News Release

Title

Mesenchymal stem cells exert renoprotection via extracellular vesicle-mediated modulation of M2 macrophages and spleen-kidney network

Key Points

- Adipose mesenchymal stem cells dramatically improved severe nephritis.
- The dynamics of adipose mesenchymal stem cells in the body were elucidated.
- This study presents a possibility for a treatment that would not involve the direct administration of adipose-derived mesenchymal stem cells into the body.

Summary

A collaboration of Dr. Yuko Shimamura (currently a postdoctoral fellow at Columbia University), Dr. Kazuhiro Furuhashi (a lecturer at the hospital), Dr. Akihito Tanaka (an assistant professor at the hospital), and Dr. Shoichi Maruyama (a professor at the Nagoya University Nephrology Department) and Dr. Hiroshi Suzuki (a professor at the Nagoya University Division of Molecular Oncology, Center for Neurological Diseases and Cancer) has found that adipose-derived mesenchymal stem cells (ASCs) dramatically improve lethal severe nephritis compared with bone marrow-derived mesenchymal stem cells. Furthermore, the therapeutic mechanism was uncovered. Although ASCs dramatically improved renal damage, ASCs themselves were rarely present in the kidney, but rather in the form of ASC-derived extracellular vesicles (EVs). EVs are an intercellular communication tool that has recently attracted much attention, in which cells wrap their own cellular components in a piece of cellular material and deliver it to the other cell. This makes it possible to pass not only one protein but also multiple proteins in EVs at the same time. In this study, we found that ASCs reaching the spleen release EVs, which are specifically transferred to immunoregulatory M2 macrophages. Moreover, the state-of-the-art imaging technology and cell function analysis revealed that the transfer of EVs enhances the immunoregulatory function of macrophages, and that these macrophages contribute to kidney repair by entering the circulating bloodstream from the spleen and reaching the kidneys. In addition, we succeeded in detecting EVs secreted in vivo by the administered ASCs, leading to the clarification of functional changes induced in immunoregulatory macrophages by ASC-derived EVs produced in vivo through RNA-seq analysis. The action of ASCs elucidated in this study will be applied to therapies that enhance the therapeutic potential of ASCs, and will be developed into new therapies using EVs that would not involve the direct administration of cells.

Research Background

Mesenchymal stem cells (MSCs) are known to have outstanding regenerative and

immunomodulatory properties, and MSCs are expected to be therapeutic for refractory diseases that cannot be treated with existing drugs. Therefore, more than 1,000 clinical trials have been conducted globally to demonstrate the efficacy of MSCs in the treatment of refractory diseases. We are also conducting clinical studies using adipose-derived MSCs (ASCs) for refractory IgA nephropathy. Although MSCs have attracted attention as a new regenerative medicine due to their high therapeutic efficacy and their therapeutic mechanism has been studied intensively, no single molecule has been able to fully explain their mechanism of action. Elucidating the mechanism of action will not only further enhance the therapeutic effects of MSCs, but may also provide clues to drug discovery that could enable treatment without the administration of cells. Up to now, most MSCs studies in animal models have used mouse or rat MSCs, but it is assumed that the actions and mechanisms of MSCs will change with different animal species. Therefore, in this study, we aimed to perform analysis by using human MSCs to directly address the clinical significance of ASCs. We took a different approach from previous mechanistic analyses based on the molecules, and clarified the action of ASCs by focusing on the dynamics of ASCs in the body and their cell-to-cell communication.

Research Results

To date, the renoprotective effects of adipose-derived mesenchymal stem cells (ASCs) have been shown, and several clinical trials using ASCs to treat kidney diseases are underway. However, the detailed therapeutic mechanisms remain unclear. Here, we report the therapeutic potential of human ASCs for nephritis, focusing on in vivo cellular dynamics and multi-organ networks. Intravenously-administered ASCs accumulated in the spleen but not the kidneys. Nevertheless, ASCs increased M2 macrophages and Tregs in the damaged kidney, decreased neutrophils and M1 macrophages, and drove strong renoprotection. Splenectomy abolished these therapeutic effects. Flow cytometry analysis revealed that ASC-derived extracellular vesicles (EVs) were specifically transferred to M2 macrophages, and intravital microscopy imaging demonstrated that EV-transferred macrophages entered the bloodstream from the spleen. EVs induced the transcriptomic signatures of macrophage activation and PGE2 stimulation in M2 macrophages and partially ameliorated glomerulonephritis. Furthermore, ASCs, ASC-derived EVs, and EV-transferred M2 macrophages enhanced Treg induction in T cells. These findings collectively suggest that specific EV transfer from spleen-accumulated ASCs to M2 macrophages and subsequent modulation of the kidney immune environment underlie the renoprotective effects of ASCs. Our results provide insights into the therapeutic mechanisms of ASCs, focusing on EV-mediated modulation of macrophages and the spleen-kidney immune network, which may lead to maximized potential of cell therapies in clinical settings.

Research Summary and Future Perspective

Our laboratory has focused on adipose-derived mesenchymal stem cells (ASCs) because they

are easier to harvest than bone marrow and have superior proliferative potential. In this study, we found that ASCs have a higher immunomodulatory and organ-protective potential than bone marrow-derived MSCs. In the future, we hope to apply ASCs clinically as a novel treatment for various refractory inflammatory diseases in addition to nephritis. We will apply the action of ASCs elucidated in this study to therapies that enhance the therapeutic potential of ASCs, and further advance them to new therapies using EVs that would not involve the direct administration of adipose-derived mesenchymal stem cells into the body.

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