Press release

A new target for improving cellular therapy of muscular dystrophies

Research conducted at IFOM and the Università degli Studi di Milano, in collaboration with University College London and the San Raffaele Hospital in Milan highlights the important role of JAM-A, an adhesion protein contained in the cells that line the inner blood vessel wall, in increasing the efficacy of stem cell transplantation for treating muscular dystrophies. The results have been published in recent days in the prestigious international journal EMBO MOLECULAR MEDICINE, which also dedicates its cover to this finding.

Getting the right cells to the right place to improve the chances of curing muscular dystrophies, this summarizes the goal of the study conducted by the team of Elisabetta Dejana at IFOM (FIRC Institute of Molecular Oncology) and the University of Milan, in close collaboration with Giulio Cossu of the San Raffaele Hospital in Milan and University College London.

Published in *EMBO Molecular Medicine,* the study describes a previously unknown mechanism that allows the special stem cell progenitors of skeletal muscle known as mesoangioblasts to reach damaged muscle more efficiently; thus, allowing more efficient repair of the damage caused by these serious diseases.

The muscular dystrophies are a class of genetic neuromuscular diseases that cause relentless, progressive degeneration of skeletal muscle. One of the most common and severe forms is Duchenne muscular dystrophy (DMD), which affects 1 in every 3500 male children born. Subjects with DMD manifest difficulty in walking in early childhood that worsens progressively, leading to immobility and finally premature death from cardiorespiratory complications.

Unfortunately, there is currently no cure for these fatal diseases. However, numerous pre-clinical and clinical studies are underway to develop novel experimental approaches, such as those conducted by Prof. Giulio Cossu at the San Raffaele Hospital in Milan, which are based on transplantation of mesoangioblasts: these cells are isolated from the muscles of compatible donors

and injected into the bloodstream of patients with DMD. However, numerous obstacles limit the effectiveness of this approach: one of the major barriers is the need for mesoangioblasts to traverse the endothelial walls of blood vessels to reach the dystrophic muscle and generate new functional muscle fibers. Only a limited number of cells can overcome this and reach the damaged tissue.

"It is precisely to overcome this limit - explains Elisabetta Dejana – that our study has identified a new mechanism for increasing the trafficking of mesoangioblasts across blood vessel walls, thus ensuring that they reach the damaged muscle." This traffic is finely regulated by special "gates", called endothelial junctions, that carefully select what can pass and when. Thus, by acting on the molecules regulating these "gates" it is possible to increase the number of mesoangioblasts reaching the dystrophic muscle. "Modulating activity of the JAM-A protein, which has an important role in endothelial junctions, increases the number of stem cells that repopulate and regenerate damaged muscle an animal model of DMD", explain the researchers Monica Giannotta and Sara Benedetti, first authors of the publication, "and this increase in muscle regeneration corresponds to a significant improvement in muscular function in dystrophic mice, allowing them to maintain and sometimes even improve their ability to run."

The study conducted at IFOM in Milan has identified molecules that could one day be used to improve the effectiveness of cellular therapies for treating muscular dystrophies. "Obviously we are still far from conducting a clinical study - says Elisabetta Dejana - but the results are encouraging and this study is a clear example of how basic research is fundamental for improving therapeutic strategies." Development of these findings - continues the researcher - may also provide valuable knowledge for cancer research, in particular on metastasis. Modulation of JAM-A might be a useful strategy for blocking tumor dissemination through blood vessel walls"

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Editorial details

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