DRGs migrates into the modiolus of cochleae, indicating the possible use of fetal DRGs as neural grafts for restoration of spiral ganglion neurons.

ESCs are also transplant candidates for the regeneration of spiral ganglion neurons. ESCs are totipotent stem cells, and methods for induction of neural differentiation have been established. Retinoic acid treatment of embryoid bodies [56, 57], and co-culture of ESCs with PA6 cells (stromal cells derived from skull bone marrow) [58] induce neural differentiation of ESCs. Moreover, a recent study has indicated that peripheral sensory neurons can be generated from ESCs [59]. Several laboratories have investigated the potential of ESC-derived neural cells for restoration of spiral ganglion neurons [60-62], which suggests the high potential of ESCs as transplants for functional restoration of spiral ganglion neurons.

The use of NSCs, fetal DRGs or ESCs involves problems on the limited availability of these cells which will restrict their clinical use. Therefore, the use of the cells that are obtained from individual's own tissues is desirable. Bone marrow stromal cells (MSCs) can be readily obtained from an individual's own bone marrow. In addition, recent studies have shown that MSCs can produce not only osteoblasts, chondrocytes, adipocytes, or myoblasts, but also neurons [63, 64], suggesting the possibility using them in the treatment of various neuronal diseases. We examined the viability of autologous MSCs in the cochlea and wanted to determine the fate of MSCs grafted into the cochlea [65]. Histological analysis has shown robust survival of grafted MSCs in the cochlea modiolus and neural marker-positive cells in grafted cells settled in the modiolus, although their number is very limited. Therefore, it is difficult to justify the use of MSCs as transplants for regeneration of spiral ganglion neurons without establishing a method to induce neuronal differentiation.

CELL THERAPY FOR DRUG DELIVERY

Grafted cells can be used as a vehicle for drug delivery where the transplanted cells for this purpose have the ability to survive and generate therapeutic agents in the inner ear. Many attempts have been made to identify drugs that protect hair cells and associated neurons. Among various agents, protective effects of neurotrophins have been well documented [20, 21]. Neurons or glial cells produce several neurotrophins; therefore, cells that can differentiate into neurons or glial cells are potentially a source for neurotrophins. In fact, the ability of NSC-derived cells to produce brain-derived neurotrophic factor (BDNF) and glial cell line-derived neurotrophic factor (GDNF) has been demonstrated [39]. In addition, transplantation of neurospheres can reportedly be utilized for local delivery of neurotrophins into the brain [36, 37]. These findings suggest that NSC transplantation is a possible strategy for sustained delivery of neurotrophins into the inner ear. However, the protective effects of NSC transplantation must be compared with conventional methods, i.e. systemic administration of steroids.

Autologous MSCs may be desirable vehicles for drug delivery into the inner ear. Implantation of MSCs has been reported to contribute to functional recovery of the brain [66] and spinal cord [67] by means of producing trophic factors. Furthermore, a previous study has revealed the potential of MSCs for survival in various portions of inner ears [65]. It may also be possible to manipulate the genes of MSCs *ex vivo* to obtain materials desired for treatment of particular inner ear diseases. If MSCs can be used as a vehicle for gene delivery to the inner ear, we could provide a novel cell-gene therapy for various inner ear diseases.

CONCLUSION

Regenerative activity of the mammalian inner ear is limited, and most degenerative inner ear diseases are incurable by conventional treatments. Several new experimental approaches including cell transplantation are being pursued to overcome degenerative inner ear diseases. Recent findings in experiments on cell transplantation into the inner ear have suggested that cell therapy is potentially applicable to protection or regeneration of hair cells and associated neurons in the inner ear.

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