Myostatin deficiency inhibits muscle wasting and improves bacterial clearance and survival in septic mice.

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HIGHLIGHTS

- Myostatin is a novel, potential molecular target to improve clinical outcomes, including survival and muscle wasting, in septic burn patients.
- Muscle wasting may not simply be a complication of sepsis, but actually drive the disease development.

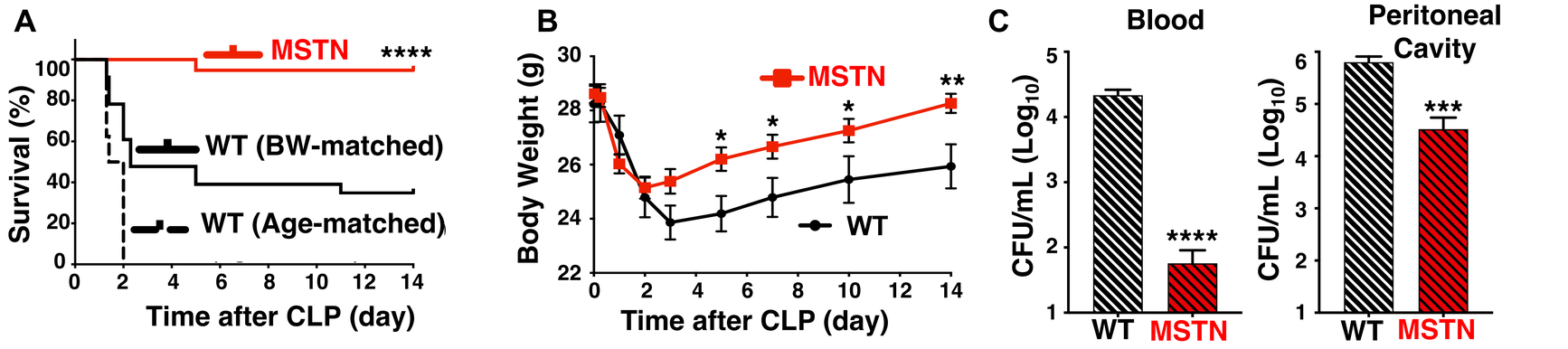

Figure 1. Myostatin deficiency improved survival (A), ameliorated body weight loss (B) and mitigated bacterial loads (C) after cecum ligation and puncture (CLP) in mice. (A) Survival was improved in myostatin- deficient (MSTN) mice (n=19) compared with age- and body weight-matched wild-type (WT) mice (n=23 per group). (B) Body weight loss was ameliorated in myostatin-deficient (MSTN) mice (n=18) compared with body weight-matched wild-type (WT) mice (n=8). (C) Bacterial loads in the circulation and peritoneal cavity were significantly lower in myostatin-deficient (MSTN) mice (n=7) than body weight-matched wild-type (WT) mice (n=8) at 16 h after CLP.

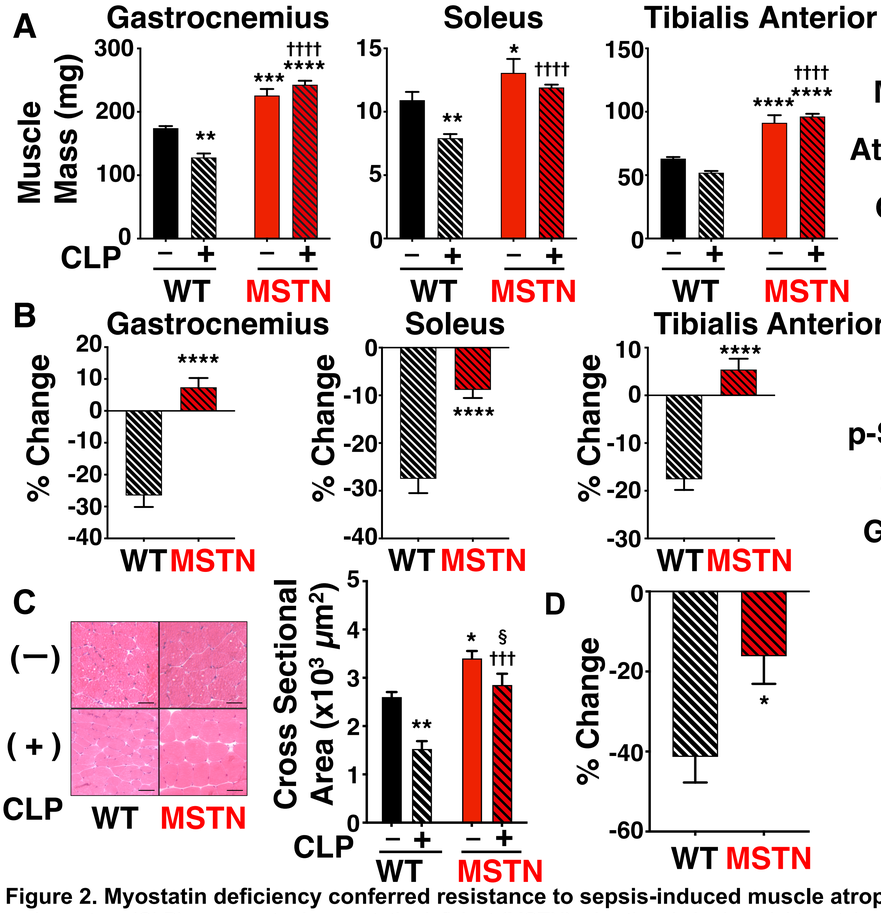

Figure 2. Myostatin deficiency conferred resistance to sepsis-induced muscle atrophy in mice. (A) The muscle mass of naïve mice and in mice at 14 days after cecum ligation and puncture (CLP) was greater in myostatin-deficient (MSTN) mice than in body weight-matched wild-type (WT) mice. (B) Cecum ligation and puncture (CLP)-induced percent changes in muscle mass were compared between myostatin-deficient (MSTN) and body weight-matched wild-type (WT) mice. (C) The cross-sectional area of gastrocnemius muscle was greater in myostatin-deficient (MSTN) mice than in body weight-matched wild-type (WT) mice. Scale bar: 50 μm. (D) The cecum ligation and puncture (CLP)-induced percent decrease in cross-sectional area was less in myostatin-deficient (MSTN) mice than in body weight-matched wild-type (WT) mice.

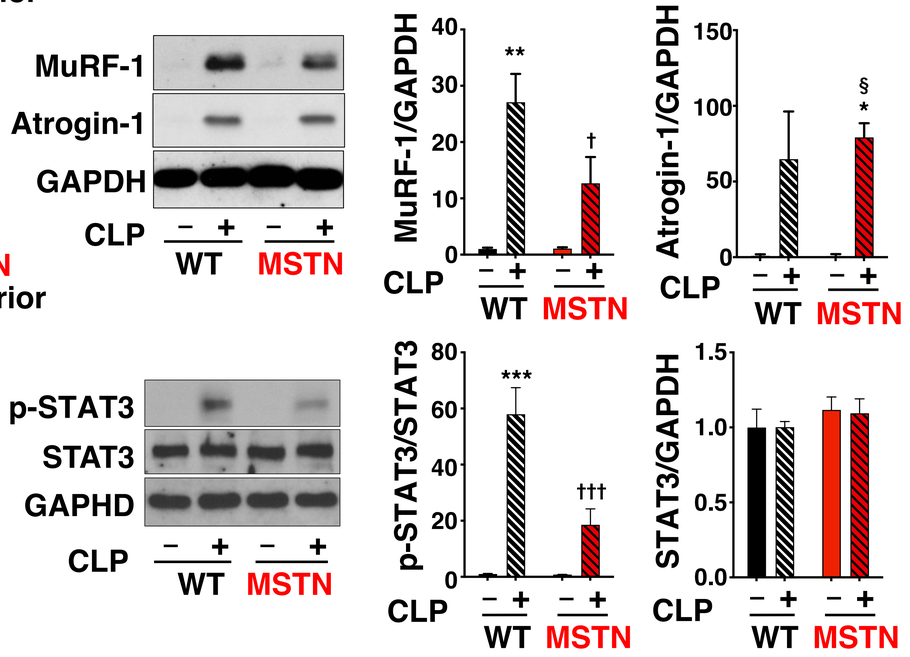

Figure 3. Effects of myostatin deficiency on sepsis-induced expression of MuRF-1 and atrogin-1 and phosphorylation of STAT3 in mouse skeletal muscle. Myostatin deficiency (MSTN) inhibited cecum ligation and puncture (CLP)-induced increases in expression of MuRF-1, but not atrogin-1 (A), and phosphorylation of STAT3 (B) in gastrocnemius muscle compared with body weight-matched wild-type (WT) mice.

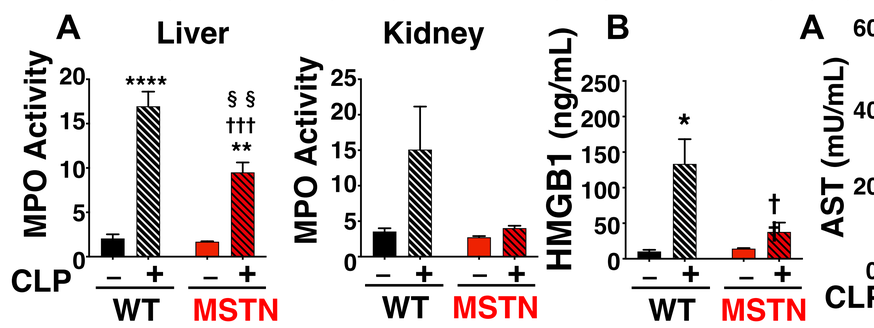

Figure 4. Myostatin (MSTN) deficiency attenuated sepsis-induced increases in MPO activity in the liver and kidney (A) and plasma HMBG1 (B) level compared with body weight-matched wild-type (WT) mice.

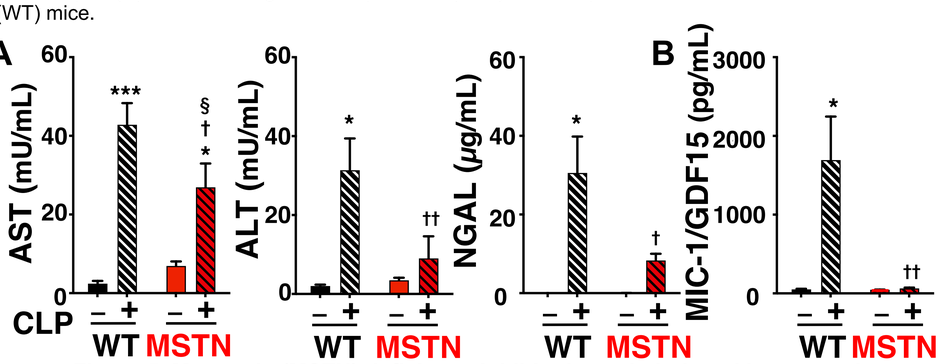

Figure 5. Myostatin (MSTN) deficiency inhibited sepsis-induced increases in plasma levels of AST, ALT, NGAL (A) and MIC-1/GDF-15 (B) compared with body weight-matched wild-type (WT) mice.

SIGNIFICANCE STATEMENT

Sepsis remains a leading cause or mortality in burn patients. Muscle wasting is a major complication of burn injury and sepsis, Our study paves the way to help develop a clinical trial to test the safety and efficacy of a myostatin inhibitor to improve clinical outcome in severely burned patients.

INTRODUCTION

Myostatin, a myokine that is primarily produced and secreted by skeletal muscle, is an inducer of muscle wasting. However, the role of myostatin in burn- and sepsis-induced muscle wasting has not yet been studied.

RESULTS

Myostatin deficiency:
(1) improved survival and bacterial clearance (Fig. 1);
(2) prevented sepsis-induced muscle wasting (Figs. 2 and 3);
(3) mitigated sepsis-induced increases in myeloperoxidase (MPO) activity in the liver and kidney, an indicator of neutrophil organ infiltration, and plasma levels of HMGB1 (a major damage-associated molecular pattern) (Fig. 4);
(4) ameliorated liver dysfunction and acute kidney injury, as indicated by plasma levels of AST, ALT and NGAL (Fig. 5A); and
(5) blocked sepsis-induced elevation in plasma level of MIC-1/GDF15 (an inducer of muscle wasting and immune dysfunction) (Fig. 5B) in septic mice compared with wild-type mice.

DISCUSSION

Our data suggest that inhibition of muscle wasting, in which myostatin play a crucial role, may improve short- and long-term clinical outcomes in septic burn patients.