



Cover Story

Exosome-based therapeutic approach for muscle regeneration



One of the strategies in regenerative medicine is cell-based therapy for improving the function and regeneration of damaged tissue. Although cell-based therapy has clear beneficial effects on tissue repair, there are still a number of concerns, such as limited survival and the reduced regenerative capacity of engrafted cells, as well as immune-mediated rejection. Exosomes are small membrane vesicles (40 ~ 120 nm) secreted by various cells for paracrine signaling, and they contain specific proteins, lipids, and/or genetic materials [1]. Research interest on the exosomes has expanded rapidly because of their diverse pathological and therapeutic effects, indicating their therapeutic potentials. Each type of exosome has a different function that depends on the function of its originating cell. Exosomes released from cells with specific functions may also induce the phenotypic and functional changes of recipient cells through the delivery of cellular cargo of the originating cells. Recent studies have shown the therapeutic potential of exosomes derived from various cells with secretory capacity (e.g., stem cells and progenitor cells) in various injured tissues, including kidney, cardiac muscle, liver, lung, cutaneous wounds, and brain [2,3].

In this issue, Professor Yong Woo Cho and his group propose exosomes as a therapeutic agent for skeletal muscle regeneration [4]. Human skeletal myoblasts (HSkMs) were used in this study as originating cells to produce the exosomes. A skeletal myoblast is a type of progenitor cell that differentiates to give rise to muscle cells by fusion. Myoblast fusion is a key cellular process that contributes to the development of muscle and regeneration of new myofibers upon injury. The Cho group successfully isolated exosomes released from HSkMs during differentiation into myotubes. These exosomes contained various myogenic factors, including in particular insulin-like growth factors, hepatocyte growth factor, fibroblast growth factor-2, and platelet-derived growth factor-AA, which could act as critical signals for skeletal muscle myogenesis. The study by the Cho group provides interesting observations towards the exploitation of exosomes as a novel cell-free therapeutic approach for muscle regeneration. Exosomes significantly contributed to myogenic differentiation of human adipose-derived stem cells (HASCs). Stimulation by exosomes rapidly altered the morphological phenotype of HASCs at early time points (7 days) and resulted in significant expression of myogenic proteins and genes.

Furthermore, differentiating HSkMs-derived exosomes accelerated skeletal muscle regeneration in a laceration mouse model by reducing the collagen deposition in injured muscle and increasing the number of regenerated myofibers during 14 days.

These findings support their hypothesis that differentiating HSkM-derived exosomes could effectively control stem cell myogenesis and provide biochemical cues favorable to the skeletal muscle regeneration. Despite accumulating evidence for the therapeutic effects of exosomes, it still remains unclear as to which factors in exosomes play a key role in controlling cell fate and promoting skeletal muscle regeneration. Identification of the molecules contained in exosomes is required to elucidate the mechanisms underlying exosome-based therapeutics. Moreover, the adverse effects that can arise from high doses of exosomes (e.g., cell apoptosis) should be considered. Nonetheless, the approach described by the Cho team in this issue is a significant advance as an alternative approach to cell-based therapy. With proper perspective and care, exosomes can become a new, clinically useful tool providing a cell-free therapeutic approach for regenerative medicine.

References

- [1] C. Théry, L. Zitvogel, S. Amigorena, Exosomes: composition, biogenesis and function, *Nat. Rev. Immunol.* 2 (2002) 569–579.
- [2] L. Biancone, S. Bruno, M.C. Deregibus, C. Tetta, G. Camussi, Therapeutic potential of mesenchymal stem cell-derived microvesicles, *Nephrol. Dial. Transplant.* 27 (2012) 3037–3042.
- [3] T. Katsuda, N. Kosaka, F. Takeshita, T. Ochiya, The therapeutic potential of mesenchymal stem cell-derived extracellular vesicles, *Proteomics* 13 (2013) 1637–1653.
- [4] J.S. Choi, H.J. Yoon, K.S. Lee, Y.C. Choi, S.H. Yang, I.S. Kim, et al., Exosomes from differentiating human skeletal muscle cells trigger myogenesis of stem cells and provide biochemical cues for skeletal muscle regeneration, *J. Control. Release* 222 (2015) 107–115.

Kinam Park
Purdue University
Departments of Biomedical Engineering and Pharmaceutics
West Lafayette, IN 47907, USA
E-mail address: kpark@purdue.edu