News Release

Title

Identification of a novel set of neuroregenerative factors derived from mesenchymal stem cells (MSC) and its use to develop a new regenerative therapy for spinal cord injury (SCI).

Key Points

- By secretomic analysis of the conditioned serum-free medium (CM) from MSC isolated from human dental pulp, we identified a previously unrecognized set of neuroregenerative factors: monocyte chemoattractant protein-1 (MCP-1) and the secreted ectodomain of sialic acid-binding Ig-like lectin-9 (ED-Siglec-9).
- The administration of MCP-1 and ED-Siglec-9 led to a marked recovery of hindlimb locomotor function after rat SCI through the induction of anti-inflammatory/tissue-regenerating macrophages.
- The induced tissue-regenerating macrophages suppressed SCI-induced tissue-destructive pro-inflammatory response and massive cell death, promoted axonal regeneration.
- This study strengthens the idea that the tissue-regenerating macrophages activate endogenous tissue-regenerating mechanisms, by which the locomotor function of SCI rats was substantially restored.

Summary

Associate Prof. Akihito Yamamoto and researcher Kohki Matsubara (Department of Oral and Maxillofacial Surgery of Nagoya University Graduate School of Medicine, Dean: Masahide Takahashi) and their collaborators identified a previously unrecognized set of neuroregenerative factors, monocyte chemoattractant protein-1 (MCP-1) and the secreted ectodomain of sialic acid-binding Ig-like lectin-9 (ED-Siglec-9), in CM from MSC of human dental pulp. Notably, the intrathecal administration of MCP-1/ED-Siglec-9 into the severely injured rat spinal cord led to a marked recovery of hindlimb locomotor function through the induction of anti-inflammatory/tissue-regenerating macrophages. The induced tissue-regenerating macrophages produced various tissue-repairing trophic factors, suppressed SCI-induced tissue-destructive pro-inflammatory response and massive cell death, and promoted axonal regeneration. This study strengthens the idea that the tissue-regenerating macrophages activate endogenous tissue-regenerating mechanisms, by which the locomotor function of SCI rats was substantially restored. This work was published online in the Journal of Neuroscience in February 11, 2015.

Research Background

Neuroregenerative therapy based on stem-cell transplantation holds great promise for treating SCI. In the last decade, a variety of stem cell types have been transplanted into the injured spinal cord of model animals. In these preclinical studies, the engrafted stem cells promote functional recovery.

However, the survival and/or differentiation of the stem-cell grafts under the severe pro-inflammatory SCI conditions are very low, and functional recovery is modest in many cases. Furthermore, for clinical applications, stem-cell therapies must avoid tumorigenesis and strong immune reactions. Thus, these serious hurdles must be overcome before stem-cell-based transplantation is established as a practical regenerative therapy. To overcome these hurdles, we aimed to identify a major therapeutic factors derived from stem cells and develop the new neuroregenerative therapy using them.

Research Results

We identified a previously unrecognized set of neuroregenerative factors, monocyte chemoattractant protein-1 (MCP-1) and the secreted ectodomain of sialic acid-binding Ig-like lectin-9 (ED-Siglec-9), in CM from MSC of human dental pulp. Notably, intrathecal administration of MCP-1/ED-Siglec-9 into the severely injured rat spinal cord led to a marked recovery of hindlimb locomotor function through the induction of anti-inflammatory/tissue-regenerating macrophages. The induced tissue-regenerating macrophages produced various tissue-repairing trophic factors, suppressed SCI-induced tissue-destructive pro-inflammatory response and massive cell death, and promoted axonal regeneration. This study strengthens the idea that the tissue-regenerating macrophages activate endogenous tissue-regenerating mechanisms, by which the locomotor function of SCI rats was substantially restored.

Future Perspective

Macrophages are central player of the innate immune response, which plays crucial roles in early host defense against invading pathogens. However, in various intractable diseases, the prolonged activation of the pro-inflammatory macrophages accelerates tissue destruction, fibrosis and subsequent organ failure. The application of MCP-1/ED-Siglec-9 would provide a novel strategy to develop effective regenerative therapies for various types of intractable diseases accompanying with tissue destructive inflammation.

The authors and title of the paper

Matsubara K, Matsushita Y, Sakai K, Kano F, Kondo M, Noda M, Hashimoto N, Imagama S, Ishiguro N, Suzumura A, Ueda M, Furukawa K, Yamamoto A. Secreted ectodomain of sialic acid-binding Ig-like lectin-9 and monocyte chemoattractant protein-1 promote recovery after rat spinal cord injury by altering macrophage polarity. *The Journal of Neuroscience,* February 11, 2015.

Japanese ver.

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