

Chapter 2: Aim of the thesis

Increasing size and strength of skeletal muscle represents a promising therapeutic strategy for muscular disorders. One possible new tool is Mstn because it plays a crucial role in regulating skeletal muscle mass. The first goal of our work was to determine whether Mstn inhibition could prevent muscle atrophy in catabolic states. As glucocorticoids play a major role in most muscle atrophy models, we planned to assess whether muscle atrophy caused by glucocorticoids in excess could be prevented by Mstn inhibition. This hypothesis is suggested by the fact that glucocorticoids increase muscle Mstn expression and that Mstn muscle overexpression is sufficient to cause muscle atrophy.

Objective 1:

To investigate whether Mstn gene disruption can prevent muscle atrophy caused by glucocorticoids.

Experimental design:

Mice harbouring a constitutive deletion of the third Mstn exon (Mstn KO mice) and WT mice will be subjected to dexamethasone treatment. The muscle atrophic effect of dexamethasone will be assessed by measuring muscle weight, muscle fiber CSA and muscle protein content.

The identification of Mstn binding proteins able to inhibit Mstn activity has led to potential new approaches for postdevelopmental muscle mass enhancement. These Mstn binding proteins include FS which shows a potent Mstn-inhibiting activity. The increase in muscle mass observed in transgenic mice overexpressing FS in muscle is even significantly larger than that observed in Mstn KO mice, suggesting that other ligands could contribute to the muscle hypertrophic effect of FS. The mechanisms involved in the FS effect are however relatively unknown.

Objective 2:

To investigate the contribution of satellite cells to the FS-induced muscle hypertrophy and to assess whether other FS ligands could act similarly to Mstn in controlling muscle growth.

Experimental design:

To test the role of satellite cells in the FS effect, we will use gamma-irradiation to destroy their proliferative capacity. The FS-induced hypertrophic effect will be measured after FS gene transfection in the TA muscle previously irradiated.

In parallel, to highlight a role of FS ligands other than Mstn in the FS hypertrophic effect, we will overexpressed FS in muscle of mice lacking Mstn (Mstn KO mice). We will also study the hypertrophic effect of a mutant FS, characterised by impaired affinity for Activin.