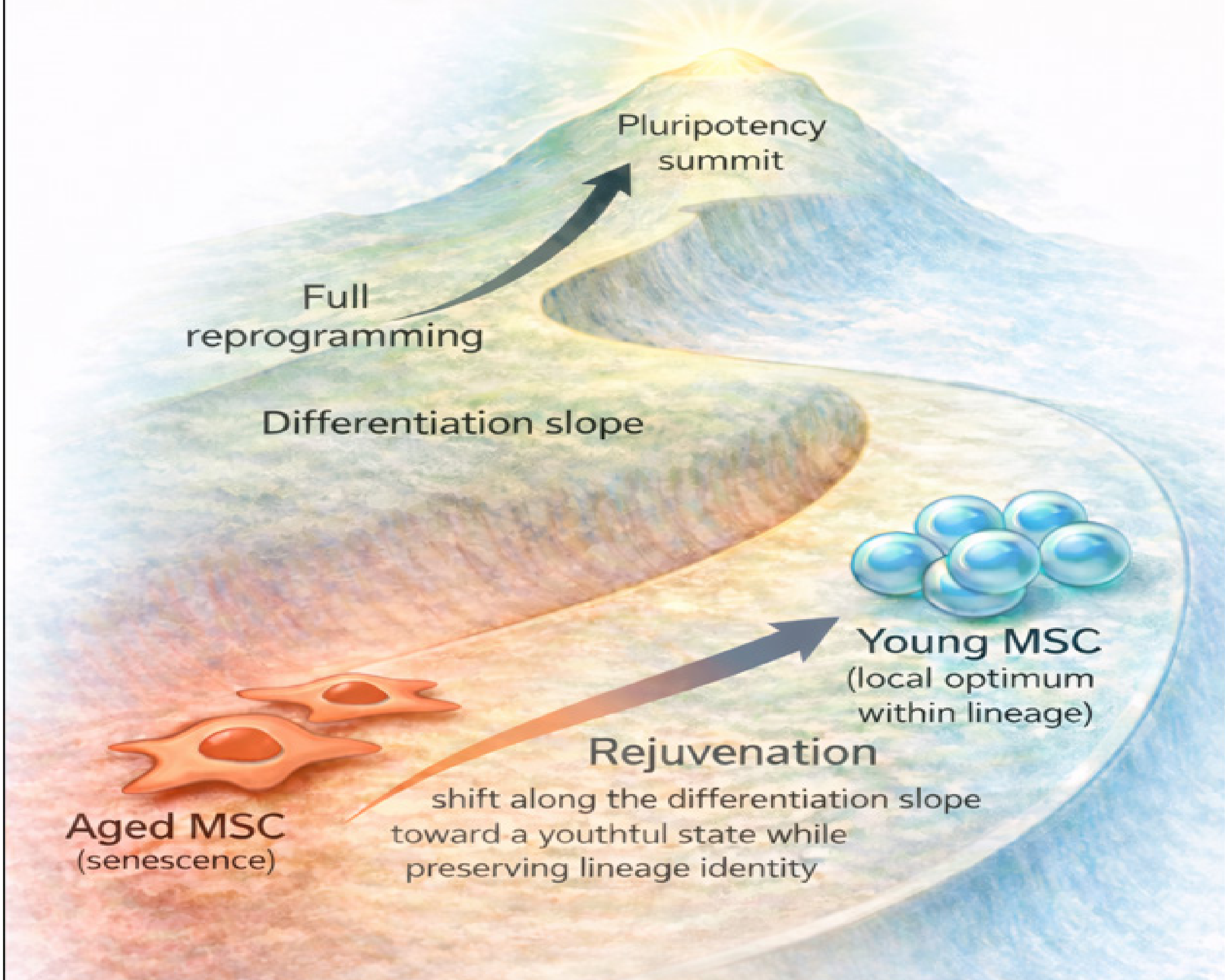
International Journal of Stem Cells and Medicine

Cellular Rejuvenation on the Slope of Waddington's Landscape



Corresponding Author: Mitsuo Oshimura
Emeritus Professor, Tottori University
Trans Chromosomics Inc., Nishi-cho 86, Yonago, Japan

https://www.mediresonline.org/

ISSN: 2836-5038

Open Access

International Journal of Stem Cells and Medicine

Review article

Partial Reprogramming Uncouples Cellular Identity from Cellular Aging in Mesenchymal Stromal Cells

Mitsuo Oshimura[1]*

[1]Emeritus Professor, Tottori University, Trans Chromosomics Inc., Nishi-cho 86,Yonago, Japan

***Corresponding Author:** Mitsuo Oshimura, Emeritus Professor, Tottori University, Trans Chromosomics Inc., Nishi-cho 86, Yonago, Japan

Received Date: 14 March 2026; **Accepted Date:** 06 April 2026; **Published Date:** 13 April 2026

Abstract

The epigenetic landscape proposed by Waddington has long provided a conceptual framework for cellular differentiation [1]. In this model, pluripotent cells positioned at the summit of a developmental landscape progressively descend toward terminally differentiated states. The discovery of induced pluripotent stem (iPS) cells demonstrated that differentiated somatic cells can be reprogrammed back to pluripotency, revising the concept of irreversibility [2].

Emerging evidence suggests that rejuvenation does not necessarily require a return to this summit. Rather, partial reprogramming may restore youthful cellular properties while preserving lineage identity [3–5].

Here, I propose a conceptual framework in which rejuvenation occurs along the slope of the Waddington landscape. In this view, cellular identity and cellular aging represent partially separable dimensions of cell state.

In mesenchymal stromal cells (MSCs), chemical, mechanical, and transient gene-expression strategies converge on restoration of youthful function without complete dedifferentiation [7–12].

This perspective suggests that partial reprogramming may enable the generation of transcriptionally diverse MSC populations, providing a conceptual basis for precision regenerative medicine.

Keywords: Waddington landscape; Rejuvenation; Partial reprogramming; MSC

Introduction

The epigenetic landscape proposed by Conrad Hal Waddington remains one of the most enduring conceptual models in developmental biology [1]. In this metaphor, pluripotent cells occupy the summit of a developmental landscape and progressively descend through branching valleys as differentiation proceeds toward terminal cell fates.

This interpretation was fundamentally revised by the induction of iPS cells, which demonstrated that differentiated somatic cells can be reprogrammed to pluripotency by defined transcription factors [2]. The ability to return cells to the summit transformed our understanding of cellular plasticity.

More recent work has shown that transient or partial reprogramming can reverse age-associated phenotypes without fully erasing cellular identity [3–5].

Here, I propose a conceptual framework that places cellular rejuvenation within the classical Waddington landscape, with a particular focus on mesenchymal stromal cells, as illustrated in Figure 1.

In this article, "rejuvenation" is operationally defined as the partial restoration of youthful cellular properties without loss of lineage identity or activation of pluripotency programs.

Rejuvenation as Mid-Slope Reprogramming

Mesenchymal stromal cells (MSCs) provide a particularly informative system [6]. MSCs occupy an intermediate position in the developmental hierarchy and possess regenerative and immunomodulatory properties. However, during ex vivo expansion they undergo replicative senescence [6].

Recent studies suggest that rejuvenation-like interventions can restore proliferative potential and reduce senescence-associated features while preserving lineage identity [10–12].

Within this framework, rejuvenation does not return cells to the pluripotency summit. Instead, it repositions cells toward a younger state along the slope of differentiation.

This is particularly relevant for MSC-based therapies, where both functional decline and heterogeneity remain major limitations.

Multiple Routes Toward Cellular Rejuvenation

Several experimental routes can induce rejuvenation-like states in somatic cells.

Chemical reprogramming has demonstrated that cell fate can be remodeled by small molecules alone [7,8], and more recent approaches have shown reversal of age-associated transcriptional states without loss of identity [9].

Mechanical conditioning has also been reported to reduce senescence-associated phenotypes and improve expansion potential in MSCs from aged donors [10].

Another route involves transient non-integrative gene expression systems, such as Sendai virus–mediated delivery of hTERT and BMI1, with or without SV40T, enabling extension of proliferative lifespan and maintenance of genomic stability [11,12].

Despite mechanistic differences, these approaches converge on restoration of youthful cellular function without complete dedifferentiation [3–5,9–12].

Rejuvenation Generates Transcriptional Diversity

Rejuvenation may expand the accessible state space within a lineage.

By extending proliferative lifespan and enabling clonal expansion, rejuvenation platforms allow the generation of functionally distinct MSC clones [11,12].

This diversity may represent a key advantage for MSC-based regenerative medicine, where functional heterogeneity can be leveraged rather than minimized [5,12].

Such MSC libraries may enable selection of clones optimized for specific therapeutic applications.

Converging Biological Mechanisms

Recent work supports the idea that distinct molecular routes converge on rejuvenation. Senescence-resistant mesenchymal progenitor cells have been shown to counter aging phenotypes in primates, implicating FOXO3-associated pathways [13].

At the same time, FOXO3 activation is unlikely to represent a universal requirement. Different rejuvenation strategies achieve similar outcomes through distinct proximal mechanisms [9–12].

This suggests convergence at the level of cellular phenotype rather than a single pathway.

In Waddington-like terms, these represent alternative routes toward a younger region of the same landscape.

A Revised View of the Epigenetic Landscape

The discovery of iPS cells demonstrated that differentiation is reversible [2].

Rejuvenation suggests that cellular aging is also reversible without erasing identity [3–5,9–13].

In this framework:

Full reprogramming → return to pluripotency summit

Rejuvenation → shift along the slope toward youth

Thus, the epigenetic landscape should be considered a dynamic and tunable system.

Conclusion

Partial reprogramming provides a conceptual framework for restoring youthful cellular function while preserving lineage identity.

In MSC biology, this supports the development of scalable, functionally diverse cell libraries for regenerative medicine.

A key challenge will be defining how far cells can be rejuvenated without destabilization.

Understanding rejuvenation within the Waddington landscape will be essential for advancing regenerative medicine and may ultimately enable controlled rejuvenation in vivo.

Further experimental validation will be required to determine the extent and limitations of this rejuvenation framework.

Competing interests

MO is also the Chief Exective Officer of a University Venture, Trans-Chromosomics, Inc.

Acknowledgement

I thank all my colleagues in chromosome engineering research center, Tottori university for valuable discussions.

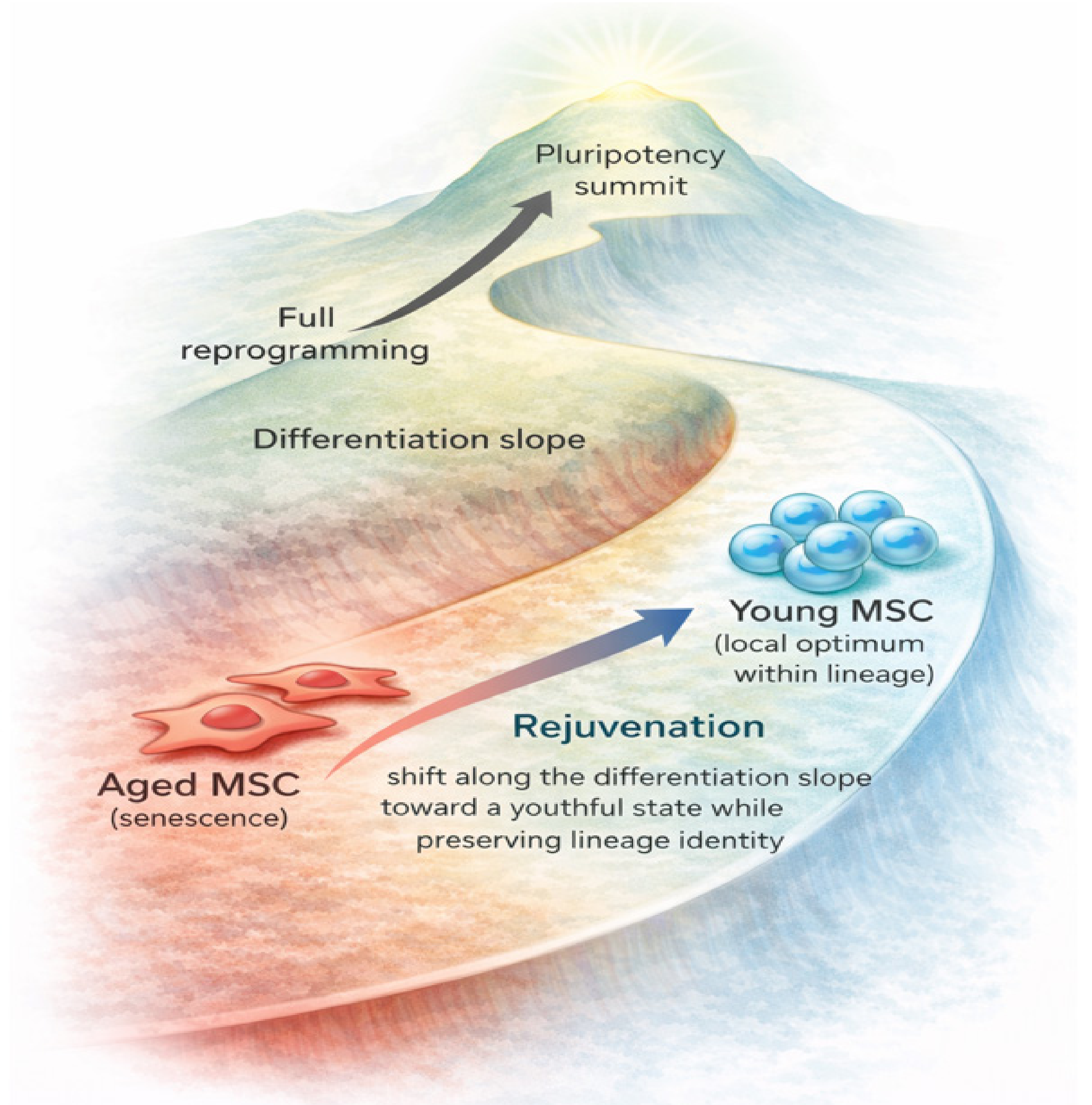


Figure 1: Rejuvenation occurs on the slope of Waddington’s landscape, distinct from full reprogramming.

In the classical Waddington landscape, pluripotent cells reside at the summit and differentiate along descending trajectories. Full reprogramming returns differentiated cells to the pluripotency summit. In contrast, rejuvenation repositions cells along the slope of differentiation toward a youthful state while preserving lineage identity. This distinction highlights that cellular aging and cellular identity represent partially separable dimensions of cell state. This framework further suggests that rejuvenation may enable the generation of functionally diverse MSC libraries.

Compared with a relatively constrained parental population, rejuvenated MSCs can occupy a broader range of transcriptional states, enabling the recovery of distinct clones with different functional biases while maintaining mesenchymal identity.

References

1. Waddington CH. The Strategy of the Genes: A Discussion of Some Aspects of Theoretical Biology. London: Allen & Unwin; 1957.
2. Takahashi, Kazutoshi, and Shinya Yamanaka. "Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors." cell 126, no. 4 (2006): 663-676.

3. Ocampo, Alejandro, Pradeep Reddy, Paloma Martinez-Redondo, Aida Platero-Luengo, Fumiyuki Hatanaka, Tomoaki Hishida, Mo Li et al. "In vivo amelioration of age-associated hallmarks by partial reprogramming." Cell 167, no. 7 (2016): 1719-1733.
4. Sarkar, Tapash Jay, Marco Quarta, Shravani Mukherjee, Alex Colville, Patrick Paine, Linda Doan, Christopher M. Tran et al. "Transient non-integrative expression of nuclear reprogramming factors promotes multifaceted amelioration of aging in human cells." *Nature communications* 11, no. 1 (2020): 1545.
5. Paine, Patrick T., Ada Nguyen, and Alejandro Ocampo. "Partial cellular reprogramming: A deep dive into an emerging rejuvenation technology." *Aging Cell* 23, no. 2 (2024): e14039.
6. Wagner, Wolfgang, Patrick Horn, Mirco Castoldi, Anke Diehlmann, Simone Bork, Rainer Saffrich, Vladimir Benes et al. "Replicative senescence of mesenchymal stem cells: a continuous and organized process." *PloS one* 3, no. 5 (2008): e2213.
7. Guan, Jingyang, Guan Wang, Jinlin Wang, Zhengyuan Zhang, Yao Fu, Lin Cheng, Gaofan Meng et al. "Chemical reprogramming of human somatic cells to pluripotent stem cells." *Nature* 605, no. 7909 (2022): 325-331.
8. Liuyang, Shijia, Guan Wang, Yanglu Wang, Huanjing He, Yulin Lyu, Lin Cheng, Zhihan Yang et al. "Highly efficient and rapid generation of human pluripotent stem cells by chemical reprogramming." *Cell stem cell* 30, no. 4 (2023): 450-459.
9. Yang, Jae-Hyun, Christopher A. Petty, Thomas Dixon-McDougall, Maria Vina Lopez, Alexander Tyshkovskiy, Sun Maybury-Lewis, Xiao Tian et al. "Chemically induced reprogramming to reverse cellular aging." *Aging* (Albany NY) 15, no. 13 (2023): 5966.
10. Massidda, Miles W., Andrei Demkov, Aidan Sices, Muyoung Lee, Jason Lee, Tanya T. Paull, Jonghwan Kim, and Aaron B. Baker. "Mechanical Rejuvenation of Mesenchymal Stem Cells from Aged Patients." *bioRxiv* (2024): 2024-06.
11. Oshimura, Mitsuo, Toshiaki Tabata, Narumi Uno, Shuta Takata, Genki Hichiwa, Iori Kanazawa, Takeshi Endo et al. "Rejuvenation of human mesenchymal stem cells using a nonintegrative and conditionally removable Sendai virus vector." *Scientific Reports* 14, no. 1 (2024): 23623.
12. Tu, Haochen, Aoi Hosaka, Genki Hichiwa, Yayan Wang, Kanako Kazuki, Toshiaki Tabata, Mitsuhiko Osaki et al. "Rejuvenation of mesenchymal stromal cells via partial reprogramming enables scalable generation of transcriptionally diverse MSC libraries." *Stem Cell Research & Therapy* (2026).
13. Lei, Jinghui, Zijuan Xin, Ning Liu, Taixin Ning, Ying Jing, Yicheng Qiao, Zan He et al. "Senescence-resistant human mesenchymal progenitor cells counter aging in primates." Cell 188, no. 18 (2025): 5039-5061.

Citation: Mitsuo Oshimura. Partial Reprogramming Uncouples Cellular Identity from Cellular Aging in Mesenchymal Stromal Cells. *Int. J. Stem Cells Med.* Vol. 5 Iss. 1. (2026) DOI: 10.58489/2836-5038/028