

## Gene signature of muscle hypertrophy

Flavio Ronzoni<sup>1</sup>, Silvio Conte<sup>1</sup>, Daniela Galli<sup>1</sup>, Rudi Micheletti<sup>1</sup>, Stefano Grifone<sup>1</sup>, Laura Benedetti<sup>1</sup>, Gabriella Cusella De Angelis<sup>1</sup>, Maurilio Sampaolesi<sup>1,2</sup>

<sup>1</sup> Department of Experimental Medicine, Human Anatomy Unit, University of Pavia, Italy

<sup>2</sup> Translational Cardiology Laboratory, SCIL K.U. Leuven, Belgium

Hepatocyte Growth Factor (HGF) is a pleiotropic cytokine of mesenchymal origin that mediates cell proliferation, survival, motility and morphogenesis. Its high affinity receptor, the tyrosine kinase Met, is expressed by a wide range of tissues. Adult myogenic precursor cells (satellite cells) express both HGF and Met. Following muscle injury, autocrine HGF-Met stimulation plays a key role in promoting activation and early division of satellite cells. Magic-F1 (Met-Activating Genetically Improved Chimeric Factor-1) is an HGF-derived, engineered protein that contains two Met-binding domains. Magic-F1 protects myogenic precursors against apoptosis, increasing their fusion ability and enhancing skeletal muscle differentiation in transgenic mice [1]. To deeply investigate gene expression profiles of wt and Magic-F1 satellite cells, microarray analysis has been performed. We described here the preliminary results of microarray analysis focusing on muscular hypertrophy and vasculogenesis gene signatures in Magic-F1 transgenic mice. In parallel we performed an *in vivo* analysis on hemizygous and homozygous Magic-F1 transgenic mice that displayed constitutive muscular hypertrophy, improving running performance and accelerating muscle regeneration following injury. Previous studies show that muscular hypertrophy could positively influence vascular network, increasing vessel number in skeletal muscle, because one of the unique features of mammalian skeletal muscle is its remarkable ability to adapt to different functional demands by changing phenotypic profiles.

Preliminary data with microarray assay show differences in expression in specific genes (growth factors, transcription factors and atrogens). In particular we observed two-fold increase in VEGF, MyoD and MURF. Furthermore VEGF-B, a key regulator for vasculogenesis in skeletal and cardiac muscles, showed higher expression in transgenic satellite cells respect to the control [2]. Consistently, transgenic mice showed 36,9% increase of muscle capillary network (5 capillaries/fiber on average), in comparison to the controls (4 capillaries/fiber). Conversely, we found a lower arterioles (34,34%) and venules (77,3%) density in the muscular tissue of the homozygous transgenic mice in comparison to the wt. These findings clearly show that Magic-F1 can positively regulate vasculogenesis, triggering VEGF signaling and increasing the capillary vessel number.

### References

[1] Cassano M et al. (2008) PLoS ONE. 3: e3223.

[2] Lohela M et al. (2009) Curr. Opin. Cell Biol. 21(2):154-65.

### Key words

VEGF, vasculogenesis, muscle hypertrophy