doi: http://dx.doi.org/10.11606/issn.1679-9836.v102i(ed.esp.)e-204415 Rev Med (São Paulo). 2023 Jan-Feb;102(ed. esp.):e-204415.

Letter to the Editor

Development of cell therapies through muscle stem cell research

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Musculoskeletal injuries represent a major public health problem that is often overlooked. National data indicate that 19% of all disability insurance allowances are due to musculoskeletal and connective tissue diseases, representing the largest single portion of all allowances granted[1]. Moreover, the impact generated by musculoskeletal disease is not restricted to the patient, but extends on to needing for caregivers, visits to the health service, and the secondary economic impacts generated by absence or disability, which are often forgotten[2]. Beyond the seriousness of the muscular injury panorama depicted above, the extensive dimension of the musculoskeletal system increments the possibilities of injury. The possibility of generating secondary deficits that significantly impact the autonomy of individuals is important, and measurable through disability-adjusted life years (DALYs).

Muscle injury can occur by different mechanisms, such as ischemia, neurological dysfunction, blunt trauma, lacerations, and extreme temperatures[3]. Although they share pathophysiological mechanisms, such as cell ablation, cell lysis, and subsequent inflammatory response, injuries cannot be generalized. It is known that the characteristic of the injury determines the quality of the regeneration response, fibrosis, and determination of the cells involved in repair[4]. Thus, comes a challenge because muscle injuries are not all the same in their cellular aspect. But from this challenge, doors are opened to study specific injury strategies to develop and standardize therapies with better muscle performance response.

An important type of muscle injury is the volumetric muscle loss (VML) injury, which occurs when there is a significant loss of muscle volume. Its importance consists in the mechanism of ablation of satellite cells, which constitute the population of muscle stem cells. These cells are responsible, in scenarios with regeneration potential, for differentiating into myoblasts, donating sarcolemma and sarcoplasm to recompose injured fibers. The importance of studying VML injury lies in the fact that there is no gold standard treatment that offers satisfactory results in terms of muscle performance. One of the recommended treatments is the use of autologous flap at the injured site, called functional free muscle transfer (FFMT), plus physical therapy[5]. There are several challenges associated, as complications related to the donor site, such as necrosis, the demand for viable donor sites, and related to recipient site, such as infection and graft/receptor failure can occur. Moreover, FFMT is not able to fully recover muscle function, and does so partially[6]. Dissatisfaction with the still insufficient gold standard therapy should motivate the search for new solutions to this frequent and disabling problem.

Preclinical studies have shown promising results for

Trabalho apresentado como Pôster Científico no COMU - Faculdade de Medicina - USP, out. 2022.

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the development of strategies onboard with full recovery of muscle function[7]. Interesting approaches involve the delivery of cells, with potential stem or more compromised stages, such as myoblasts, arranged in three-dimensional structures and augmented with biomolecular tools, such as biomaterials, for efficient and functional tissue delivery. However, numerous challenges are reported, such as triggering immunological and inflammatory reactions to grafting materials, delineating the optimal quantity of cells to be delivered, and most importantly, the survival of the cells in the recipient tissue.

Thus, studying ways to deliver cells with preserved viability and functionality in architectural conformations mimicking the in vivo microenvironment is at the core of the mission to efficiently treat VML injury while maintaining functionality. The delivery of the correct cell type with therapeutic potential, in a suitable vehicle, biocompatible and allowing positive microenvironment interactions for proliferation and regeneration opens doors for advancement in the treatment of muscle injury, thus mitigating the multiple impacts of musculoskeletal disorders and exponentiating opportunities for adequate treatment development.

Authors participation: *LPM* and *RSS* drafted the original manuscript. *LPM, GZI, MSN, SS, FMY, EAS* and *RSS* contributed with experimental design and execution.

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