced Industrial Science and Technology (AIST). Central 5, 1-1-1 Higashi, Tsukuba Science City, Ibaraki, 305-8565, Japan. e-mail: t.warashina@aist.go.jp.

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Introduction

Aging is an inevitable physiological process that takes place in organisms from the moment of birth. Various organs including the brain, nerves, heart, blood, and skeletal muscle show a progressive decline with aging, and these changes may be the cause of certain diseases, and ultimately death, in humans (Park and Yeo, 2013). Aging research has been expanded in recent years, with the discovery of gerontological genes. These genes participate in biological pathways that are conserved across species and increase the lifespan when overexpressed or mutated. This discovery has been helpful for understanding how aging is regulated, and has pioneered a new era in the development of pharmacological treatments that can extend healthy living and delay human aging (Moskalev et al., 2014).

A variety of model organisms have been used to identify numerous genes whose activity can be altered by mutation to prolong the lifespan, including *IGF1, PI3K, TOR, MAPK, AMPK, PKC, NF-κB,* and *TGF-β*. These genes are involved in signaling pathways that regulate energy balance, cellular plasticity, growth, homeostasis, and reproduction under conditions in which

the stress-resistance proteins are activated and hormonal stimulation of growth is blocked (Barzilai et al., 2012). These signaling cascades are conserved across species, from invertebrates to mammals (Kim, 2007).

In addition to the signaling cascades described above, Wnt signaling is known to regulate aging in various tissues. Wnt is a family of highly conserved secreted signaling molecules that play an essential role in the development and function of various tissues. Wnt proteins typically bind to the Frizzled receptor (Fzd) located in the plasma membrane (Clevers and Nusse, 2012; Sethi and Vidal-Puig, 2010). Wnt-Fzd interactions induce a variety of intracellular responses (Nusse, 2012).

The most widely studied of these is canonical Wnt signaling, which involves the activation of β-catenin/T-cell factor (TCF)/lymphoid enhancer factor (LEF) transcriptional complexes. β-Catenin is a subunit of the cadherin protein complex, which associates with a degradation complex, composed of axin, adenomatous polyposis coli (APC), and the serine-threonine kinase glycogen synthase kinase-3β (GSK-3β). In the inactive state (i.e. in the absence of Wnt-Fzd binding), β-catenin is phosphorylated by GSK-3β leading to ubiquitin-dependent degradation. When Wnt proteins bind to Fzd receptors, β-catenin is stabilized by the inactivation of GSK-3β and acts as a transducer of intracellular signaling. Accumulated β-catenin translocates into the nucleus and associates with TCF/LEF transcription factors to promote the transcription of target genes (Katoh and Katoh, 2007; Nusse, 2012). In contrast with canonical Wnt signaling, non-canonical Wnt signaling pathways are not activated through β-catenin/TCF/LEF transcriptional complexes. Non-canonical pathways activate the small GTPases Rho and Rac. This leads to cytoskeletal remodeling, the induction of Jun target genes, and increased intracellular Ca^{2+} concentrations, resulting in the activation of protein kinase C (PKC) or the transcription factor, nuclear factor of activated T cells (NFAT) (Nusse, 2012; von Maltzahn et al., 2012).

Some reports suggest that Wnt signaling regulates aging in a variety of tissues. For example, the activity of Wnt signaling declines with aging in the brain (Okamoto et al., 2011), leading to the dysfunction of neural stem-cell differentiation (Jessberger et al., 2009). Wnt signaling also decreases with aging in the lungs (Hofmann et al., 2014), with decreased expression of *Tle1* and *Lef1*, which positively mediate Wnt signaling, and increased expression of Frzb, which is an extracellular inhibitor of Wnt ligands (Hofmann et al., 2014). By contrast, Wnt signaling is activated with increasing age in some tissues (Brack et al., 2007; Liu et al., 2007). Liu et al. have suggested that the Klotho-deficient mouse model of accelerated aging shows increased senescence of progenitor cells, which may be mediated by upregulation of Wnt signaling activity (Liu et al., 2007). Administration of exogenous Wnt accelerates cell senescence *in vivo* and *in vitro*, and soluble Klotho binds to various Wnt ligands, inhibiting their biological activity (Liu et al., 2007). Brack et al. have also demonstrated that increased Wnt signaling in aged skeletal muscle may inhibit myogenesis (Brack et al., 2007). Skeletal muscle stem cells isolated from aged (24–26 month-old) mice showed lower expression of the myogenic marker Pax7 than young mice. Brack et al. have also reported that treating isolated skeletal-muscle stem cells treated with the canonical Wnt inhibitor Sfrp3 results in an increased proliferation and the revival of myogenesis (Brack et al., 2007). The above reports imply that Wnt signaling reliably regulates aging in various tissues. Of these, neuronal tissue appears to be the most affected by Wnt signaling.

The alteration in neurogenesis with aging

Aging of the nervous system

Mammalian aging is an inevitable process associated with a general reduction in the ability of adult tissues to maintain and repair themselves and a progressive deterioration in physiological function. Importantly, the basic processes involved in aging of the central nervous system are commonly characterized by a loss of synaptic contacts and neuronal apoptosis, provoking an age-dependent decline in sensory processing, motor performance, and cognitive function (Rutten et al., 2003). The hippocampus, a brain structure involved in spatial memory, exhibits marked functional decline with aging in mammals such as humans (Wilkniss et al., 1997), monkeys (Lai et al., 1995; Rapp et al., 1997), dogs (Head et al., 1995), rats (Barnes, 1979; Markowska et al., 1989), and mice (Bach et al., 1999). These studies reveal deficits in the performance of tasks designed to test spatial navigation in aged animals. For example, age-related impairments have been described in rodents performing hippocampus-dependent spatial, and contextual learning, such as water-maze and fear-conditioning tasks (Rosenzweig and Barnes, 2003; Ward et al., 1999). Moreover, it has been shown that decreased hippocampal volume accompanies age-related deficits in the performance of hippocampus-dependent tasks in humans (Driscoll et al., 2003) and rats (Sykova et al., 2002). Thus, hippocampal function is vulnerable to the effects of aging, including hippocampus-dependent learning and memory, and these functional declines are associated with a reduction in hippocampal volume.

Age-induced impairments in cognitive function may be attributed in part to decreases in certain signaling molecules, including IGF1 and brain-derived neurotrophic factor (BDNF), as well as Wnts. It is well known that the Wnt pathway is involved in many developmental processes such as neuronal maturation, migration, neuronal connectivity, and synapse formation (Toledo et al., 2008; Inestrosa and Arenas, 2010; Ortiz-Matamoros et al., 2013). Wnt3 is one of the major Wnt proteins in hippocampal astrocytes. The levels of Wnt3 and the number of Wnt3-secreting astrocytes are both decreased during aging (Okamoto et al., 2011). Lentivirus-mediated inhibition of Wnt signaling results

in a decrease in hippocampal neurogenesis and the impairment of hippocampus-dependent spatial learning and memory in rats (Jessberger et al., 2009). Since Wnts have a pivotal role in neurogenesis, cognitive impairment could be attributed to an age-associated decline in neurogenesis through a decline in the hippocampal secretion of Wnts. IGF1 is also reported to directly stimulate the proliferation of adult hippocampal progenitor cells in vitro (Aberg et al., 2003), and the administration of IGF1 has been shown to increase the rate of neurogenesis in the adult hippocampus of adult rodents (Aberg et al., 2000; Lichtenwalner et al., 2001). Aging is associated with reduced expression of IGF1 and its receptor in particular brain regions, including the hippocampus in rodents (Sonntag et al., 1999; Lai et al., 2000), and reductions in serum IGF1 have also been observed in aging humans (Ghigo et al., 1996). Reduced IGF1 signaling during aging probably contributes to cognitive deterioration since intracerebroventricular administration of IGF1 attenuates both the reduction in neurogenesis and the cognitive impairment that has been observed in aged rats (Markowska et al., 1998; Lichtenwalner et al., 2001). A recent study has shown that advancing age is associated with smaller hippocampal volumes, reduced serum levels of BDNF, and cognitive decline in humans (Erickson et al., 2010). In a gene-knockout study in mice, heterozygous knockout of *BDNF* also resulted in a reduction in hippocampal volume (Lee et al., 2002; Magarinos et al., 2011). These studies suggest that BDNF is involved in the maintenance of hippocampal volume, and aging disrupts the function of BDNF. Along with Wnts and IGF1 (Aberg et al., 2003; Jessberger et al., 2009), BDNF is also thought to be involved in adult neurogenesis (Bergami et al., 2008) (Fig. 1). Therefore, the regulation of adult neurogenesis by extrinsic factors may help prevent cognitive dysfunction that is due to aging.

Neurogenesis

Neurogenesis is defined as the generation of new neurons from neural stem cells (NSCs), which are characterized by the capacity for self-renewal. Multipotent progenitors are capable of differentiating into multiple neural lineages, including neurons, astrocytes, and oligodendrocytes (Gage, 2000). Neurogenesis in the mammalian brain is a multi-step process that includes the proliferation of neural progenitor cells, fate determination, migration, maturation, and the functional integration of newborn cells into the existing neuronal circuitry (Fig. 1). Although neurogenesis almost completely ceases after birth, recent studies have demonstrated that neurogenesis does in fact persist in the adult brain of mammals, including rodents, primates, and humans (Bayer, 1983; Kuhn et al., 1996; Kempermann et al., 1997; Eriksson et al., 1998; Kukekov et al., 1999; Pencea et al., 2001). In rodents, new neurons are actively generated in two discrete regions: the subventricular zone (SVZ) of the lateral ventricles, and the sub-granular zone (SGZ) of the dentate gyrus in the hippocampus. Immature neurons migrate from the SVZ along the rostral migratory stream to the olfactory bulb where they differentiate into multiple types of interneurons. In the hippocampus,

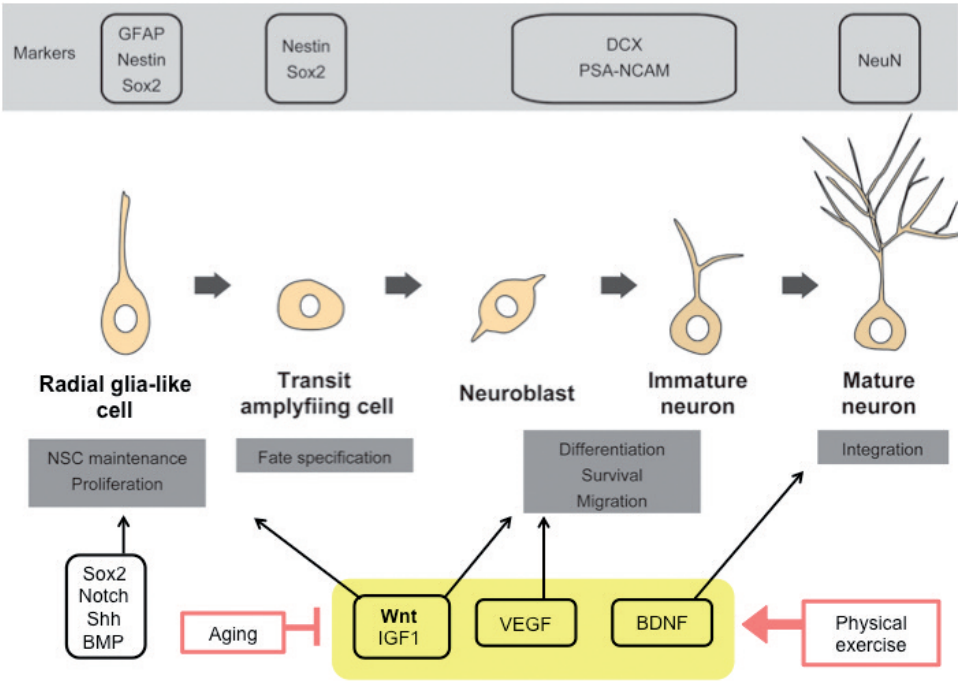

Fig. 1. Schematic diagram of regulation of adult neurogenesis. Adult NSCs are primarily located in two distinct regions of the brain: the SVZ of the lateral ventricles and the SGZ of hippocampal dentate gyrus. Radial glia-like cells have the potential to serve as NSCs. The progression from radial-like cells to mature neurons in adult SVZ and SGZ is a multistep process with distinct stages and is controlled by several factors. There are several cell-specific markers during the various stages of development. Aging inhibits the expression of some factors involved in adult neurogenesis such as Wnts, IGF1, VEGF and BDNF, while physical exercise promotes the activation of these factors, which leads to the activation of adult neurogenesis. SVZ, subventricular zone, SGZ, subgranular zone.

proliferating cells in the SGZ differentiate into immature neurons and migrate into the granule cell layer to become granule cells of the dentate gyrus. Recent studies have shown that newly formed neurons are incorporated into the functional networks of both the olfactory bulb and the dentate gyrus, which suggests a significant impact by adult neurogenesis on brain functions such as learning, memory processing, and odor discrimination (Gheusi et al., 2000; Kempermann, 2002; van Praag et al., 2002; Carleton et al., 2003; Kee et al., 2007).

NSCs are distinguished by the expression of marker proteins, by morphology, and by their proliferative behavior. In the adult SVZ, radial glia-like progenitor cells are present next to the ependymal layer. These cells are relatively quiescent and are thought to be multipotent NSCs (Doetsch et al., 1999). Radial glia-like progenitor cells generate transit-amplifying cells, which rapidly proliferate and subsequently give rise to neuroblasts. These neuroblasts express doublecortin (DCX) and PSA-NCAM, and migrate along the rostral migratory stream to the olfactory bulb, where they differentiate into GABA-producing and dopamine-producing interneurons (Alvarez-Buylla and Garcia-Verdugo, 2002; Zhao et al., 2008). In the SGZ, NSCs that can give rise to granule cells are present at the border between the hilus and the granule cell layer (Gage, 2000). Radial glia-like NSCs in the SGZ are slowly dividing or quiescent and are thought to be undifferentiated precursors of neurons (Seri et al., 2001; Kempermann et al., 2004). They extend a single radial process towards the molecular layer and are characterized by the expression of nestin, GFAP, and Sox2. Recently, a second class of radial glia-like NSCs has been identified morphologically as having multiple horizontal processes (Lugert et al., 2010). When activated, they give rise to transit-amplifying progenitors that have the potential to differentiate into neurons and astrocytes (Kronenberg et al., 2003; Kempermann et al., 2004; Lugert et al., 2010; Bonaguidi et al., 2011; Hsieh, 2012). These transit-amplifying cells express nestin and Sox2, but not GFAP (Kempermann et al., 2004). Sox2 is a transcription factor and NSCs expressing Sox2 can self-renew and give rise to neurons and astrocytes, according to Suh et al (Suh et al., 2007). Thus, Sox2 is an important factor for maintaining the pluripotency and self-renewal capacity of NSCs. These transit-amplifying progenitors then commit to the neuronal lineage as neuroblasts, which are proliferative and express DCX, but not nestin or Sox2 (Kronenberg et al., 2003). Neuroblasts then become immature neurons that extend their dendrites toward the molecular layer of the dentate gyrus and project their axons into the CA3 region. The immature neurons eventually differentiate into mature neurons and are integrated into the pre-existing hippocampal circuitry as functional granule cells (Zhao et al., 2006; Mathews et al., 2010; Varela-Nallar and Inestrosa, 2013). Thus, neurogenesis can be divided into sequential stages: activation of quiescent stem cells, proliferation, neuronal fate specification, maturation, and integration of newborn neurons.

Astrocytes, endothelial cells, ependymal cells, and oligodendrocytes are present in the neurogenic niche, as well as mature neurons and NSCs. A transplantation study has revealed the importance of the neurogenic niche in determining the fate of adult NSCs. Neural stem cells derived from the adult hippocampus or spinal cord can give rise to neurons after grafting into the dentate gyrus, but not into the spinal cord (Shihabuddin et al., 2000). Moreover, recent work by Song et al. has suggested that specified microenvironments provide the unique niche that enables adult neurogenesis (Song et al., 2002). In this in vitro study, astrocytes from the hippocampus were found to preferentially instruct adult NSCs to differentiate into neurons, but astrocytes from the adult spinal cord could not. This evidence suggests that the local environment dictates the fate of adult NSCs, and astrocyte-derived soluble and membrane-bound factors promote neurogenesis. Other components of the neurogenic niche have also been identified as supporting neurogenesis, such as endothelial cells (Shen et al., 2004), microglia (Sierra et al., 2010), and the vascular system (Palmer et al., 2000). Therefore, the microenvironments of the SVZ and SGZ, but not other brain regions, are thought to possess specific factors that permit the differentiation and integration of new neurons. A variety of molecules serve as niche signals to regulate the maintenance, activation, and fate choice of adult NSCs, including Notch, BMPs, Noggin, and Shh, growth and neurotrophic factors, and Wnts (Fig. 1) (Faigle and Song, 2013). Through intrinsic and extrinsic factors, adult neurogenesis is tightly regulated in order to allow the maintenance and self-renewal of the stem cell pool and the generation of fully functional neurons.

Stem cells and aging

Although adult neurogenesis occurs in these specific regions, there is a progressive reduction in hippocampal neurogenesis that is evident during aging in different species (Kuhn et al., 1996; Gould et al., 1999; Leuner et al., 2007; Olariu et al., 2007; Varela-Nallar et al., 2010), including humans (Knoth et al., 2010). Similarly, SVZ neurogenesis declines with increasing age in different species (Maslow et al., 2004; Luo et al., 2006; Bunk et al., 2011). In rodents, for example, the total number of proliferating cells in the SVZ of aged (20–24 month-old) animals is reduced by 50–75% (Tropepe et al., 1997; Doetsch et al., 1999; Jin et al., 2003; Enwere et al., 2004; Maslov et al., 2004; Luo et al., 2006). The numbers of proliferating neuroblasts reaching the olfactory bulb are reduced by 75% in aged mice, which results in a functional decline in fine odor discrimination (Tropepe et al., 1997; Enwere et al., 2004).

Recent studies suggest that the age-related decrease in neurogenesis in the dentate gyrus is primarily attributable to the decreased production of new cells. NSCs expressing Sox2 have the ability to self-renew and the potency to give rise to neurons and astrocytes (Suh et

al., 2007), so Sox2 is used as a persistent marker for multipotent neural stem cells. Interestingly, the number of Sox2+ NSCs did not decrease in the SGZ of aged rats, but the number of Sox2+ cells also expressing the proliferative marker Ki67 was greatly reduced compared with young adult rats (Hattiangady and Shetty, 2008). In the SVZ, there was a severe reduction in both the number of Sox2-expressing cells and the number of proliferating Sox2+ cells in aged rats (Ahlenius et al., 2009). The study also showed that NSCs isolated from the SVZ of both aged and young adult rats can generate neurons, astrocytes, and oligodendrocytes in culture conditions, but NSCs isolated from the SVZ of aged rats proliferate more slowly compared with those from the SVZ of younger adult rats. These investigations show that the proliferative activity of multipotent NSCs is greatly reduced compared with young adult rats, and suggest that the decline in neurogenesis is due to the inactivity of NSCs. In addition, shortages in the neural stem and precursor cell pools have been linked to the functional declines observed during aging, and may be correlated with some of the observed cognitive deficits that are associated with aging (Tropepe et al., 1997; Enwere et al., 2004).

Astrocytes, one of the major components of the neurogenic niche, also show age-related changes that may be responsible for altering the neurogenic niche and contributing to the low rates of neurogenesis seen in aged animals. In the microenvironment of the hippocampal neurogenic niche, the density of astrocytes that express fibroblast growth factor 2 (FGF2) declines considerably with age in the dentate gyrus as well as other regions of the hippocampus, even though the total number of astrocytes does not decrease (Shetty et al., 2005). The levels of hippocampal growth factors that promote neurogenesis, including IGF1, FGF2, vascular endothelial growth factor (VEGF), and BDNF, are also significantly reduced in aged rats compared with young rats. These results suggest that the local environment of neural progenitor cells becomes progressively less supportive of neurogenesis with age.

Wnt regulation of neurogenesis and aging

Several studies have described the role of Wnt signaling in adult neurogenesis. For example, Wnt3 is strongly expressed in hippocampal astrocytes, and NSCs express major components of the Wnt/β-catenin pathway (Lie et al., 2005; Wexler et al., 2009). Therefore, NSCs could receive Wnt signals and stimulate the canonical Wnt/β-catenin pathway. A co-culture study of NSCs with hippocampal astrocytes has shown that astrocyte-derived Wnts stimulate neuroblast proliferation and neuronal differentiation in adult hippocampal NSCs through the Wnt/β-catenin pathway (Lie et al., 2005). In addition to astrocyte-derived Wnts, autocrine Wnt signaling in hippocampal NSCs, since several Wnts are expressed in these cells (Wexler et al., 2009). Interestingly, inhibition of autocrine Wnt stimulation promotes neurogenesis, and reduces the numbers of multipotent progenitors. This indicates that the Wnt autocrine pathway promotes the differentiation of progenitors into neurons, but also helps to maintain the pool of stem cells. The injection of a lentiviral vector expressing Wnt3 or dominant-negative Wnt into the dentate gyrus of mice also showed that the activation of Wnt signaling increases adult neurogenesis, while inhibition of Wnt signaling reduces neurogenesis significantly. Furthermore, the inhibition of Wnt signaling in the dentate gyrus of adult rats also results in the impairment of spatial memory and object recognition (Jessberger et al., 2009). These results indicate the profound role of Wnt signaling in adult neurogenesis and its involvement in cognitive function.

One of the major Wnt-mediated transcription factors is NeuroD1, which is a basic helix-loop-helix transcription factor that works as a downstream mediator of Wnt-induced neurogenesis from adult hippocampal neural progenitors (Kuwabara et al., 2009). Interestingly, NeuroD1 is selectively expressed in dividing neural progenitors and in immature granule neurons in the adult dentate gyrus, but not in Sox2-expressing hippocampal neural progenitors. Furthermore, *in silico* analysis of the NeuroD1 promoter showed that there is a dual regulatory element that could bind to Sox2 and TCF/LEF, the major downstream transcription factors of the Wnt/β-catenin pathway. In vitro transcriptional analysis has also demonstrated that the NeuroD1 promoter is directly activated by TCF/LEF through the Wnt pathway, but is silenced by Sox2 and other extrinsic factors that inhibit neurogenesis. Using NeuroD1 conditional knockout mice, Gao et al. demonstrated that NeuroD1 is required for neurogenesis in the adult hippocampus *in vivo* by facilitating the survival and maturation of adult-born neurons (Gao et al., 2009). Complementary *in vitro* studies showed that NeuroD1 is sufficient to induce neuronal differentiation and that Wnt-mediated neurogenesis requires NeuroD1 in adult hippocampal neural progenitor cells. Activation of the canonical Wnt pathway causes β-catenin accumulation, which induces the transcription of NeuroD1 in NSCs, and therefore induces neuronal differentiation. On the other hand, Sox2+ multipotent progenitor cells silence NeuroD1 transcription and maintain undifferentiated NSCs. In another study, it was demonstrated that NeuroD1 directly activates *insulin* gene expression in NSCs from the adult hippocampus and the olfactory bulb (Kuwabara et al., 2011). Several studies have reported that Insulin/IGF signaling has an important role in controlling the differentiation of NSCs (Aberg et al., 2000, 2003; Arsenijevic et al., 2001; Hsieh et al., 2004; Kuwabara et al., 2011), and that neurogenesis is impaired in diabetes (Hidaka et al., 2013; Ramos-Rodriguez et al., 2014). The activation of Insulin/IGF signaling stimulates the proliferation of neural stem cells in an undifferentiated state, induces the differentiation of oligodendrocytes, and increases the survival of neurons and oligodendrocytes (Hsieh et al., 2004). Thus, the

activation of Wnt3 could result in the activation of Insulin/IGF signaling via NeuroD1 activation.

Recently, Wnt7a has been shown to promote the proliferation and self-renewal of adult NSCs through the canonical Wnt signaling pathway in neurogenic regions of the adult brain (Erickson et al., 2010). In the adult SVZ, overexpression of Wnt3a and Wnt5a has been shown to promote proliferation and neuronal differentiation of adult SVZ neural progenitor cells in vitro (Hattiangady and Shetty, 2008). In addition, the stabilization of β-catenin by retrovirus-mediated expression was shown to promote the proliferation of neural progenitor cells in the SVZ in vivo, resulting in increased neurogenesis in the olfactory bulb (Adachi et al., 2007). Therefore, the regulation of Wnt signaling is essential for adult neurogenesis (Fig. 1).

A recent study using rodents has indicated that a decline in Wnt signaling is associated with an age-dependent reduction in neurogenesis (Fig. 1). During aging, the levels of Wnt3 protein in hippocampal astrocytes and the number of Wnt3-secreting astrocytes decline (Okamoto et al., 2011). The study also demonstrated that there is a progressive decrease in the expression of Wnt3 and Wnt3a in the dentate gyrus of rats aged between 2 and 22 months of age, with a decrease in the expression of NeuroD1. Wnts derived from hippocampal astrocytes are essential factors for the stimulation of Wnt/β-catenin signaling in neural progenitors, and induce their neural differentiation. This study suggests that the decline inWnt3/Wnt3a expression in astrocytes may cause the decreased expression of proneural genes and a consequent decrease in neurogenesis. More recently, the expression of the Wnt inhibitor Dickkopf 1 (Dkk1) has been shown to increase with age, and its loss enhances neurogenesis in the hippocampus (Seib et al., 2013). Inducible deletion of Dkk1 in the adult CNS resulted in the increased self-renewal of neural progenitors and increased generation of immature neurons. According to the study, this suggests that suppression of Wnt signaling by this inhibitor may downregulate neurogenesis during aging. An association between Wnt3 levels and cell proliferation has also been reported in the human hippocampus (Gerber et al., 2009), which implies that the Wnt pathway may also regulate neurogenesis in the human brain.

Activation of neurogenesis by exercise

A number of studies have shown that physical exercise increases neurogenesis. Originally, van Praag et al. demonstrated that voluntary physical exercise in young adult (3 month-old) mice increased cell proliferation, cell survival, and neurogenesis within the dentate gyrus (van Praag et al., 1999). Subsequent studies confirmed exercise-mediated increases in neurogenesis in the dentate gyrus of the hippocampus in young, adult, and aged animals (Kempermann et al., 1998; Kitamura and Sugiyama, 2006; Kronenberg et al., 2006; Naylor et al., 2008; Wu et al., 2008; Creer et al., 2010). Importantly, voluntary physical exercise has also been shown to increase neurogenesis in the dentate gyrus of aged (19 month-old) mice (van Praag et al., 2005).

Several signaling pathways have recently been implicated in the exercise-mediated activation of neurogenesis (Fabel et al., 2003). Fabel et al. reported that peripheral VEGF is an essential factor, based on the finding that VEGF blockade abolished exercise-induced neurogenesis while baseline levels were maintained in non-running animals. Similarly, IGF1 has been implicated as having an important role in the exercise-mediated activation of neurogenesis (Trejo et al., 2001). The immunoneutralization of IGF1 blocks the ability of exercise to enhance neurogenesis. Thus, IGF1 was identified as an essential factor for the neurogenesis induced by physical activity.

Exercise also modulates the expression of genes involved in Wnt signaling (Stranahan et al., 2010). Running was found to significantly increase the expression of Wnt3 in astrocytes of the dentate gyrus and to increase the population of Wnt3 expressing cells in young and aged mice (Okamoto et al., 2011). Running has also been shown to improve hippocampus-dependent learning in aged mice and humans (Colcombe and Kramer, 2003; van Praag et al., 2005; Weuve et al., 2004). In addition, the inhibition of Wnt signaling in the dentate gyrus of adult rats results in the impairment of spatial memory and object recognition (Jessberger et al., 2009). These studies indicate that exercise improves cognitive function in the aged brain, through the induction of neuronal differentiation by astrocyte-derived Wnt3. The activation of NeuroD1 by Wnt3 is also able to promote the activation of Insulin/IGF signaling, which may increase the proliferation of undifferentiated NSCs and enhance neurogenesis in the aged brain.

According to these studies, neurogenesis declines with aging because of impairments in the function of several factors regulating neurogenesis, including Wnts, IGF1, and BDNF (Fig. 1). However, physical exercise could enhance the production of these factors that decline with age, resulting in the activation of neurogenesis even in older brains. The activation of neurogenesis by physical exercise may help to maintain the cognitive function in the aged brain.

The alteration in myogenesis with aging

The atrophy of skeletal muscle with aging; Sarcopenia

Skeletal muscle is the largest organ in the body and accounts for a large proportion of body weight: approximately 31% for women and 38% for men (Janssen et al., 2000). Similar to the neuronal tissue described in the previous section, skeletal muscle can become weaker with aging. The decline in skeletal muscle mass with aging is known as sarcopenia. Sarcopenia refers to the age-related loss of muscle mass

and function, which may emerge as early as 50 years of age in humans (Di lorio et al., 2006). The age-related decrease in muscle strength has been reported as averaging 20–40% (Doherty, 2003). Sarcopenia develops primarily in the lower extremities, which may be related to decreased physical activity with aging, or to a greater reduction in the number of motor units in the legs than in the arms (Janssen et al., 2002; Narici and Maffulli, 2010). Since the age-associated decline in skeletal muscle mass leads to the impairment of muscle strength and power, the prevention of sarcopenia is important for maintaining quality of life.

There are various factors that contribute to sarcopenia, including both environmental and biological factors. For example, decreases in nutrient intake and of physical activity induce sarcopenia (Doherty, 2003; Degens, 2007; Buford et al., 2010). Many elderly individuals tend to lower their food intake and receive insufficient protein and Vitamin D. This may impair protein synthesis and result in the loss of muscle mass (Doherty, 2003; Buford et al., 2010). In addition to poor nutrition, many elderly individuals may restrict their physical activity because of orthopedic pathology, and this may also result in the loss of muscle mass and strength (Degens, 2007). However, it is evident that elderly individuals who are highly active also have less muscle mass than their younger counterparts, suggesting that a decrease in physical activity may not be the sole cause of sarcopenia (Klitgaard et al., 1990a,b). Although lifestyle is a notable factor for developing sarcopenia, the age-related loss of muscle mass and function is mainly caused by multiple biological systems that are described in the following paragraphs.

Various biological systems show increases or decreases with age. Firstly, the major factors that increase with sarcopenia are pro-inflammatory cytokines, intramuscular fibrosis, and adiposity. Aged skeletal muscle is associated with chronic inflammation. Previous studies have reported that the levels of pro-inflammatory cytokines are increased in the skeletal muscle of the elderly, including tumor necrosis factor α (TNF-α) and interleukin-6 (IL-6). For example, some human studies have demonstrated a 2.8 fold increase in TNF-α and IL-6 expression in the skeletal muscle of aged subjects compared with young subjects (Leger et al., 2008; Della Gatta et al., 2014). Furthermore, an animal study has reported the increased expression of TNF-α in the soleus and vastus lateralis (VL) of aged (26 month-old) rats relative to adult (6 month-old) rats (Phillips and Leeuwenburgh, 2005). Although the relationship between the upregulated pro-inflammatory cytokines and sarcopenia is not well defined, TNF-α and IL-6 may contribute to sarcopenia by promoting insulin resistance and delaying muscle regeneration (Hamada et al., 2005; Dirks and Leeuwenburgh, 2006; Liao et al., 2010).

Sarcopenic muscle predominantly consists of connective and adipose tissue. Aged skeletal muscle includes more fibrosis than young muscle, and this is related to increased amounts of collagen (as interstitial matrix protein) (Brack et al., 2007; Serrano and Munoz-Canoves, 2010). In addition, aged myofiber explants have shown greater expression of fibronectin, which is also a component of the interstitial matrix, compared with young myofiber explants (Brack et al., 2007). The infiltration of adipose tissue into skeletal muscle increases with aging (Goodpaster et al., 2001; Song et al., 2004). In obese aged individuals, this alteration is termed sarcopenic obesity (Narici and Maffulli, 2010).

The other major factors that influence sarcopenia are muscle fiber size and number, sex hormones, and protein synthesis. Muscle fiber size and number decreases with aging and is associated with sarcopenia. There is firm evidence that the size of type II fibers preferentially decreases compared to type I fibers with aging (Larsson et al., 1978; Lexell et al., 1983; Klitgaard et al., 1990a,b). More recently, the cross sectional area of type II fibers in 85+ year-old individuals has been shown to be 57% smaller than that of 25 year-old individuals, but type I fibers also tend to be 25% smaller in the older individuals (Andersen, 2003). Considering the subtypes of type II fibers, a greater decline in type IIb fibers than of type IIa fibers has been observed in older men and women (Klitgaard et al., 1990a,b; Coggan et al., 1992). A decline in muscle fiber number has also been reported previously (Lexell et al., 1983, 1988).

There are reports that the depletion of sex hormones such as testosterone and estrogen may contribute to sarcopenia (Di lorio et al., 2006; Lee et al., 2007). An age-related decrease in testosterone and estrogen induces upregulation of pro-inflammatory cytokines IL-6 and TNF-α, and accelerates the loss of muscle mass during sarcopenia (Maggio et al., 2005; Lee et al., 2007). In connection with the depletion of sex hormones, the levels of growth hormone (GH) and insulin-like growth factor 1 (IGF-1) decrease with aging, and may contribute to the development of sarcopenia (Kalleinen et al., 2008; Maltais et al., 2009). Postmenopausal (58–70 year-old) subjects have shown lower GH levels than premenopausal (45–51 year-old) subjects (Kalleinen et al., 2008). It has been reported that depletion of GH promotes intramuscular fat accumulation and loss of muscle mass (Lee et al., 2007).

The rate of protein synthesis decreases in aged muscle. There are reports of reduced myofibrillar protein content and myosin heavy chain (MHC) expression (Hasten et al., 2000; Tavernarakis, 2008). The cause of reduced protein synthesis in aged skeletal muscle could be due to the decline in circulating and tissue-associated GH and IGF-1 (Perrini et al., 2010). The age-related decrease in IGF-1 induces high expression of muscle growth inhibitors, including the pro-inflammatory cytokines IL-6 and TNF-α (Leger et al., 2008; Lang et al., 2010), and decreased phosphorylation of Akt, the mammalian target of rapamycin (mTOR), and p70 S6 kinase, resulting in decreased protein synthesis (Paturi et al., 2010). Although sarcopenia develops from the interaction of various factors, its most notable cause is

the loss of skeletal muscle stem cells.

Wnt regulation of satellite cells

Skeletal muscle is an abundant source of adult stem cells. Satellite cells are muscle-specific stem cells that contribute to the postnatal maintenance, growth, repair, and regeneration of skeletal muscle (Kuang and Rudnicki, 2008). Satellite cells are located adjacent to the plasma membranes of myofibers under the basal lamina (Alameddine et al., 1989). In adult skeletal muscles, satellite cells are in a quiescent state under normal physiological conditions and represent 2.5–6% of all the nuclei in myofibers. However, in response to muscle injury or exercise, satellite cells are activated, and can then proliferate, undergo self-renewal, and differentiate into mature new fibers (Charge and Rudnicki, 2004). A previous study has demonstrated that skeletal muscle depleted of satellite cells cannot repair itself after injury (McCarthy et al., 2011). Thus, satellite cells appear to be essential for the regeneration of injured muscle fibers.

Satellite cells demonstrate at least two states during skeletal muscle turnover: quiescent and activated. Both quiescent and activated satellite cells express the stem cell-specific marker, Pax7 (Zammit et al., 2006). Quiescent satellite cells express Pax7 alone, whereas activated satellite cells coexpress Pax7, Myf5, and MyoD, which are myogenic regulatory factors (MRFs) and key transcription factors for myogenic lineage progression and differentiation (Zammit et al., 2006). Although most activated satellite cells proliferate and differentiate through Pax7 downregulation, others quit the cell cycle and return to a quiescent state (Zammit et al., 2004). Myf5 is a target of the Pax7 transcription factor. Pax7 upregulates Myf5 expression through recruitment of the histone methyltransferase (HMT) complex, and this complex directly methylates histone H3 lysine 4 (H3K4) on the promoter of the Myf5 locus (McKinnell et al., 2008). Pax7(+)/Myf5(+) co-expressing satellite cells can upregulate MyoD and trigger cell proliferation (Olguin and Olwin, 2004; Zammit et al., 2004). Furthermore, MyoD associates with MEF2d to initiate the transcription of myogenin and other muscle-specific genes (Rampalli et al., 2007). Thus, MyoD acts as a master regulator of myogenesis and activates the transcription of muscle-specific genes.

It has been revealed that Wnt signaling is an important factor in the regulation of myogenesis, because of its influence on expression of the MRFs. Wnt1 induces the expression of Myf5, whereas Wnt7a or Wnt6 preferentially activate MyoD in explant cultures of mouse paraxial mesoderm (Tajbakhsh et al., 1998). Wnt/β-catenin canonical signaling initiates the differentiation of satellite cells by replacing Notch signaling, which regulates the cell fate and proliferation of various cell types (Brack et al., 2008). It has been reported in a recent study that myogenic differentiation is positively regulated by R-spondin, which activates canonical Wnt signaling and leads to the enhancement of β-catenin-dependent gene transcription (Han et al., 2011). Moreover, Wnt7a drives satellite cell expansion and controls the homeostatic level of satellite cells via non-canonical Wnt signaling (Le Grand et al., 2009). This suggests that Wnt signaling plays a variety of important roles in embryonic and postnatal skeletal muscle development, including the determination of cell fate choice and the proliferation of satellite cells.

In addition to its functions in the embryonic and postnatal development of skeletal muscle, Wnt signaling is involved in myogenesis in adult skeletal muscle. Wnt signaling has been shown to have an essential role in myogenic stem cells in adults (Brack et al., 2007). Brack et al. have demonstrated that the overnight addition of the Wnt inhibitor sFRP3 to cultures of single myofibers 3.5 days after isolation induces a decreased proportion of myogenin- or desmin-expressing satellite cells, suggesting that Wnt signaling contributes to the myogenic differentiation of adult satellite cells (Brack et al., 2008). Wnt signaling is also critical for muscle regeneration. Wnt may indirectly affect muscle regeneration by inducing muscle specification of resident $CD45^+$ adult stem cells (Polesskaya et al., 2003). Moreover, there is some evidence that Wnt signaling is activated after skeletal muscle injury (Polesskaya et al., 2003; Brack et al., 2008, 2009). The mRNA expression of *Wnt5a, Wnt5b, Wnt7a,* and *Wnt7b* increases in skeletal muscle four days after cardiotoxin-induced muscle injury (Polesskaya et al., 2003). Four days after myofiber explantation, there is increased expression of *Wnt3a, Fzd1, Fzd2* and *Axin2*, which is a downstream target of Wnt signaling (Brack et al., 2008). Brack et al. have reported that there is an increase in TCF reporter activity in myogenic cells two and five days after muscle injury (Brack et al., 2008). They have also shown the increased expression of the Wnt signaling co-activator BCL9 in differentiating myoblasts (Brack et al., 2009), and these results suggest that Wnt signaling plays a critical role in the regeneration of skeletal muscle. Recently, it has been shown that Wnt signaling contributes to the activation of adult satellite cells in the absence of skeletal muscle injury. Fujimaki et al. have demonstrated that wheel-running-induced activation of Wnt signaling directly regulates the activation of satellite cells through upregulated *Myf5* or *MyoD* transcription (Fujimaki et al., 2014). Furthermore, Jones et al. have reported that Wnt/β-catenin signaling accelerates myogenic differentiation by stimulating the expression of myogenin and follistatin, a secreted glycoprotein that antagonizes members of the TGF-β superfamily (Jones et al., 2015). Thus, Wnt signaling is an important factor for regulating the activation and differentiation of satellite cells in mature skeletal muscle.

Satellite cells and aging

It is important for satellite cells to maintain their

regenerative potential in order to prevent a decline in skeletal muscle mass. Satellite cells lose their regenerative potential with aging (Hikida, 2011), and this is especially true of sarcopenic muscle (Zwetsloot et al., 2013). One of the major causes of sarcopenia is the decline in satellite cell numbers with age, and many investigators have reported that the number of satellite cells decreases in aged skeletal muscle (Snow, 1977; Hawke and Garry, 2001; Renault et al., 2002; Shefer et al., 2006; Carlson et al., 2009; Shefer et al., 2010). Carlson et al. have demonstrated a decrease in satellite cell numbers in resting aged (70 year-old) human muscle relative to young (20 year-old) muscle using Pax7, neural cell adhesion marker (NCAM), and M-cadherin satellite cell markers (Carlson et al., 2009). Using a mouse model, Shefer et al. have shown a 60% decrease in Pax7-positive satellite cells in aged (19–25 month-old) extensor digitorum longus (EDL) muscle fibers relative to young (3–6 month-old) EDL muscle fibers (Shefer et al., 2006). Despite a considerable amount of evidence supporting an age-related decline in satellite cell numbers, it should be noted that there have been some reports showing no difference in satellite cell numbers with aging (Beccafico et al., 2007; Brooks et al., 2009). Brooks et al. have reported that there are no significant differences in satellite cell numbers between aged (24 month-old) and adult (5 month-old) soleus muscle in Fischer rats (Brooks et al., 2009).

In addition to the decline in their cell numbers, many studies have suggested that satellite cells intrinsically alter with aging, especially their proliferation potential. A previous study has reported that the proliferation rate of isolated satellite cells decreases with age (Schultz and Lipton, 1982). Carlson and Conboy have demonstrated that culturing satellite cells in aged mouse serum reduced their proliferation potential compared with those cultured in young serum, using BrdU immunohistochemistry techniques (Carlson and Conboy, 2007). Shefer et al. have reported that there is only a 10-fold increase in the proliferation of myogenic cells from cultured aged (28–30 month-old) mouse myofibers, while there is a 15-fold increase in cells from cultured adult (3–4 month-old) myofibers at the same time point (after culture for 2 days) (Shefer et al., 2006). Moreover, some studies have indicated that aging severely influences the ability of satellite cells to proliferate (Conboy et al., 2003; Carlson et al., 2009). An age-associated decline in the proliferative ability of satellite cells impairs the regeneration potential of skeletal muscle and induces sarcopenia.

The candidates for controlling the regenerative potential of satellite cells are Notch and Wnt signaling. Notch signaling activity has been shown to regulate cell fate and proliferation in satellite cells (Buas and Kadesch, 2010). The binding of Notch receptors to their DSL ligands (Delta/jagged, Serrate or Lag2) releases the Notch intracellular domain (NICD) (Kopan and Ilagan, 2009). NICD binds to recombining binding protein-Jκ (RBP-Jκ), which is a key mediator of Notch signaling, and translocates into the nucleus (Jarriault et al., 1995; Kato et al., 1996). The translocated NICD/RBP-Jκ complex leads to up-regulation of transcription factors (Hes, Hey) resulting in the activation of myoblast proliferation. Notch signaling is impaired in regenerating aged skeletal muscle (Buas and Kadesch, 2010). There are fewer Notch1 receptors and Delta1 ligands present in aged activated satellite cells compared with young activated satellite cells (Conboy et al., 2003; Carlson et al., 2008). While young muscles show significant up-regulation of Delta ligands in response to muscle injury and in Delta expression on the surface of satellite cells, aged muscles fail to show upregulation of Delta after injury (Conboy et al., 2003). Disrupting Notch signaling activity leads to a decline in satellite cell proliferation in aged skeletal muscle after injury (Conboy et al., 2003). Conboy et al. have demonstrated that culturing aged satellite cells in media containing young serum rejuvenates them and that rescues their regenerative potential (Conboy et al., 2005). They have also shown that the population of Notch-positive satellite cells is reduced in aged skeletal muscle, while it is increased by exposure to young serum (Conboy et al., 2005). BrdU-positive aged satellite cells can be increased by exposure to young serum, and this activation is hampered when Notch signaling is inhibited (Conboy et al., 2005). Additionally, satellite cell-specific activation of Notch signaling increases the number of satellite cells both *in vivo* and *in vitro* (Bjornson et al., 2012). By contrast, satellite cell-specific inhibition of Notch signaling decreases the number of satellite cells (Liu et al., 2012), suggesting that Notch regulates the satellite cell pool in skeletal muscle. During this phase, Notch regulates satellite cell self-renewal and proliferation, and Notch inactivation by aging disrupts muscle regeneration due to declines in the satellite cell pool.

In addition to alterations in Notch signaling, Wnt signaling may also contribute to the impaired regeneration potential of skeletal muscle with aging. Axin2, a downstream target of Wnt signaling, is expressed at high levels in satellite cells derived from aged muscle, indicating the progressive activation of Wnt signaling during aging (Brack et al., 2007). The age-related activation of Wnt signaling may cause myogenic-to-fibrogenic trans-differentiation of satellite cells resulting in the impaired regenerative capacity of old mice (Fig. 2). Brack et al. have reported that the young muscle-derived satellite cells degenerate into non-myogenic cells when they are cultivated in young serum that contains exogenous Wnt3a, and the injection of Wnt3a into young regenerating muscle after injury leads to the increased accumulation of connective tissue (Brack et al., 2007). Furthermore, neutralization of Wnt signaling in aged mice using DKK1, which is an antagonist of Wnt signaling, restores efficient muscle regeneration (Brack et al., 2007). By contrast, there is a report indicating that the activation of Wnt signaling does not induce the accumulation of connective tissue in skeletal muscle. Fujimaki et al. have demonstrated that

exercise-induced up-regulation of Wnt signaling in both adult and aged mice leads to the myogenic differentiation of satellite cells by upregulating *Myf5* or *MyoD* transcription, but does not lead to muscle fibrosis (Fujimaki et al., 2014). Further investigation is needed in order to understand the role of Wnt signaling in the degeneration of aged satellite cells to a fibrogenic lineage. The findings of previous studies generally suggest that Wnt signaling can stimulate both myogenic differentiation and the loss of myogenic cell fate, and final fate determination may depend on additional factors such as the severity of muscle damage, intrinsic and extrinsic cues and interactions with other intracellular signaling pathways (Fig. 2).

The effects of exercise on satellite cells

Since sarcopenia is a severe problem in today's aged society, its prevention is of profound and increasing importance. Skeletal muscle has a high degree of plasticity and various external stimuli can prevent muscle atrophy. Above all, exercise brings about large effects and can be relatively easily performed by many people. Studies have demonstrated that exercise causes skeletal muscle hypertrophy (Mayhew et al., 2009; Miyazaki et al., 2011), and the benefits of exercise on the prevention of muscle atrophy have been investigated (Fluckey et al., 2002; Fujino et al., 2009). Fluckey et al. reported that resistance exercise attenuates the loss of skeletal muscle mass in rodents subjected to tail suspension, which is a model of muscle atrophy in which rodents have no grounding stimulation to their hindlimbs (Fluckey et al., 2002). Fujino et al. showed that low-intensity treadmill running has a protective effect on tail-suspension-induced muscle atrophy (Fujino et al., 2009). In addition to maintaining skeletal muscle mass, exercise has a positive effect on satellite cells, whose loss contributes significantly to sarcopenia. To prevent sarcopenia, it is important to suppress the age-related decline in satellite cell numbers and their proliferative ability. Several studies have demonstrated that the number of satellite cells increases after acute or chronic exercise (Umnova and Seene, 1991; Smith et al., 2001). This increment in satellite cell numbers is also observed in human skeletal muscle (Kadi et al., 2004). The long-term effects of exercise on satellite cells are apparent in the skeletal muscle of well-trained power lifters, who have 70% more satellite cells than control subjects (Kadi et al., 1999). The increased number of satellite cells after training gradually decreases during detraining (Kadi et al., 2004), suggesting that the continuation of exercise is required for maintaining an abundant pool of satellite cells in skeletal muscle. There is a report indicating that the intensity, rather than duration, of exercise is important for the accretion of the satellite cell pool (Kurosaka et al., 2012). As for the style of exercise, the most effective method for increasing or maintaining the pool of satellite cells is still being investigated (Martin

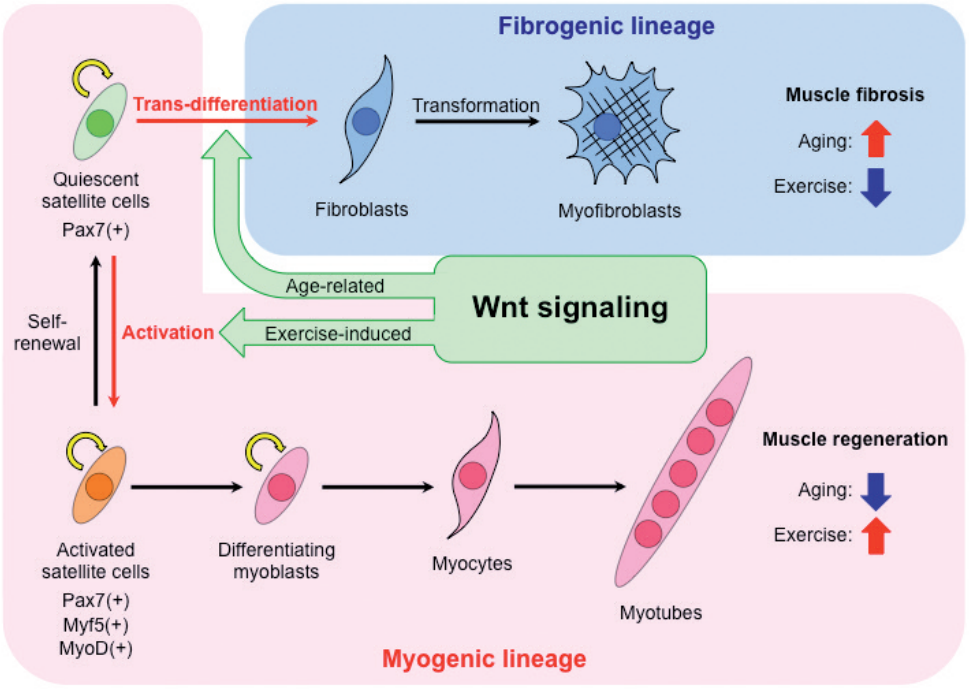

Fig. 2. Schematic image of the regulation of satellite cell activation and trans-differentiation into fibrogenic lineage by Wnt signaling. Although satellite cells are mainly in a quiescent state, they are activated in response to muscle injury or exercise. Activated satellite cells can proliferate, undergo self-renewal, and differentiate into myoblasts then to myocytes. Myocytes can mutually fuse and generate myofibers. The phases of satellite cell are determined by the expression of marker genes. Quiescent satellite cells express Pax7 (a stem cell-specific transcription factor) alone, whereas activated satellite cells co-express Pax7, Myf5, and MyoD, which are key transcription factors for myogenic differentiation. Exercise-induced upregulation of Wnt signaling converts satellite cells into activated state via accelerating the transcription of Myf5 and MyoD genes, resulting in increases in muscle regenerative potential. In contrast, satellite cell numbers and function decline with aging, resulting in attenuation of regenerative potential. On the other hand, age-related upregulation of Wnt signaling induces trans-differentiation of satellite cells into fibrogenic lineage. Fibroblasts transform into myofibroblasts, resulting in an increase in muscle fibrosis. Therefore, Wnt signaling may regulate both the activation of satellite cells induced by exercise and the trans-differentiation of satellite cells into fibrogenic lineage with aging.

and Lewis, 2012). An exercise-induced increase in satellite cell numbers is also observed in aged skeletal muscle. Fujimaki et al. have shown that voluntary wheel running induces an increase in Pax7-positive cell numbers in both adult (12-week-old) and aged (24-month-old) mice (Fujimaki et al., 2014). They have demonstrated not only an increase in satellite cell numbers, but also alterations in satellite cell function. Using Pax7 and MyoD immunohistochemical analysis and BrdU labeling, it has been shown that less-stressful exercise induces the activation and proliferation of satellite cells in both adult and aged mice (Fujimaki et al., 2014).Thus, exercise may be a useful measure for suppressing the decline in satellite cell numbers and function with aging.

On the other hand, the effects of unloading on satellite cells have also been investigated. After tail suspension, the number of satellite cells in skeletal muscle is decreased compared with weight-bearing control mice (Darr and Schultz, 1989). Darr and Schultz have shown that the decline in satellite cell numbers is dependent on the time course of tail suspension (Darr and Schultz, 1989). They demonstrated a reduction in satellite cell numbers and mitotic activity after 3 days of tail suspension in both the soleus and the EDL. The reduced number and proliferation of satellite cells persisted throughout the subsequent period in the soleus, but proliferation return to normal after 10 days of tail suspension in the EDL. Wang et al. have also investigated the mechanisms underlying changes in satellite cells after tail suspension. Their results suggest that the regulation of satellite cells is dependent on the mechanical loading and the location of the satellite cells in the muscle fiber (Wang et al., 2006): a decline in satellite cell numbers has been observed predominantly in the central region of muscle fibers (Wang et al., 2006). In contrast to the above description, recent human studies have indicated that the number of satellite cells does not change with muscle atrophy. For instance, 14 days of immobilization or 28 days of bed rest have not induced changes in satellite cells numbers in the skeletal muscle of subjects (Brooks et al., 2010; Snijders et al., 2014). However, individuals with atrophy, due to severe disuse or spinal cord injury, had significantly fewer satellite cells in their skeletal muscle (Verdijk et al., 2012). Thus, the conclusions about the effects of unloading on satellite cells have not been consistent, and further investigation is required.

Although the molecular mechanisms underlying the effects of exercise on increasing satellite cell numbers and function remain unclear, there have been some reports showing that Wnt signaling is activated by exercise. Functional overload by ablation of synergistic muscle, which is a model of resistance training and induced muscle hypertrophy, has revealed activated β-catenin in the plantaris muscle (Armstrong and Esser, 2005). Acute treadmill running can induce a reduction in β-catenin phosphorylation accompanied by increases in GSK-3β phosphorylation and Dvl-GSK-3β association (Aschenbach et al., 2006). Furthermore, voluntary wheel running also increased *Wnt3, Wnt5a* and *Wnt5b* expression and the accumulation of β-catenin (Fujimaki et al., 2014). In addition, Fujimaki et al. suggested that exercise-induced upregulation of Wnt signaling directly promotes *Myf5* and *MyoD* transcription in adult satellite cells (Fujimaki et al., 2014). Their study showed that voluntary wheel running, which is a less stressful form of exercise, induces the conversion of satellite cells to an activated state, and leads to the accumulation of β-catenin in the limb skeletal muscle of both adult and aged mice. Using chromatin immunoprecipitation assays, they also demonstrated that upregulated Wnt/β-catenin signaling directly modulates the chromatin structures of both *Myf5* and *MyoD* genes and upregulates their transcription, resulting in increases in the mRNA expression of *Myf5* and *MyoD* and the number of proliferative Pax7(+)/Myf5(+) and Pax7(+)/MyoD(+) cells in skeletal muscle. Therefore, the effects of exercise on increasing satellite cell number and function may be due to the activation of Wnt signaling (Fig. 2).

Diseases regulated by Wnt signaling

Wnt signaling in cancer

It is known that Wnt signaling-pathway mutations cause cancer. Germ line mutations in the APC gene lead to a hereditary cancer termed familial adenomatous polyposis (FAP) (Nishisho et al., 1991). The main feature of FAP is the formation of multiple polyps in the rectum and the colon, resulting in an increased risk of colorectal cancer. Loss of APC function induces the inappropriate accumulation of β-catenin and the constant formation of β-catenin/Tcf4 transcriptional complexes (Korinek et al., 1997). In addition to APC, mutations in Axin2 or point mutations in β-catenin also cause colorectal cancers in rare cases (Morin et al., 1997; Liu et al., 2000). Recently, it has been confirmed that the majority of colorectal cancer is due to inactivating APC mutations (Wood et al., 2007). These findings suggest that Wnt signaling may be a target for the treatment of FAP.

Wnt signaling in neurodegenerative disease

Many studies indicate that Wnt signaling is altered or may be involved in the pathophysiology of neurodegenerative diseases, such as Alzheimer's disease (AD), Parkinson's disease (PD), and Huntington's disease (HD). AD is a progressive neurodegenerative disorder and the most common cause of dementia in the elderly. AD is characterized by the accumulation of amyloid-β (Aβ), which induces apoptosis in newly generated neurons (He and Shen, 2009) and plays a key role in the cognitive impairment observed in AD (Selkoe, 2001). There is evidence to show that Aβ-dependent neurotoxicity induces dysfunctional Wnt signaling (De Ferrari et al., 2003; Fuentealba et al.,

2004). GSK-3β upregulation and hyperphosphorylation of tau proteins, which are abundant in neurons of the central nervous system and act to stabilize microtubules, have been observed in primary cultures of hippocampal and cortical neurons with Aβ neurotoxicity, resulting in the loss of the microtubule network (Busciglio et al., 1995; Takashima et al., 1998). Toledo et al. have reported that Aβ treatment induces apoptosis of neurons and promotes tau hyperphosphorylation by GSK-3β activation (Toledo et al., 2008). In contrast, they have also shown that the inhibition of GSK-3β protects neurons from Aβ-induced damage. Moreover, the upregulation of β-catenin during tau hyperphosphorylation prevents cell apoptosis, and the knockdown of β-catenin promotes cell apoptosis and antagonizes the anti-apoptotic function of tau proteins (Li et al., 2007). These results suggest that Wnt signaling may contribute to the development of AD.

PD is the second most widespread neurodegenerative disease in the world after AD. Individuals with PD present with typical motor symptoms, such as tremor, rigidity, slowness of movement, and postural instability, caused by the progressive loss of ventral midbrain dopaminergic neurons in the substantia nigra pars compacta (Gasser, 2009). Although mutations in the *PARK* gene have been considered a cause of familial PD over the last 15 years (Gasser, 2009), the initial cellular mechanisms triggering PD remain largely uncharacterized. Some previous studies have suggested that dysregulated Wnt signaling may be a potential cause of PD. The E3 ubiquitin ligase Parkin, encoded by *PARK2*, has been reported to suppress Wnt signaling activity by ubiquitination and degradation of β-catenin (Rawal et al., 2009). Therefore, Parkin dysfunction induces the accumulation of β-catenin, resulting in the upregulation of canonical Wnt signaling. It has been shown that β-catenin protein levels are significantly increased in the ventral midbrain, but not in other brain regions, of Parkin-knockout mice compared with wild-type mice (Rawal et al., 2009), suggesting that the change is highly associated with PD. The increase in canonical Wnt signaling in Parkin-knockout mice has been considered relevant to the increase in Cyclin E expression and the death of primary dopaminergic neurons. Thus, one of Parkin's functions may be to protect dopaminergic neurons from excessive Wnt signaling (Rawal et al., 2009). In addition, LRRK2 (Leucine-Rich Repeat Kinase 2), encoded by *PARK8*, also regulates Wnt signaling activity through the association of GSK-3β and Dvl (Lin et al., 2010; Berwick and Harvey, 2011). The GSK-3β-Dvl association is strengthened by the pathogenic LRRK2 G2019S mutation, resulting in an increase in tau phosphorylation (Lin et al., 2010). Moreover, a GSK-3β polymorphism has been discovered in PD patients, indicating that GSK-3β interacts with tau haplotypes to modify the PD risk (Kwok et al., 2005). These results suggest that Wnt signaling may also contribute to the development of PD.

HD is a fatal progressive neurodegenerative disease and the first symptoms of HD are observed in patients between the ages of 35 and 50 in most cases. Patients with HD exhibit severe movement impediments and declines in cognitive function, as well as behavioral abnormalities. HD is caused by the expansion of the polyglutamine repeat region in the Huntingtin gene (Kalathur et al., 2012). Although there is less research on the cellular mechanisms triggering HD compared with AD and PD, Wnt signaling may also be implicated in its development. Downregulated canonical Wnt signaling has also been observed in cell models of HD (Carmichael et al., 2002). Gines et al. have also reported that GSK-3β phosphorylation and β-catenin stabilization are inhibited in HD model mice (Gines et al., 2003). These findings suggest that Wnt signaling contributes to the development of HD.

The neurodegenerative diseases described in this section are more common in the elderly and their incidence increases with aging. Thus, the age-related dysfunction of Wnt signaling may be a likely cause for the development of these diseases.

Wnt signaling in age-related heart disorders

A variety of heart disorders increase with aging, such as left ventricular hypertrophy, diastolic dysfunction, and atrial fibrillation. Aging also causes an increase in intimal thickening and vessel stiffness that occurs before the onset of clinical diseases (Naito et al., 2010). These conditions may be associated with the alteration of Wnt signaling during aging. It has been shown that β-catenin stabilization promotes cardiomyocyte growth and is essential for the development of cardiac hypertrophy (Haq et al., 2003; Chen et al., 2006). Canonical Wnt signaling-activated (β-catenin-stabilized) transgenic mice have impaired cardiac growth with normal contractile function (Baurand et al., 2007). Downregulation of canonical Wnt signaling in cardiac myocytes is observed in arrhythmogenic right ventricular cardiomyopathy (Garcia-Gras et al., 2006). On the other hand, cardiac fibrosis is increased in aged hearts and is associated with atrial fibrillation and diastolic dysfunction (Burstein and Nattel, 2008; Ouzounian et al., 2008). It has been reported that activated Wnt signaling contributes to the formation of lung and kidney fibrosis, and Wnt inhibition suppresses damage after renal injury (Konigshoff et al., 2008; He et al., 2009). These findings suggest that Wnt signaling also regulates cardiac fibrosis in the aged heart. It has also been reported that Wnt signaling regulates cardiac progenitor cells. The genetic ablation of β-catenin in the second heart field, which comprises a population of multipotent cardiac progenitor cells giving rise to a major part of the amniote heart, leads to the loss of second heart field-derived tissues. In contrast, the stabilization of β-catenin in the second heart field results in the accumulation of Islet1-positive cardiac progenitors and the inhibition of further differentiation into mature

cardiomyocytes in the heart (Ai et al., 2007; Kwon et al., 2007; Qyang et al., 2007). Thus, Wnt signaling promotes the proliferation of cardiac progenitors and inhibits their differentiation into mature cell types. These findings suggest that Wnt signaling may play a critical role in age-related heart disorders, but more investigation is required for a thorough understanding of the mechanisms.

Concluding remarks

The present review describes the age-related changes in various tissues, including the role of Wnt signaling in these changes. In particular, Wnt signaling has been shown to act as an essential contributor to the aging process in the central nervous system and skeletal muscle. In neuronal tissue, neurogenesis is attenuated during aging by the downregulation of Wnt signaling, and this alteration leads to some age-related clinical diseases. In skeletal muscle, muscle mass and muscle function decline with aging in a process termed sarcopenia. One of the causes of sarcopenia is muscle fibrosis induced by excessive upregulation of Wnt signaling. Exercise is very useful for preventing age-related alterations in neuronal tissue and skeletal muscle. The effects of exercise implicate the upregulation of Wnt signaling, resulting in the activation of neurogenesis in adult neuronal tissue and myogenesis in mature skeletal muscle. Although more investigation is required for a thorough understanding of age-related changes and their biological mechanisms in a variety of tissues, this review proposes exercise as a useful therapy for the elderly to prevent the negative effects of aging, and maintain their quality of life.

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