The interference with IL-6 trans-signaling modulates secondary mechanisms of dystrophic muscle

Carmen Miano[a], Laura Forcina[a], Carmine Nicoletti[a] and Antonio Musarò[b]

[a]*Institute Pasteur Cenci-Bolognetti (DAHFMO-Unit of Histology and Medical Embryology, IIM, Sapienza University of Rome, Rome, Italy)*
[b]*Center for Life Nano Science@Sapienza (IstitutoItaliano di Tecnologia, Rome, Italy)*

carmen.miano@uniroma1.it

Duchenne muscular dystrophy (DMD) is an X-linked genetic disorder caused by mutations in dystrophin gene. The absence of dystrophin protein leads to a cascade of pathological events including muscle fiber degeneration, fibrosis and necrosis. Among factors involved in the pathogenesis of DMD the extent of chronic inflammatory response and oxidative stress might be responsible for the appearence and progression of pathological changes in dystrophic muscles. To date inflammation is considered the principal determinant of degenerative processes in dystrophic muscle and the glucocorticoids are the only available anti-inflammatory treatment for DMD. However these aspecific molecules present long-term side effects, hence the needs of identifying and studying factors that can reduce both inflammation and oxidative damage, slowing down the progression of pathology. A potential candidate linked to inflammation is Interleukin 6 (IL-6), a pleiotropic cytokine with pro and anti-inflammatory effects, depending on the signaling that it will activate: IL-6 classic signaling has regenerative and anti-inflammatory effects whereas IL-6 trans-signaling, principally mediated by the IL-6 receptor alpha (IL6R), has pro-inflammatory actions. Particularly IL-6 is highly expressed in DMD patients and in mdx mouse model and it is involved in the transition from acute to chronic inflammation. In addition we recently demonstrated that IL-6 over-expression in mdx mice (mdx/IL6 mouse) is sufficient to induce the exacerbation of dystrophic phenotype, closely approximating the disease progression in DMD human patients. Based on these evidences we generated a new mouse model in which IL-6 trans-signaling is inhibited by the genetic ablation of IL6R, (mdxIL6R$^{-/-}$), to verify whether the modulation of IL-6 trans-signaling could ameliorate the dystrophic phenotype. In particular, we analysed key players involved in secondary mechanisms of the pathology leading to muscle wasting. In the present study we performed analysis of relevant markers of the inflammatory response and redox status at the acute phase of the pathology in muscles of mdxIL6R$^{-/-}$ and mdx mice. Furthermore to evaluate whether the interference with IL-6 trans-signaling could influence the robustness of dystrophic muscles we analysed myofiber necrosis and muscle functionality.