

# The role of sulforaphane on duchenne muscular dystrophy by activation of Nrf2

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## Abstract

Sulforaphane (SFN) possesses powerful chemo-preventive effects and plays a crucial role on oxidative stress and inflammatory. In our recent study, SFN treatment could relieve muscular dystrophy in *mdx* mice by activating Nrf2 (NF-E2 related factor 2). Moreover, our findings indicated that SFN-activated Nrf2 alleviated muscle inflammation in dystrophin-deficient *mdx* mice through suppressing NF- $\kappa$ B signaling pathway. Collectively, SFN-induced Nrf2 molecular pathway might be a promising approach for treatment of the patients with Duchenne muscular dystrophy.

**Abbreviations:** DMD: Duchenne muscular dystrophy; SFN: Sulforaphane; Nrf2: nuclear factor erythroid 2-related factor 2 ; HO-1: heme oxygenase-1; ARE: antioxidant response element; NQO1: NADH/NADPH quinone oxidoreductase 1

Duchenne muscular dystrophy (DMD) is the most common type of muscular dystrophy, which is also regarded as a severe muscle disease with an incidence of 1 in 3,500 live male newborns in the world [1-3]. The leading cause is dystrophin gene mutations, which lose regulation of the muscle protein [4]. Cell death, progressive damage of muscle fibers, oxidative stress, and inflammation are the remarkable characteristics of DMD in humans and *mdx* mice [5]. Glucocorticoid play a role on boosting muscle function and strength in a short time in DMD therapy, but it is not effective and with plentiful side effects, like hypertension, diabetes, mood/behavioral affection for a long time using [6-8]. Therefore, there is not noticeably effective method for treatment of DMD yet.

Nrf2 (NF-E2 related factor 2) is one of the momentous transcription factors, which exists in biological body and affect genes expression of numerous oxidative stress proteins, detoxifying enzymes and antioxidant enzymes [9-10]. Investigations show that Nrf2 is a promising protector against oxidative stress via activation of ARE and its downstream HO-1 and NQO1 [11-12]. Nrf2 could also prevent skeletal muscle from exhaustible exercise induced damage in rats via function of an antioxidant [13]. Additionally, some investigations demonstrate that Nrf2 might play a role of on anti-inflammation in a variety of tissues through inhibition of NF- $\kappa$ B signaling pathway [11,14]. Moreover, Nrf2 is also considered as a guardian in inflammation mediated airway response [15], emphysema [5] and colon cancer [16-17].

Sulforaphane (SFN) is described as glucoraphanin in many vegetables of brassicaceae family, which possesses powerful chemopreventive effects and is a useful isothiocyanate in our daily diet [18]. Increasing evidence shows that SFN attenuates oxidative stress by regulation of Nrf2 [19-20]. Furthermore, early studies indicate that the function of SFN is impacted via various mechanisms, such as inhibition of cell proliferation, promotion of apoptosis and

suppression of metastasis and angiogenesis [9, 21-22]. Although it has been demonstrated with chemo preventive function, the underlying efficacy of SFN on DMD has not been estimated yet.

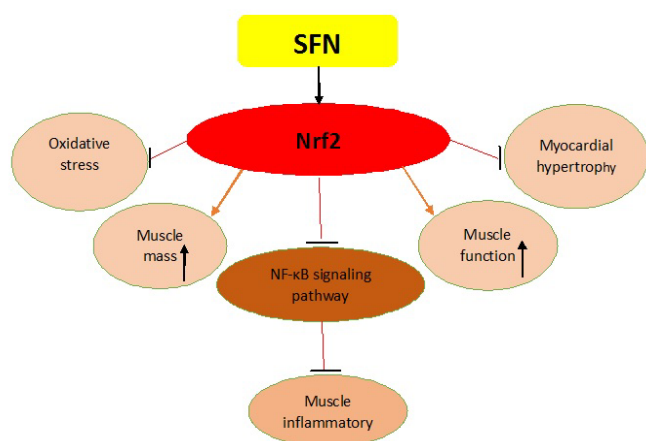
Previous study indicated that SFN pretreatment alleviated liver damage in rats, owing to its powerful anti-oxidative efficacy via activation of Nrf2-ARE signaling pathway [23]. In our recent studies, we explored the function of SFN on *mdx* mice, which are perceived as the perfect animal models for the pathogenesis research of DMD [1]. SFN treatment could promote gastrocnemius mass, myocardial hypertrophy and exercise capacity in *mdx* mice, meanwhile morphological features and body weight were also improved [24]. Moreover, we found the proteins and mRNAs of phase II detoxifying enzymes NQO1 and HO-1 of the signaling pathway Nrf2/ARE were significantly upregulated after SFN treatment in *mdx* mice [24-26]. We also found SFN treatment attenuated oxidative stress response and exercise-induced damage by activating Nrf2-ARE molecular pathway in *mdx* mice [24].

Inflammation is a critical factor that contributes to progressive damage of muscle and oxidative stress in DMD patients [27]. Therefore, it is urgent to investigate a useful approach to therapy inflammation of DMD patients. Many studies have indicated that Nrf2 protects various cells, tissues and organ systems against wide toxic insults and disease pathogenesis [28]. We explored the anti-inflammatory function of SFN on *mdx* mice, our findings demonstrated that SFN played a pivotal role regarding treatment of inflammation in *mdx* mice, and improved the syndrome of dystrophic muscles [29]. The phenomenon might be attributed to inflammation relief in dystrophic muscles

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**The function of SFN in DMD**

**Figure 1.** The function of Sulforaphane in Duchenne muscular dystrophy by activating Nrf2. SFN treatment could promote muscle mass, GAS hypertrophy, myocardial hypertrophy and exercise capacity in *mdx* mice, and keep dystrophic muscle from oxidative stress damage by activation of Nrf2. Furthermore, SFN had protective effects in muscular inflammation of *mdx* mice through Nrf2-mediated repression of the NF- $\kappa$ B signaling pathway.

because we found numbers of immune cells were decreased in aspect of infiltration. Additionally, the levels of proinflammatory cytokines, such as IL-6, IL-1, TNF- $\alpha$ , and inflammatory cytokine CD45 were remarkably decreased and the potential mechanism might through repression of the NF- $\kappa$ B signaling pathway, which showed that the SFN had protective effects in muscular inflammation of *mdx* mice through Nrf2-mediated repression of NF- $\kappa$ B signaling pathway [29-32].

Taken together, SFN plays a crucial role on oxidative stress and chemopreventive effect, which could attenuate muscular dystrophy in *mdx* mice by activating Nrf2. Moreover, our findings indicated that SFN-induced Nrf2 alleviated muscle inflammation in dystrophin-deficient *mdx* mice through suppression of NF- $\kappa$ B molecular pathway. Then we conclude that SFN-induced Nrf2 might be a promising approach for treatment of the patients with DMD. However, whether there is other mechanism or function of SFN in DMD need further investigate.

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## Disclosure of potential conflicts of interest

The authors disclose no potential conflict of interest.

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