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Editorial overview: 3Rs update: a new era in cellular identity and therapeutic plasticity

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Peng Du is a Professor in the College of Life Sciences/Peking-Tsinghua Center for Life Sciences at Peking University. His research focused on identifying and studying posttranscriptional RNA regulatory pathways and exploring their biological relevance in mammalian early embryonic development, ESCs, and human disease. As well, Dr. Du is interested in cross-species bioengineering and its applications in translational medicine. Recently, his lab first captured mouse and human totipotent blastomere-like cells using RNA splicing repression. Additionally, using the plant immune protein RDR, they achieved a broad antitumor response.

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The field of cell reprogramming and regeneration has witnessed profound conceptual and technical advancements in the past few years. The 2025 volume of *Current Opinion in Genetics & Development* captures this vibrant landscape with nineteen expert reviews spanning totipotency, lineage plasticity, somatic rejuvenation, transcriptional and translational regulation, and therapeutic regeneration. Together, these papers provide an updated view on 3Rs, i.e., cell *r*eprogramming, *r*egeneration, and *r*epair, deepening our understanding of how cellular identity can be reshaped across both developmental and pathological contexts.

Defining totipotency and expanded potential

Stem cell biology has long wrestled with the true definition of totipotency. The concept has evolved from a developmental benchmark to a mechanistic challenge, prompting renewed interest in *in vitro* systems capable of mimicking the earliest stages of embryogenesis. Defining the boundaries between totipotency, pluripotency, and newly proposed states, such as 'plenipotency', remains critical for stem cell classification and translational relevance.

This section features five reviews that converge on this theme. Wen and Wang [1] introduce the concept of 'plenipotency' to describe stem cells with expanded embryonic and extraembryonic potential but lacking complete organismal competence. Li et al. [2] revisit the concept of totipotent stem cells (TotiSCs), reviewing key breakthroughs in deriving various TotiSCs through spliceosomal and epigenetic manipulation. Huang et al. [3] highlight recent advances in interspecies chimeras and blastocyst complementation, which challenge species barriers in organogenesis. The limited contribution of donor pluripotent stem cells, particularly to the organs derived from both embryonic and extraembryonic lineages (e.g., placenta-competent models) suggests that more potent stem cells, possibly TotiSCs, might overcome developmental asynchrony and improve embryo complementation. Guo et al. [4] review *in vitro* embryo culture systems and the improvements that enable long-term observation of mammalian embryos. Liu et al. [5] apply naïve pluripotent stem cells to model human embryo implantation and trophoblast invasion.

pluripotency networks, as well as the generation of innovative *in vivo* models for mechanistic interrogation. His NIH-funded work has recently expanded to include the study of nucleolar dynamics, RNA modifications, and stem cell tumorigenicity, contributing transformative insights to both stem cell biology and regenerative medicine.

These reviews collectively demonstrate that totipotency is not a binary trait but exists along a continuum. The notion of plenipotency reflects the growing appreciation for intermediate states that retain developmental competence beyond conventional pluripotency. Moreover, the implementation of culture systems that allow for extended embryo development and the ability to test stem cell contributions to both embryonic and extraembryonic tissues highlights the pressing need for improved *in vitro* proxies to assess potency. These advancements lay the groundwork for future synthetic embryogenesis platforms and more refined ethical frameworks around human stem cell research, as well as potential regenerative medicine applications in the future. Importantly, they also help anchor terminology that is often used interchangeably but deserves more biological nuance.

Epigenetic and nuclear remodeling in cell fate control

Reprogramming cell identity involves not only transcriptional reactivation but also profound changes in chromatin organization and DNA and RNA epigenetic regulation. These processes underlie the capacity of cells to escape lineage constraints and enter more plastic, developmentally potent states.

Liu et al. [6] review dynamic nuclear remodeling during transitions between totipotency and pluripotency, with emphasis on how three-dimensional genome architecture, chromatin accessibility, and transcription factor reconfiguration govern early cell fate. They discuss new tools that reveal zygotic genome activation as a key window of chromatin plasticity and identify key regulatory factors such as DUX and ZSCAN4 involved in resetting the nuclear landscape. Scalf et al. [7] examine the chromatin mechanisms that contribute to the so-called 'privileged' cell state, in which somatic cells exhibit enhanced reprogramming efficiency. They focus on histone modifications, nucleosome positioning, and the regulatory interplay between chromatin remodelers and transcription factors, highlighting how chromatin priming enables noncanonical reprogramming routes. Yang et al. [8] detail the role of m^6A methylation in RNA–chromatin interactions that modulate chromatin accessibility and influence gene expression during stem cell self-renewal and early embryogenesis. Their review emphasizes the emerging epitranscriptomic axis as a modulator of nuclear organization and transcriptional plasticity.

Together, these reviews reinforce the concept that chromatin architecture is not merely permissive but actively instructive in cell fate transitions. Through physical reorganization of the genome and modification of epigenetic marks, cells can traverse otherwise inaccessible identity landscapes. The insights presented in this section converge on a model where chromatin and RNA modifications co-govern the rewiring of gene regulatory networks, enabling precise and programmable control of developmental potential.

Rejuvenation, aging, and partial reprogramming

Aging is increasingly regarded as a plastic and potentially reversible process. Rather than a linear decline, accumulating evidence suggests that cellular aging results from regulated changes in gene expression, chromatin structure, and metabolic states, all of which are amenable to partial reprogramming.

Adams et al. [9] argue that the transient expression of OSKM factors triggers dedifferentiation resembling natural regenerative processes. Both partial reprogramming and injury-induced regeneration involve temporary suppression of somatic identity programs, chromatin reconfiguration, and a return to fetal-like transcriptional states. Their synthesis presents a unifying model of tissue rejuvenation, where transcriptional and epigenetic resets enable the restoration of function without erasing identity entirely. García-Vílchez and Guallar [10] add another critical layer by exploring how chromatin state and epitranscriptomic modifications suppress or exacerbate transposable element (TE) activity during aging. TE reactivation contributes to genomic instability, inflammation, and functional decline in aged tissues. The review highlights how DNA methylation, histone modifications, and RNA-based silencing pathways collaborate to suppress TE expression and maintain genome integrity. Notably, aging disrupts this repression, suggesting that restoring these silencing pathways could become a viable rejuvenation strategy. Huang et al. [11] examine chronic inflammation as a driver of aging and age-related diseases. They highlight the role of systemic inflammatory cues, originating from cellular debris, infections, or metabolic imbalances, in promoting tissue degeneration. Importantly, the review outlines pharmacological strategies for mitigating inflammaging, emphasizing interventions that could complement or potentiate rejuvenation via reprogramming.

Together, these reviews provide a multifaceted perspective on aging as a modifiable biological state. The intersection of partial reprogramming, transposon silencing, and inflammation control offers exciting avenues for extending healthspan. The field now turns to address the challenge of safely translating these findings into therapies, minimizing oncogenic risk while maximizing regenerative benefit.

Transcriptional and translational control

Gene expression regulation, encompassing both transcriptional and translational axes, is crucial for achieving precise cell fate outcomes during development and regeneration.

Ascic and Pereira [12] showcase synthetic transcription factor engineering to reprogram somatic cells into antigen-presenting cells for immunotherapy directly. Amiri et al. [13] delve into translational control during tissue repair, emphasizing how ribosome biogenesis, mTOR signaling, and RNA-binding proteins coordinate protein synthesis during regeneration.

Together, these papers reflect a paradigm shift in regenerative biology: one that recognizes the power of manipulating mRNA translation and synthetic transcription factors to unlock new cell states. Importantly, this approach complements traditional gene editing and epigenetic reprogramming by focusing on real-time regulation of gene output. Such strategies are particularly relevant in immunotherapy, where precision programming of immune cell identity can determine therapeutic success. These findings also highlight a broader trend: those temporal dynamics of gene expression, not just static cell states, are emerging as key determinants of regenerative potential.

Modeling human development and disease

As *in vivo* access to human tissues remains limited, stem cell–derived organoids and models are crucial for understanding human development and disease.

Choe et al. [14] refine cortical organoids to better mimic forebrain patterning and connectivity, providing relevance to neurodevelopmental disorders. Wong et al. [15] assemble single-cell atlases and endometrial organoid systems to illuminate uterine regeneration and hormonal regulation. Yu et al. [16] focus on placental trophoblasts and their nutrient transport mechanisms, highlighting imprinted genes and macropinocytosis in maternal–fetal allocation. Fu et al. [17] discuss pluripotent stem cell–derived mesenchymal stem cells (MSCs) and their dual role in regenerative therapy and cancer biology. Huang et al. [18] advocate the use of induced pluripotent stem cell (iPSC)-based cancer models to study clonal evolution, drug response, and tumor heterogeneity. Yang et al. [19] explore central nervous system development and neural regeneration, reviewing how neural progenitors integrate internal and external signals during early patterning. Their synthesis extends the scope of regenerative strategies into the nervous system, a traditionally recalcitrant tissue.

These studies demonstrate the maturation of human model systems toward translational fidelity. Their convergence on organoid fidelity, lineage complexity, and therapeutic utility reflects a field ready for clinical translation. With the support of spatial transcriptomics, single-cell atlases, and artificial intelligence (AI)-assisted analysis, these models are beginning to inform both regenerative medicine and disease modeling with unprecedented precision. Furthermore, the integration of these models into pharmacogenomic and developmental toxicology pipelines suggests a future in which regenerative therapies can be both patient-specific and mechanistically grounded.

Concluding perspective

Collectively, the nineteen reviews in this volume chart the rapid convergence of stem cells, cell reprogramming, chromatin biology, developmental modeling, and regenerative therapeutics. From synthetic totipotency to senescence reversal, from immune cell reprogramming

to human tissue engineering, these papers reflect the maturation of a field defined by programmability.

As Editors, we believe this volume captures not only the current state of cell identity manipulation but also its trajectory toward precision regenerative medicine. Moving forward, we anticipate greater integration of spatial biology, AI–guided lineage modeling, and epigenome editing platforms. The era of tissue- and disease-specific reprogramming is already underway, and this collection offers the conceptual scaffolding for future advances.

Precision manipulation of cellular identity is no longer aspirational; it is the cornerstone of next-generation developmental and therapeutic strategies. This issue on the '3Rs' stands as both a reflection and a roadmap for the decade ahead, which is expected to usher in a new era in cellular identity and therapeutic plasticity.

Declaration of Competing Interest

Peng Du and Jianlong Wang declare no competing interests.

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