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REVIEW

Roles of folate in skeletal muscle cell development and functions

Seong Yeon Hwang[1] · Bokyung Sung[1] · Nam Deuk Kim[1]

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Abstract Folate is the generic term for both naturally occurring food folate and folic acid, the fully oxidized monoglutamate form of the vitamin that is used in dietary supplements and fortified foods. It is a water-soluble vitamin B9 and is important for health, growth, and development. As a precursor of various cofactors, folate is required for one-carbon donors in the synthesis of DNA bases and other essential biomolecules. A lack of dietary folate can lead to folate deficiency and can therefore result in several health problems, including macrocytic anemia, elevated plasma homocysteine, cardiovascular disease, birth defects, carcinogenesis, muscle weakness, and difficulty in walking. Several studies have implied that folate might exert a positive effect on skeletal muscle development. However, the precise effects of folate in skeletal muscle development are still poorly understood. Thus, this review provides an updated discussion of the roles of folate in skeletal muscle cell development and the effects of folic acid supplementation on the functions of skeletal muscle cells.

Keywords Folate · Folic acid · Supplementation · C2C12 cells · Differentiation · Akt · Sarcopenia

Introduction

Folate is a water-soluble vitamin B9 that affects DNA synthesis and plays an important role in cell division and growth. Folate has been associated with muscle function, but its precise molecular mechanism and roles in muscle cell development are still elusive. In this paper, we review the research related to folate and its biological functions in the growth and differentiation of muscle cells and how folate deficiency affects muscle cell development. In addition, we also discuss the benefits and risks of folic acid supplementation.

Folate versus folic acid

Folate is the naturally-occurring form of vitamin B9 found mostly in green vegetables, peanuts, legumes, strawberries, and oranges, predominantly as polyglutamates (Chanarin 1979). Before entering the bloodstream, the digestive system converts it into the biologically active form of vitamin B9, 5-methyltetrahydrofolate (5-MTHF) (Moat et al. 2004). Alternatively, folic acid, which is a synthetic form of vitamin B9 also known as pteroylmonoglutamic acid, is added to foods because it is better absorbed. Unlike most folate, most the folic acid is not converted to the active form of vitamin B9, 5-MTHF, in the digestive tract. Instead, it needs to be converted in the liver or other tissues later (Patanwala et al. 2014). Even though folate and folic acid are often used interchangeably, there is a distinct difference. Therefore, roles of folate in vitro will be mainly discussed and folic acid supplement will be briefly discussed.

Seong Yeon Hwang and Bokyung Sung are equal contributors.

✉ Nam Deuk Kim
nadkim@pusan.ac.kr

[1] Department of Pharmacy, Molecular Inflammation Research Center for Aging Intervention, College of Pharmacy, Pusan National University, 63beon-gil 2, Geumjeong-gu, Busan 46241, Republic of Korea

Folate deficiency

Folate is essential for one-carbon metabolism, which plays a role in numerous cellular reactions such as intracellular DNA synthesis, repair, and methylation as well as nucleotide and amino acid biosynthesis (Shane 1995). Thus, folate is critical for numerous biological functions, and inadequate folate intake, especially deficiency, has been implicated in numerous adverse health conditions including neural tube defects, congenital heart disease, pregnancy-related complications, various psychiatric diseases, osteoporosis, and cancer. Therefore, adequate intake of folate is essential to reduce the incidence of these diseases (Blom and Smulders 2011; Czeizel et al. 2013; Pena and Claro 2014).

Folate deficiency is common in pregnant women, infants, children, adolescents, and elderly adults (Clarke et al. 2004). The well-known causes of folate deficiency are poor diet, such as lack of legumes and green leafy vegetables, excessive consumption of alcohol, inflammatory bowel disease, celiac disease, genetic defects, and smoking (Wu et al. 1975; Elsborg and Larsen 1979; Jacques et al. 1996; Okumura and Tsukamoto 2011). Folate deficiency can lead to the inhibition of *S*-adenosylmethionine, resulting in DNA hypomethylation (Miller et al. 1994; Kim et al. 1997). Previous reports imply that hypomethylation of myogenesis-specific DNA can attenuate development of skeletal muscle (Tsumagari et al. 2013; Carrio and Suelves 2015; Miyata et al. 2015). Li et al. (2013) also reported that folate deficiency has been reported to have a negative effect on skeletal muscle development in piglets during early-mid pregnancy.

In addition, folate deficiency induces the elevation of plasma homocysteine (Hcy), which is referred to as hyperhomocysteinemia (HHCy) (Linhart et al. 2009). Several studies demonstrated that HHcy triggers oxidative stress, inflammation, and matrix degradation leading to various diseases in various organs in the body (Kim et al. 2018). Elevated plasma Hcy has been linked to reduced muscle function (Swart et al. 2013; Veeranki et al. 2015). HHcy induces skeletal muscle weakness, as indicated by decreased physical performance, force generation, and muscle fiber size in mice (Veeranki et al. 2015). Moreover, HHcy has been reported to reduce physical performance and muscle strength in older women (Swart et al. 2013).

On the contrary, folate inhibits high levels of Hcy by remethylation of Hcy to methionine (Stam et al. 2005). In addition, supplementation during pregnancy in pigs with methylation-related micronutrients such as folate, vitamin B6, vitamin B12, methionine, choline, and zinc can promote sex-specific myogenic maturation processes related to organismal growth and muscle metabolism (Oster et al. 2017). Therefore, folic acid supplements are standard for pregnant women and women who plan to become pregnant. Folic acid supplements reduce the risk for birth defects of a baby's brain and spine, spina bifida (split spine) and anencephaly, by 50% or more (Molloy et al. 2017). Folic acid supplements may also lower the risk of preeclampsia and preterm labor (Halimi Asl et al. 2017; De Ocampo et al. 2018).

Skeletal muscle development

Skeletal muscle tissue contains satellite cells (skeletal muscle-derived stem cells) which lie quiescent underneath the basal membrane and make up the necessary stem cell pool for myogenesis (Mauro 1961). When satellite cells are activated, after an injury, for example, they enter the myogenic differentiation process. During this process, satellite cells and myoblasts transverse through a strict sequential expression pattern of different transcription factors and structural muscle proteins (Tajbakhsh 2009). Skeletal muscle differentiation is a multistep process controlled largely by the family of muscle-specific transcription factors that share homology within a basic-helix-loop-helix motif. Four members of the myogenic regulatory factor (MRFs), myogenic factor 5 (Myf-5), myogenic differentiation 1 (MyoD), MRF4, and myogenin, bind to the consensus E-box sequence (CANNTG) in the promoter and enhancer regions of muscle-specific genes, and are essential in the differentiation and commitment of cells to the muscle phenotype during development (Cao et al. 2006, 2010). The sequences flanking the E-box also make important contributions to the binding affinity of these myogenic transcription factors and contribute to the overall consensus sequence determined for MyoD and myogenin (Blackwell and Weintraub 1990; Cao et al. 2010).

Sarcopenia

Sarcopenia is defined as the degenerative loss of skeletal muscle mass (0.5–1% loss per year after the age of 50), quality, and strength associated with aging (Phillips 2015). The Centers for Disease Control and Prevention (CDC) in the U.S. established an "International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) code for sarcopenia. The code, M62.84, has been available for use by the medical community since October 1, 2016 (Anker et al. 2016). Sarcopenia is associated with the normal aging process and is the involuntary loss of skeletal muscle mass and strength. It is characterized first by muscle atrophy (a decrease in the size of the muscle). Muscle atrophy may occur in any condition of inactivity, including normal aging-related conditions and/or chronic pathological conditions such as myopathy, denervation-

associated atrophy, cachexia, and obesity (Tedesco et al. 2010; Mangner et al. 2012). Skeletal muscle atrophy and sarcopenia can lead to reduced quality of life, which represents a major public health burden in several countries.

Management of sarcopenia

Lack of exercise is thought to be a significant risk factor for sarcopenia, and therefore, exercise is seen as its best treatment. There is a body of evidence that indicates that there is an increased ability and capacity of skeletal muscle to synthesize proteins in response to short-term resistance exercise (Yarasheski 2003). Progressive resistance training in older adults can improve physical performance (gait speed) and muscle strength, which are two key components of sarcopenia. Protein intake and physical activity are important factors for muscle protein synthesis (McGlory et al. 2018). A number of expert groups have proposed an increase in dietary protein recommendations for older age groups to 1.0–1.2 g/kg body weight per day (Bauer et al. 2013; Deutz et al. 2014). As of October 2018, there are no approved medications for the treatment of sarcopenia. Several approved medications and nutrients are under investigation as possible treatments for sarcopenia including β-hydroxy β-methylbutyrate (Wu et al. 2015), ghrelin (Tamaki et al. 2017), vitamin B12 (Kelly et al. 2016), folate (Wee 2016), vitamin D (Robinson et al. 2018), angiotensin converting enzyme inhibitors (Kilsby et al. 2017), eicosapentaenoic acid (Wakabayashi and Sakuma 2014), leucine (Tessier and Chevalier 2018), and omega-3 fatty acids (Tessier and Chevalier 2018).

Impact of folate on muscle aging

A recent study reveals that serum folate levels are significantly correlated to reduction of leg and grip strength in older people (> 65 years) with diabetes mellitus, especially in women (Wee 2016). The results of a study suggest that folate deficiency is associated with muscle strength decline, while there is a difference in the effect of folate deficiency by gender. Reduced dietary intake of micronutrients including folate has major impact on muscle health as shown by decreased force- generating capacity and fatigue resistance as well as impaired physical activity, without an effect on muscle mass in aged mice (van Dijk et al. 2018).

Roles of folic acid in vitro

Effects of folic acid on skeletal muscle cell differentiation

Recently, Hwang et al. (2015) investigated the effect of folic acid supplementation on muscle cell differentiation. More specifically, they examined the effects of folic acid on neo-myotube maturation and differentiation using murine myoblast C2C12 cells, derived from satellite cells, which can be spontaneously differentiated into myotubes when changed from high serum medium to low serum medium (Yaffe and Saxel 1977). Supplementation with low serum medium containing folic acid promoted the formation of multinucleated myotubes, and increased the fusion index and creatine kinase activity in a concentration-dependent manner. Furthermore, folic acid supplement significantly increased the expression levels of the muscle-specific marker myosin heavy chain (MyHC), as well as those of the MRFs, MyoD and myogenin, in myotubes (Hwang et al. 2015).

The activation of Akt is major mechanism that contributes to folic acid-stimulated myogenesis. Blocking of the Akt pathway with a specific inhibitor, LY294002, revealed that it was necessary for mediating the stimulatory effects of folic acid on muscle cell differentiation and fusion (Fig. 1). The crucial role of Akt in myogenic differentiation and hypertrophy has been previously demonstrated by several reports (Jiang et al. 1999; Sumitani et al. 2002; Yuan et al. 2017; Sassoli et al. 2018), and has been shown to contribute to the increase in size of C2C12 myotubes (Rommel et al. 2001; Jang et al. 2018; Li et al. 2018a). Overall, these studies demonstrate that folic acid plays a positive role in myogenesis.

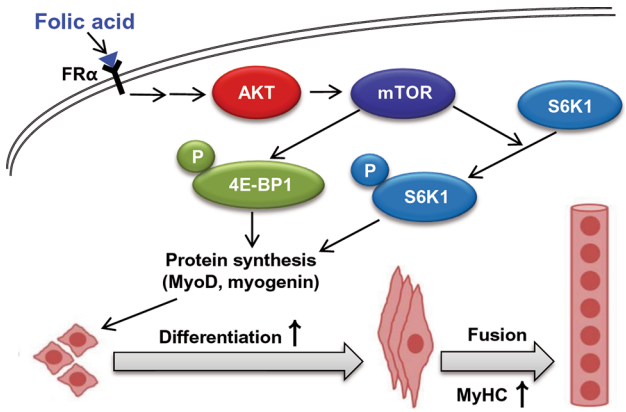

Fig. 1 Simplified overview of the mechanisms of folic acid on the differentiation of C2C12 cells. Folic acid treatment increases skeletal muscle myoblast differentiation, particularly affecting the differentiation process and myotube morphology. This effect implies that folic acid increases phosphorylation of Akt and mTOR and consequently activates 4E-BP1 and S6K1, which are key downstream targets of the Akt/mTOR signaling cascade. This pathway leads to the increased expression of the MyoD and myogenin and the promotion of myoblast differentiation. *FRα* folate receptor α

Effects of folic acid deficiency on proliferation and differentiation of murine myoblasts

Even though a study has reported on the beneficial effects of folic acid supplementation on skeletal muscle development (Hwang et al. 2015), the effects of folic acid deficiency on the differentiation of myoblasts and skeletal muscle development have not been fully described. Recently, Hwang et al. (2018) reported the effect of folic acid deficiency on myogenesis in skeletal muscle cells. They found that folic acid deficiency inhibited C2C12 myoblast proliferation and promoted an exit from the cell cycle as well as cellular senescence. Folic acid deficiency also inhibited the differentiation of myoblasts and the expression of myogenic markers MyHC and myogenin. Moreover, DNA damage increased in folic acid-deficient C2C12 cells cultured in differentiating medium as compared to cells cultured in normal differentiating medium (containing 2% horse serum). It was therefore interesting to note that folic acid re-supplementation reversed the effects of folic acid-deficiency on the cell cycle and senescence but failed to restore the reduced differentiation of C2C12 cells. A recent study also demonstrated that folate deficiency and supplementation can influence the differentiation, genome-wide DNA methylation level and the expression of myogenesis-related genes in C2C12 cells line (Li et al. 2018b). The results of this study indicated that folate deficiency (low folate; 0 mg/L) inhibits differentiation and high folate supplementation (40 mg/L) promotes the differentiation and the expression of myogenesis-related genes (e.g., myogenin and MyoD). Therefore, folic acid-deficient C2C12 cells did not undergo normal differentiation due to the dysregulation of cell cycle-related genes and strong DNA damage at the early stage of differentiation. Altogether, these findings suggest that folic acid is necessary for normal development of skeletal muscle cells in vitro (Fig. 2).

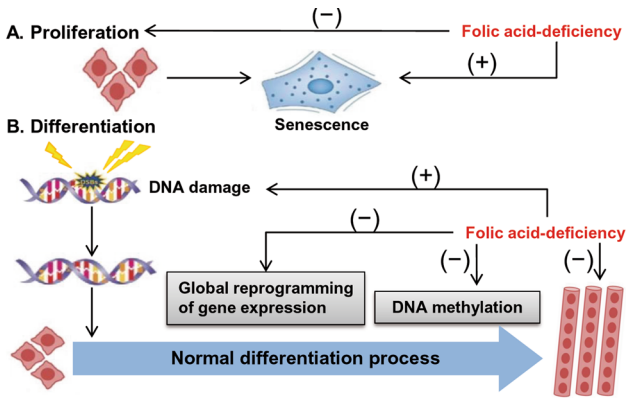

Fig. 2 Scheme depicting the effects of folic acid deficiency on the proliferation and differentiation of C2C12 cells. Folic acid deficiency decreases the proliferation (**a**) and differentiation (**b**) of C2C12 cells. This effect implies that folic acid deficiency induces deregulation of cell cycle-relate genes and increases DNA damage in differentiating C2C12 cells

The benefits and risks of folic acid supplementation

Benefits of folic acid supplementation

As described above, it has been found that folate plays an important role not only in the development of muscle cells in vivo and in vitro, but also in the physiological functions of the human body. Proper folate intake is very important, but if the folate is not properly ingested, then it must be maintained through a folic acid supplement. The recommended daily amount of folate for adults is 400 μg. Adult women who are planning pregnancy or could become pregnant should be advised to get 400 to 800 μg of folic acid a day (Deniz et al. 2018).

Risks of folic acid supplementation

There are safety concerns regarding the excessive ingestion of folic acid over a long period time, and these concerns are limited to synthetic folic acid, not food-derived folate. The results of the Norwegian Vitamin (NORVIT) trial showed that there was no significant effect of folic acid (0.8 mg/daily) and vitamin B12 (0.4 mg/daily) on the risk of the recurrent myocardial infarction, stroke, or sudden death from coronary artery disease, in spite of adequate homocysteine lowering. In addition, unexpectedly, there was a trend toward more myocardial infarctions, as well as a marginally significant trend toward fewer strokes, among patients receiving folic acid, vitamin B12, and vitamin B6 as compared to those receiving a placebo (Bønaa et al. 2006). Other research suggests that taking a high-dose of folic acid (1 mg/day) might also increase the risk of colorectal or prostate cancer (Cole et al. 2007). Therefore, until more is known, individuals with a history of cancer should avoid high-doses of folic acid supplementation. Another risk of excessive folic acid intake is that it might mask anemia caused by vitamin B12-deficiency and delay appropriate treatment (Cuskelly et al. 2007).

Recommended intake

Table 1 lists the current recommended dietary allowance for folate as micrograms (μg) of dietary folate equivalents (DFEs) (https://ods.od.nih.gov/factsheets/Folate-Consumer/). The Food and Nutrition Board (FNB) at the Institute of Medicine of the National Academies in the

Table 1 Recommended dietary allowances (RDAs) for folate

Age group	Daily requirement (μg)
Birth to 6 months	65
Infants 7–12 months	80
Children 1–3 years old	150
Children 4–8 years old	200
Children 9–13 years old	300
Children over 14 and adults	400
Pregnant women and women who are trying to conceive	600
Nursing mothers	500

United States developed DFEs to reflect the higher bioavailability of folic acid than that of food folate. At least 85% of folic acid is estimated to be bioavailable when taken with food, whereas only about 50% of folate naturally present in food is bioavailable (Carmel 2005). Based on these values, the FNB defined DFE as follows:

- 1 μg DFE = 1 μg food folate
- 1 μg DFE = 0.6 μg folic acid from fortified foods or dietary supplements consumed with foods
- 1 μg DFE = 0.5 μg folic acid from dietary supplements taken on an empty stomach

Conclusion

In this paper, we have described the current understanding of the roles of folate in skeletal muscle development in terms of the molecular mechanisms in vitro. In addition, serum levels of folate are strongly and significantly related to muscle strength in older people. Therefore, folate has a critical role in development of skeletal muscle cells and their functioning. However, it is not recommended to consume copious amounts of folic acid for muscle development. As mentioned above, it has been found that when ingesting excessive amounts of folic acid, various side effects may occur. Therefore, it would be wise to ingest folic acid within the daily recommended range, but to enjoy the benefits of folic acid through folate intake from natural foods rather than by folic acid supplementation or by fortified foods.

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Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

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