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Mini Review

Regenerative Medicine at a Crossroads: Transition from Stem Cell Therapy to Secretome-Based Medicine

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Abstract

Regenerative medicine has undergone several paradigm shifts over the past four decades. Initially developed to overcome organ shortages in transplantation medicine, the field evolved from cultured tissue transplantation to tissue engineering and stem cell therapy. More recently, increasing attention has focused on cell-free therapeutic approaches utilizing stem cell-derived secretomes and extracellular vesicles.

Accumulating evidence suggests that many therapeutic effects previously attributed to stem cells are mediated primarily through paracrine signaling rather than direct cellular engraftment. This mini-review summarizes the historical evolution of regenerative medicine, discusses the limitations of conventional stem cell therapies and highlights the therapeutic potential of conditioned medium derived from stem cells from human exfoliated deciduous teeth (SHED-CM).

Particular emphasis is placed on the immunomodulatory and neuroregenerative properties of SHED-derived secretomes and their potential application in neurodegenerative disorders such as Amyotrophic Lateral Sclerosis (ALS) and Alzheimer's disease.

Keywords: Regenerative medicine, Stem cell transplantation, Tissue engineering, Neurodegenerative diseases

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Introduction

Regenerative medicine has rapidly evolved into a multidisciplinary field integrating stem cell biology, tissue engineering, biomaterials science, and translational medicine. Initially, the primary objective of regenerative medicine was to replace damaged tissues and organs that could not be restored through conventional therapies. The shortage of transplantable organs, particularly for the heart, liver, and kidneys, served as a major driving force for the development of regenerative medicine. However, despite major advances in stem cell technology, many challenges remain unresolved. The clinical application of stem cell transplantation is frequently limited by poor engraftment efficiency, cellular heterogeneity, immune reactions, high manufacturing costs, and safety concerns including tumorigenicity and embolic complications.

Recent studies increasingly suggest that the therapeutic benefits of stem cells are mediated not by direct tissue replacement but rather through bioactive factors secreted by the cells. This realization has accelerated the transition toward cell-free regenerative medicine based on secretomes and extracellular vesicles.

Historical evolution of regenerative medicine

The first generation of regenerative medicine emerged in the 1980s with cultured epidermal transplantation for severe burns. A landmark achievement was reported by Green and colleagues, who successfully regenerated cultured epidermis sufficient to treat extensive burn injuries. This achievement established the revolutionary concept that a small number of cells could generate clinically useful tissues.

The second generation focused on tissue engineering. This approach combined cells with scaffold materials and signaling molecules to create more structurally organized tissues. Applications included cartilage, cornea, and skin regeneration. The concept demonstrated that tissue regeneration requires not only cells but also a microenvironment capable of supporting cell proliferation and differentiation.

The third generation involved stem cell transplantation. Mesenchymal stem cells, neural stem cells, and induced pluripotent stem cells (iPSCs) became major targets for regenerative therapy. Although iPSC technology represented a major scientific breakthrough, practical clinical application remains difficult because of manufacturing complexity, cost, and safety concerns. These limitations have contributed to the emergence of fourth-generation regenerative medicine based on secretome therapy. This strategy utilizes bioactive substances released from stem cells rather than the cells themselves.

Secretome and extracellular vesicles

Stem cell-derived conditioned medium contains cytokines, chemokines, growth factors, extracellular vesicles, and exosomes that collectively regulate inflammation, angiogenesis, tissue repair, and neuroprotection. The term "secretome" generally refers to the entire spectrum of bioactive substances released by cells during culture **(Figure 1).** Among secretome components, extracellular vesicles and exosomes **[1, 2]** have attracted particular attention because they contain proteins, lipids, mRNA, and microRNA capable of modulating recipient cell function. These vesicles are believed to play important roles in intercellular communication and tissue regeneration. Compared with live-cell transplantation, secretome-based therapies offer several theoretical advantages. These include lower embolic risk, improved storage stability, easier quality control, repeated administration, and superior penetration into target tissues. Importantly, extracellular vesicles may cross the blood–brain barrier, making them attractive candidates for neurological disorders.

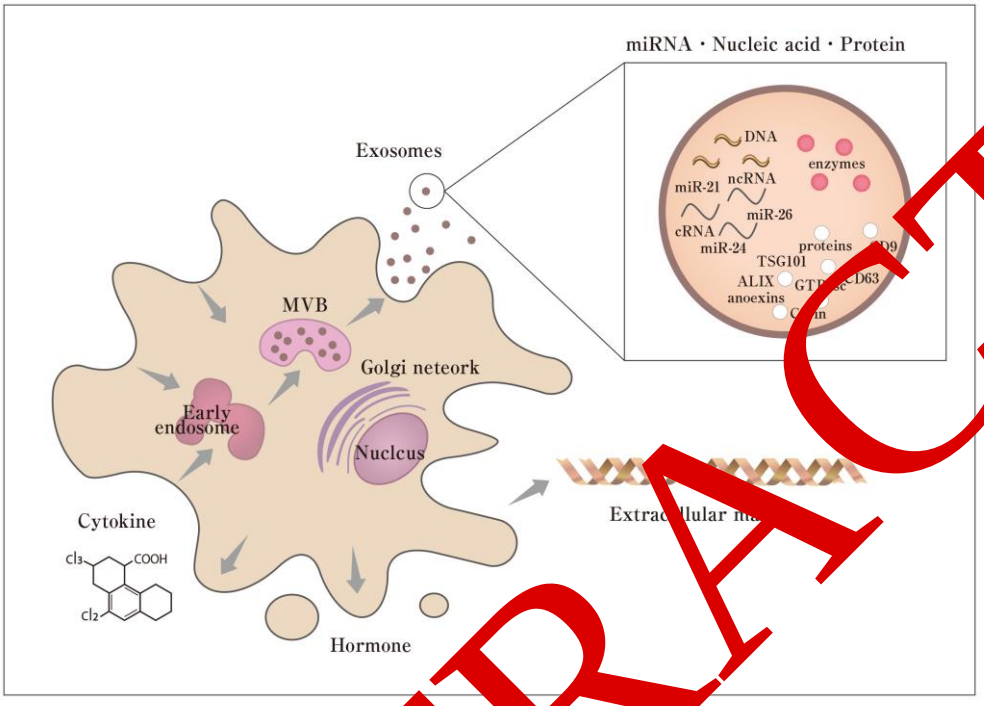

Figure 1: Composition and biological functions of stem cell-derived secretome.

SHED-derived conditioned medium

Stem cells from human exfoliated deciduous teeth (SHED) are neural crest-derived mesenchymal stem cells with high proliferative capacity and potent neuroregenerative properties. Because of their developmental origin, SHED exhibit characteristics favorable for central nervous system repair.

Previous studies from Aichi-Gakuin University **[3-5]** and other institutions have demonstrated that SHED-derived conditioned medium promotes recovery in models of spinal cord injury, cerebral ischemia, autoimmune encephalomyelitis, and Alzheimer's disease. Mechanistically, MCP-1 and Fc-Siglec have been identified as key bioactive components involved in macrophage polarization toward the anti-inflammatory M2 phenotype. This process suppresses neuroinflammation and promotes tissue repair.

In addition, SHED-derived secretomes contain multiple neurotrophic and angiogenic factors that may support neuronal survival and

regeneration. These findings suggest that SHED-CM represents a promising candidate for next-generation regenerative medicine targeting neurodegenerative diseases.

Regulatory and ethical considerations

The rapid commercialization of exosome and conditioned medium therapies has progressed faster than the development of appropriate regulatory frameworks in many countries. In Japan, secretomes lacking viable cellular components are not currently classified as specified cell-derived products under the Act on the Safety of Regenerative Medicine. Consequently, some therapies are being introduced into clinical practice without sufficient scientific validation. This situation highlights the urgent need for international standards governing manufacturing quality, safety assessment, efficacy evaluation, and ethical oversight.

Although secretome therapy offers considerable promise, treatments should not be administered without adequate scientific evidence and informed consent. Clinical research must adhere to internationally accepted ethical principles, including the Declaration of Helsinki.

Future perspectives

Secretome-based regenerative medicine may represent a scalable and clinically practical alternative to conventional stem cell transplantation. Future research should focus on large-scale manufacturing technologies, standardization of quality control, optimization of purification methods, and clarification of molecular mechanisms. Particularly important will be the development of therapies targeting neurodegenerative diseases such as ALS, Alzheimer's disease, spinal cord injury, and age-related inflammatory disorders. Combination strategies involving physical stimulation technologies such as ultrasound may further enhance the biological activity of secretomes and improve therapeutic efficacy. As regenerative medicine enters a new era, cell-free therapeutic approaches may become central to future clinical applications.

Discussion & conclusion

Regenerative medicine is currently undergoing a major conceptual transition from cell transplantation toward cell-free therapeutic strategies. Accumulating evidence suggests that many regenerative effects previously attributed to stem cells are mediated through secreted bioactive factors.

SHED-derived conditioned medium possesses strong immunomodulatory and neuroregenerative potential and may represent a promising next-generation therapeutic platform for neurological diseases. Although substantial scientific and regulatory challenges remain, advances in secretome research may fundamentally reshape the future of regenerative medicine.

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