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# Modification of mesenchymal stromal cells by silibinin-loaded PLGA nanoparticles for regenerative medicine

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Mesenchymal stromal cells (MSCs) have been widely used for cells-based therapy due to the ability to self-renew, the multipotent ability to differentiate into adipocytes, chondrocytes, and osteoblasts, ease to isolate and harvest. Moreover, their ability to migrate to injured sites and immunomodulatory properties. Therefore, over 1,300 clinical trials related to MSCs have been used to treat various diseases. Despite MSCs can be easily and reliably isolated from the bone marrow and other tissues, ex vivo expansion is needed to meet the transplantation related treatments, and the low survival transplanted rate increases the reliance on the in vivo expansion. After cells delivery, another reason influences the cell survival is that the cells are exposed to harsh environment factors, including oxidative stress. The excess intracellular reactive oxygen species (ROS) or endogenously induced oxidative stress impairs the MSC proliferation, self-renewal, and differentiation capacity. Reactive oxygen species (ROS) and nonspecific inflammation generated at the ischemic site of injury have been hypothesized to lead to loss of transplanted MSCs from this site. Therefore, strategies that attenuate oxidative-induced damage are required to improve MSC clinical translation outcomes.

Silibinin (SBN) is the active component of silymarin extracted from milk thistle which has been widely used for treatment of different liver diseases due to its hepatoprotective and antifibrotic effects. SBN has been reported to possess anti-inflammatory effects through the actions that interfere the NF-$\kappa$B and NAD+/SIRT2 pathway, suppress the generation of TNF$\alpha$, leukotrienes and nitric oxide biosynthesis. Another advantage is its antioxidant action, SBN alone can scavenge ROS and also promote the synthesize of protective molecules. In this research, we synthesized SBN loaded PLGA nanoparticles (PLGA/SBN) and used these particles to modify mouse MSCs by internalization. By our results, PLGA/SBN can be effectively endocytosed by MSCs in 30 minutes without influencing the cell viability. In addition, both SBN and PLGA/SBN stimulated MSCs to generate Nrf2 which is related to the activation of antioxidative responses and protected MSCs against tert-Butyl hydroperoxide induced oxidative stress. This non-genetic modification approach on MSCs improved the cell ability against ROS and secretory properties which are meaningful for the application of MSCs on regenerative medicine.