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Immunological characterization of a rat model of Duchenne's disease and increase in muscle strength after anti-CD45RC antibody treatment.

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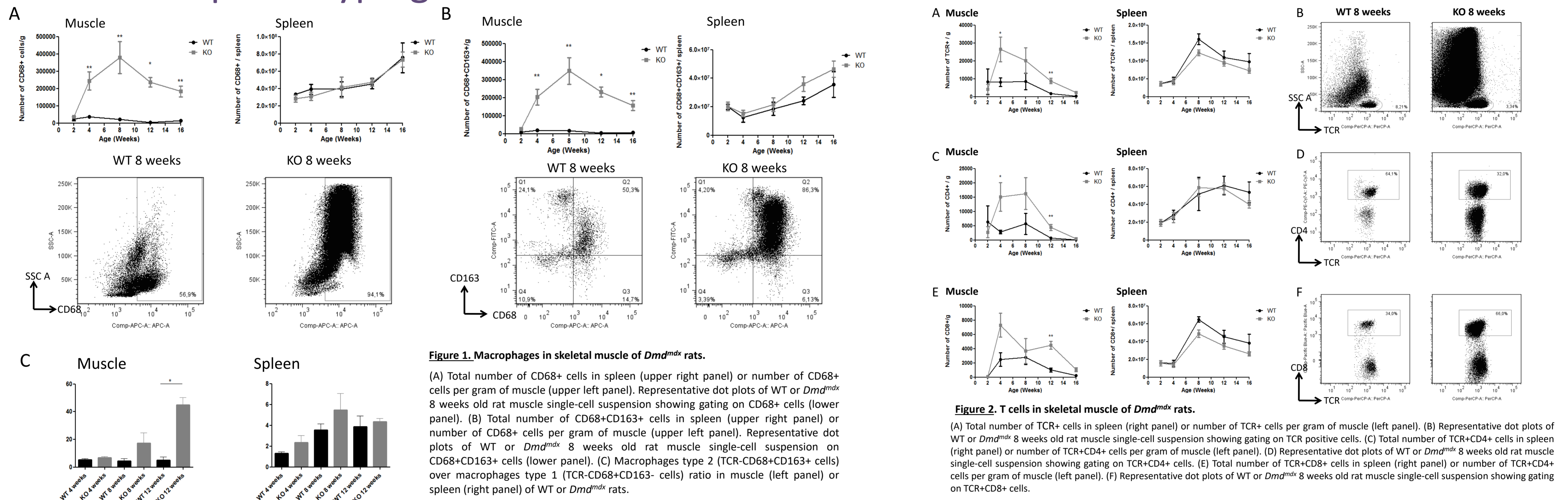
Introduction

Duchenne Muscular Dystrophy (DMD) is a severe genetic muscle-wasting disorder due to the lack of dystrophin characterized by a progressive muscle weakness and a cardiomyopathy leading to premature death. The dystrophin-deficient *Dmd*^{mdx} rats were generated using TALENs and offer a more reliable representation of human DMD, with marked muscle strength reduction, cardiomyopathy and muscle fibrosis that are higher than those observed in the *mdx* mouse model (1). A role for inflammation and autoimmune responses in muscle damages was shown both in DMD patients and the *mdx* mouse model (2).

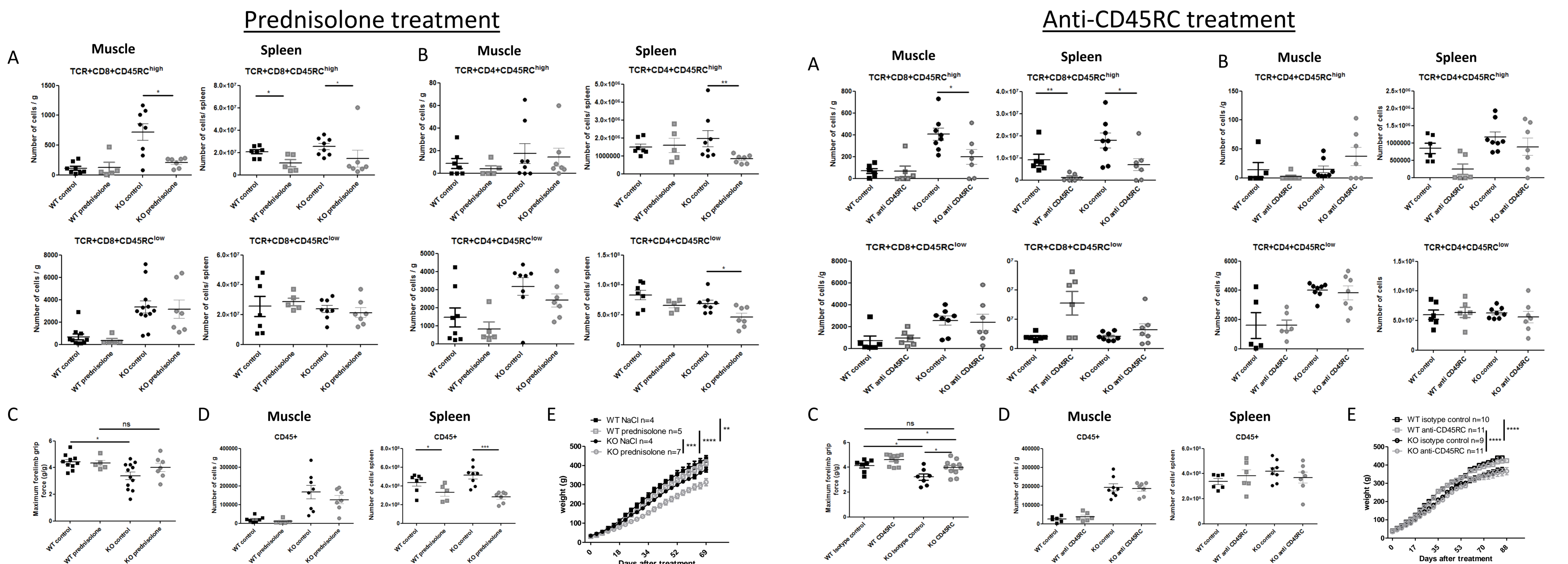
In this study, we assessed by flow cytometry and immunohistochemistry the immune cell subsets infiltrating *Dmd*^{mdx} rat skeletal and cardiac muscles especially immunoregulatory and pro-inflammatory subsets (M1 and M2 macrophages, CD4⁺ and CD8⁺ T cells or Tregs...).

Then, we investigated the possibility of reducing disease in *Dmd*^{mdx} rats by administrating immunomodulatory treatments. The standard therapy for DMD patients is corticoids that decrease inflammation and immune responses but with variable responses, limited efficacy and important and numerous side effects. Therefore, there is need for new anti-inflammatory and pro-tolerogenic treatments that could replace or decrease the doses of corticoids. Anti-CD45RC monoclonal antibody (MAb) treatment has induced immune tolerance in models of organ transplantation and GVHD.

Immunophenotyping



Immunomodulatory treatments



Conclusion

In this study, we phenotyped by flow cytometry and immunohistochemistry (data not shown) the immune cell subsets infiltrating *Dmd*^{mdx} rat skeletal and cardiac muscles. Leukocyte infiltrates were absent or very low at 2 weeks of age, peaked at 4 and 8 weeks and decreased at 12 weeks. M2 macrophages represented >90% of infiltrating immune cells and T cells were the majority of the remaining ones. We also analyzed muscle enzymes and cytokines in sera. Creatin kinase was increased at weeks 4 and 8 and decreased at week 12 and thereafter (data not shown). This results are consistent with those observed in *mdx* mice model.

Anti-CD45RC MAb treatment of young *Dmd*^{mdx} rats normalized skeletal muscle strength associated to a depletion of effectors CD45RC^{high} cells and no obvious side-effects. As a control prednisolone treatment of *Dmd*^{mdx} rats similarly increased skeletal muscle strength and was also associated to a depletion of effectors CD45RC^{high} cells but resulted in severe weight loss.