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Sulforaphane Alleviates Muscular Dystrophy in Mdx Mice by Activation of Nrf2

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Abstract : Backgrounds: Sulforaphane, one of the most important isothiocyanates in the human diet, is known to have chemopreventive and antioxidant activities in different tissues via activation of NF-E2-related factor 2 (Nrf2)-mediated induction of antioxidant/phase II enzymes, such as heme oxygenase-1 (HO-1) and NAD(P)H quinone oxidoreductase 1 (NQO1). However, its effects on muscular dystrophy remain unknown. This work was undertaken to evaluate the effects of Sulforaphane on Duchenne muscular dystrophy (DMD). Methods: 4-week-old mdx mice were treated with SFN by gavage (2 mg/kg body weight per day) for 8 weeks. Blood was collected from eye socket every week, and tibial anterior, extensor digitorum longus, gastrocnemius, soleus, triceps brachii muscles and heart samples were collected after 8-week gavage. Force measurements and mice exercise capacity assays were detected. GSH/GSSG ratio, TBARS, CK and LDH levels were analyzed by spectrophotometric methods. H&E staining was used to analyze histological and morphometric of skeletal muscles of mdx mice, and Evas blue dye staining was made to detect sarcolemmal integrity of mdx mice. Further, the role of Sulforaphane on Nrf2/ARE signaling pathway was analyzed by ELISA, western blot and qRT-PCR. Results: Our results demonstrated that SFN treatment increased the expression and activity of muscle phase II enzymes NQO1 and HO-1 with Nrf2 dependent manner. SFN significantly increased skeletal muscle mass, muscle force (~30%), running distance (~20%) and GSH/GSSG ratio (~3.2 folds) of mdx mice, and decreased the activities of plasma creatine phosphokinase (CK) (~45%) and lactate dehydrogenase (LDH) (~40%), gastrocnemius hypertrophy (~25%), myocardial hypertrophy (~20%) and MDA levels (~60%). Further, SFN treatment also reduced the central nucleation (~40%), fiber size variability, inflammation and improved the sarcolemmal integrity of mdx mice. Conclusions: Collectively, these results show that SFN can improve muscle function, pathology and protect dystrophic muscle from oxidative damage in mdx mice through Nrf2 signaling pathway, which indicate Nrf2 may have clinical implications for the treatment of patients with muscular dystrophy.

Keywords : sulforaphane, duchenne muscular dystrophy, Nrf2, oxidative stress
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