Overexpression of PRDM16 Improves Muscle Function after Rotator Cuff Tears

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Role of muscle Follistatin that promote muscle growth demonstrated an improved forelimb function due to the overexpression of PRDM16 (Figure 2B). PRDM16 overexpression showed no significantly improved the forelimbs function after massive tendon tears through a transgenic mouse model with high levels of PRDM16. We hypothesize that the overexpression of PRDM16 would improve muscle function and ameliorate fibrosis and FI.

RESULTS SECTION:

Considered when staining was used to determine the fat infiltration. Of PRDM16 in adipose tissue was detected by Western Blot. post the TTDN injury suprascapular nerve transection (TTDN) as described previously. Transgenic Ap2 driven PRDM16 over-expression mice [5] and C57BL/6j mice underwent unilateral supraspinatus (SS) tendon transaction and suprascapular nerve transaction (TTDN) as described previously (N=8 in each group) [6]. Digi Gait was performed to evaluate forelimb function at 6 weeks post the TTDN injury. Bilateral SS muscles, interscapular brown fat, epididymal white fat and inguinal beige fat were harvested for analysis. The expression of PRDM16 in adipose tissue was detected by Western Blot. Masson’s trichome staining was conducted to evaluate the muscle fibrosis and Oil Red O staining was used to determine the fat infiltration. Muscle fiber type was determined by MHC expression via immunostaining. All data was presented in the form of means±SD. T-test and Two-way ANOVA analysis was performed to determine a statistically significant difference between groups. Significance was considered when P<0.05.

RESULTS SECTION:

Western blot data showed an increased expression of PRDM16 protein in both white and brown fat in PRDM16-overexpression mice compared to wild type (WT) mice (Figure 1A). Even though PRDM16 overexpression had no effect on increasing muscle weight (Figure 1B), it significantly improved the forelimbs function with longer brake, stance and stride time, larger stride length and paw area in mice after RCT (Figure 1C). PRDM16 overexpression showed no effect in improving fibrosis (Figure 2A), however, it significantly reduced the fatty infiltration area (%) after injury (Figure 2B). Additionally, compared to WT mice, PRDM16 overexpression significantly increased the MHC-IIx fiber percentage in supraspinatus muscle after TTDN (Figure 3). Overexpression PRDM16 expression is highly enriched in BAT, and it activates a robust brown fat phenotype when expressed in white fat cell progenitors. In this study, we found higher expression of PRDM16 in white and brown fat in transgenic mice compared to WT mice. In addition, results from our study demonstrated an improved forelimb function due to the overexpression of PRDM16. BAT has been reported to secrete several growth factors like IGF1 and Follistatin that promote muscle growth [3]. Except for its role in thermogenesis, a previous study showed that genetic loss of PRDM16 could mimic the effect of aging in promoting fibrosis [7]. Even though no change was found in fibrosis, PRDM16 overexpression led to significantly less fatty infiltration in muscle after RCT. Interestingly, we also found the overexpression of PRDM16 significantly increased the MHC-IIx fiber type after RCT. The functional role of MHC-IIx fiber type in rotator cuff muscle metabolism and function remains unknown. Further study is needed to explore their relationship between BAT and muscle fiber type after rotator cuff injury.

SIGNIFICANCE/CLINICAL RELEVANCE: Overexpression of PRDM16 significantly improved muscle function and reduced fatty infiltration after rotator cuff tears. Promoting BAT activity is beneficial in improving rotator cuff muscle quality and shoulder function after RCT.


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