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Extended Abstract

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Extracellular matrix engineered with extracellular vesicles supports tissue regeneration in a murine model of volume muscle loss

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Repair of skeletal muscle loss due to trauma, surgical resection or malformations represent a challenge for clinicians. Several attempts to create a bioscaffold to substitute skeletal muscle have been done and the use of extracellular matrix (ECM) from decellularized tissues to replenish volume muscle loss defects is one of the most promising approaches. However, the development of fibrosis still represents a major drawback. It is known that intercellular signals mediating tissue repair such as tissue renewal, vascularization and immune regulation, are convoyed via extracellular vesicles (EVs), biologically active nanoparticles secreted by the cells and composed of a lipid bilayer including cytoplasmic content. The aim of this work is to analyze the biological effects of EVs added to ECM scaffolds in a murine model of chronic volume muscle loss. ECM samples were obtained using a detergentenzymatic protocol and were embedded with EVs isolated either from Wharton Jelly mesenchymal stromal cells (MSC-EV) or from BJ fibroblast cell line (BJEV). ECM-EVs were transplanted in mice after tibialis anterior damage. 72 hours post implant, EVs were administered by local and systemic injections. Samples were analyzed by immunofluorescence, flow cytometry and qPCR. Myogenic and macrophage markers were clearly directed toward tissue rebuilding in MSC-EV treated mice with respect to controls and to the BJ-EV treated group, as confirmed by qPCR and flow cytometry analysis. Thirty days post implant the fibrosis (collagen quantification) was significantly reduced in the MSC-EV treated group. Marker of neo angiogenesis and new born centrally nucleated fibers (CNFS) were present in a statistically higher percentage in MSC-EV treated mice with respect to controls and to EV-BJ treated group. ECM engineered with EV-MSC showed a boost on actively replenishing the loss of muscle tissue. The crucial role of the ECM environment in the stem cell niche, and in the regulation of stem cell identity and differentiation, organogenesis and tissue homeostasis has been a topic of extensive and intriguing study. In the field of regenerative medicine this has allowed for the development of an increasing number of tissue engineering strategies, in which scaffold materials are used to mimic in vivo the biological microenvironment of the ECM, providing the components needed to drive cells toward the regeneration of the tissue of interest. Despite the incredible improvements that have been made in 3D bioprinting technology, the bona-fide reproduction of a scaffold capable to accurately mimic complex tissues, such as skeletal muscle, remains a matter that cannot be technically solved. The 3D interactions existing among different components of the ECM is far for being a simple overlay of proteins organized in a layer-by-layer fashion. Indeed, ECM components not only interact with each other in specific fashions, but each single component, and also defined isoforms of a same component, are tissue-specific and even site-specific inside a defined tissue. Such complexity, which likely has a biological meaning for cells, can be preserved in scaffolds only by taking advance of the native tissue themselves, that is achieved by decellularizing tissues or whole organs. Upon the removal of nuclear content and cellular elements, decellularized or acellular scaffolds still retain the architecture and complexity of the native tissues, including vasculature and biofactors present in the ECM. These characteristics make decellularized matrices the ideal bio-scaffold necessary to guide host or donor cells toward the regeneration of new and functional tissues. Several studies have already demonstrated the possibility of successfully obtaining acellular scaffolds from many organs, such as heart, kidney, pancreas, lung, liver, esophagus and intestine. Importantly, some of these decellularization protocols have been adopted to decellularize simple hollow organs such as the trachea, which have then been successfully transplanted in patient after autologous cell seeding, i.e., trachea. Importantly, the trachea transplant has been achieved without immunosuppression, a great advantage over conventional transplantation because it avoids potential risks for patients, including frequent infections and cancer. Acellular tissues are biocompatible and the absence of rejection after allogeneic or xenogeneic transplantation make them the ideal scaffold for translational medicine applications and organ replacement. Even though skeletal muscle has a remarkable capacity to undergo regeneration, several pathological conditions can lead to extensive and irreversible muscle loss: i.e., congenital defects, traumatic injuries, surgical ablations, and neuromuscular diseases. Failure of normal regeneration results in VML, with loss of muscle function, often associated with scar tissue formation and adipose tissue substitution. Current treatments for such conditions have limited success, leading to considerable social and economic burden. Therefore, there is a great need for new regenerative medicine strategies aimed at treating VML conditions. Skeletal muscle is a complex tissue in which myofiber 3D organization and function is intimately linked to other tissue components, such as motor neurons, vasculature, myogenic stem cells (including satellite cells, SCs), interstitial cells, and ECM.

Bottom Note: *This work is partly presented at Joint Event on Biotechnology, Biochemistry and Aquaculture* August 08-09, 2019 | Paris, France