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Strategies for Therapeutic Repair: The “R³” Regenerative Medicine Paradigm

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Abstract

Beyond the palliative reach of today, medical therapies of tomorrow aim to treat the root cause of chronic degenerative diseases. Therapeutic repair encompasses the converging triad of *rejuvenation*, *regeneration* or *replacement* strategies that rely on self-healing processes, stem cell regeneration, and/or organ transplantation. Natural healing or rejuvenation exemplify inherent, baseline repair secured by tissue self-renewal and *de novo* cell biogenesis, particularly effective in organs with a high endogenous reparative capacity. Transplant medicine exploits the replacement strategy as a valuable option to recycle used parts and restore failing organ function by means of exogenous substitutes—it is, however, limited by donor shortage. Stem cell-based regeneration offers the next frontier of medical therapy through delivery of essentially unlimited pools of autologous or allogeneic, naive or modified, progenitor cells to achieve structural and functional repair. Translation into clinical applications requires the establishment of a regenerative medicine community of practice capable to bridge discovery with personalized treatment solutions. Indeed, this multidisciplinary specialized workforce will be capable to integrate the new science of embryology, immunology, and stem cell biology into bioinformatics and network medicine platforms, ensuring implementation of therapeutic repair strategies into individualized disease management algorithms.

Keywords

tissue regeneration; therapeutic repair; regenerative medicine

Introduction

The global epidemic of chronic degenerative diseases represents an increasing burden on all healthcare systems.^{1,2} In part, the current standard of care, based largely on palliative therapies, has allowed patients to survive with a prolonged course of their disease, contributing to the expansion of healthcare expenditure. Further, the aging population is particularly susceptible to degenerative diseases, which equates to an added healthcare responsibility.³ Dedicated efforts have been implemented to address this unmet need through home healthcare programs, addition of specialized practitioners in primary care settings, and education for awareness and utilization of community resources. However, the scope of chronic degenerative diseases ultimately mandates targeted interventions to treat the root cause of disease linked to progressive cell destruction and irreversible loss of tissue function. This creates an ever-growing need for the development of effective therapies that are able to repair the underlying pathobiology and restore the native cellular architecture and organ function.⁴

Concept of Tissue Repair

Description of tissue regeneration may date back to the Greek mythology, where Prometheus is punished by Zeus for stealing from Mount Olympus the sacred fire for humankind. The myth describes a vulture that feasts from an open wound in the liver, yet the liver renews daily, demonstrating a unique capacity to regenerate.⁵ The concept of regeneration is commonly observed, but often unappreciated in daily medical practice. The rapid healing of skin cuts and abrasions exemplifies natural repair processes in which new tissue formation is derived from multiple stem cell populations, including epidermal, mesenchymal, neural crest-derived, and circulating stem cells. The capacity for regeneration is particularly evident in the young, in comparison to those with degenerative diseases or the elderly who typically are stress intolerant. Repair mechanisms remain, however, active even in advanced senescence as elderly patients can heal well after major surgical injuries. This active, self-reparative process of regeneration throughout the lifespan establishes the essential elements for the maintenance of tissue homeostasis and serves as the basis for the emerging field of therapeutic repair and stem cell-based regenerative medicine.

The evolution of pharmacotherapy toward reparative paradigms exploits the growing understanding of disease pathways and natural repair mechanisms to discover, validate, and ultimately, apply stem cell therapeutics targeted to the cause of disease. The multidisciplinary and complementary sciences of molecular medicine, bioengineering, and network biology have catalyzed the growth of stem cell applications. Tailored to the genetic and molecular profile of the individual patient, regenerative medicine integrates stem cell biology with personalized therapeutic, diagnostic, prognostic, and preventive solutions across human diseases, providing a cornerstone of modern individualized medicine practice (Figure 1).

Curative Therapy

Regenerative medicine, propelled by the recent progress made in transplant medicine, stem cell biology, and related biomedical fields, is primed to expand the therapeutic armamentarium available in the clinical setting, and thereby, ameliorate disease outcome while reducing the burden of chronic therapy. This progress offers a transformative paradigm with curative objectives and goals to address disease management demands unmet by traditional (pharmaco) therapy. In particular, stem cell-based regenerative medicine is poised to drive the evolution of medical sciences from traditional palliation, which mitigates symptoms, to curative therapy aimed at treating the disease cause.⁶

Stem cells have a unique aptitude to differentiate into specialized cell types and form new tissue, thus providing the active ingredient of regenerative therapy.⁶ Guided by the increasingly understood principles of molecular embryology, stem cell biology has transformed the understanding of tissue and organ formation and has contributed to the decoding of mechanisms underlying tissue homeostasis and repair. Strategies to promote, augment, and re-establish developmental processes utilized in natural embryogenesis are at the core of translating the science of stem cell biology into the practice of regenerative medicine.

Specialized application of therapeutic repair starts with the use of standardized stem cell-based platforms such as the increasingly established embryonic, perinatal, and adult stem cell sources and their cell progeny derivatives. Embryonic stem cells have the advantage of an unequalled pluripotent differentiation plasticity associated with a robust repair capacity, yet access for clinical applications remains a significant limitation, along with a risk of uncontrolled growth and immunological intolerance.⁷ While methods for lineage restriction are increasingly developed and validated,^{8,9} the adult stem cells—hematopoietic or mesenchymal in origin—have the benefit of autologous immunologic status and are readily available for clinical applications, although the induction of reliable tissue-specific differentiation remains a

possible limitation.¹⁰ Perinatal stem cells incorporate advantageous characteristics from both embryonic and adult stem cells, including potential autologous status and broader differentiation capacity than adult stem cells, and provide the most available stem cell source when harvested at birth.¹¹ Alternatively, bioengineered platforms, including therapeutic cloning and nuclear reprogramming, further offer generation of hybrid cells and tissues. In this context, enabling biotechnology platforms have most recently emerged to create hybridized stem cell types designed to systematically address cell characteristics that currently limit the clinical translation of more standard cell-based therapeutics. Exploiting genetic and epigenetic factors to regulate phenotypic outcomes, the biotechnology platforms achieve guided genetic reprogramming of adult cells back to an embryonic-like state. These platforms bypass the need for embryo extraction to generate categorical pluripotent stem cell phenotypes and recycle somatic nuclei to form autologous, immunotolerant cell-based products.¹² Reprogramming of the adult stem cells to generate customized embryonic-like stem cells offers, thereby, an attractive tool to engineer patient-specific regenerative therapies.

Goals of Regenerative Medicine

Regenerative medicine, regardless of the utilized platform, aims to restore normal structure and function following tissue injury. Stem cells and their natural or engineered products—collectively recognized as biologics—provide the functional components of a regenerative therapeutic regimen. Autologous or allogeneic, resident or ectopic, the stem cells maintain an autonomous self-renewal potential and respond to guiding signals to differentiate into replacement tissues.¹³ By healing an injury, stem cells have the capacity to cure the underlying tissue damage through *de novo* formation of proper structure and function. Restoration of diseased tissues offers a sustained therapeutic advantage in conditions ranging from congenital disease to acquired, age-related pathologies. The outcome depends on the aptitude of the stem cell population to secure maximal, tissue-specific repair and the production of a nurturing niche environment in diseased tissue that enables the execution of repair.¹⁴

Beyond restoration of structure and function, regenerative medicine paves a pathway for prevention and delay in disease progression through prophylactic repair. Stem cells provide a unique platform to select, guide, and engineer cellular characteristics required for enhanced tolerance while effectively treating and/or preventing disease manifestation. By anticipating the needs of disease-susceptible tissues, the goal of regenerative medicine becomes the repair of threatened tissues with stress-tolerant cells to prevent irreversible damage. Pre-emptive regenerative therapy requires the ability to predict disease susceptibility based on molecular profiling at the earliest stages in order to guide appropriate and timely stem cell-based interventions.¹⁵

Therapeutic Repair Strategies: The “R³” Paradigm

The scope of stem cell-based regenerative medicine is defined by the convergent repair triad of replacement, regeneration, and rejuvenation (Figure 2). The “R³” paradigm of therapeutic repair highlights that these strategies overlap in practice while inherent distinctions conceptualize the scope of regenerative medicine, ranging from transplantation of used parts (“replacement”) to development of new parts (“regeneration”) to induction of self-renewed parts (“rejuvenation”).

Replacement

Replacement strategy refers to transplantation of a cell-based product that re-establishes homeostasis for the recipient through continuation of the tissue function from the donor.¹⁶ The field of surgery pioneered the concept of replacement with the advent of solid organ transplantation. If the heart was damaged beyond the ability to palliate the condition, then

replacing the diseased tissue with a functioning donor heart became the only option. In addition to solid organ transplantation, cell-based replacement is routinely used in the form of red blood cell transfusions to replace the circulating blood in order to increase the oxygen-carrying capacity and treat life-threatening blood loss or anemia. This strategy “recycles” used parts of cells, tissues, or organs to “restore” physiologic function. A significant limitation of the replacement strategy remains the shortage of appropriate donors and the difficulty to match the immunological criteria for a safe and effective transplantation.

Regeneration

Regenerative strategy refers to engraftment of progenitor cells that require *in vivo* growth and differentiation to establish recipient homeostasis through *de novo* function of the stem cell-based transplant. Advances in hematology gave rise to the concept of regeneration with the identification of bone marrow-derived stem cells that once harvested could be transplanted in small quantities into the peripheral blood to engraft and reconstitute the functioning bone marrow through continuous production of the entire hematopoietic system.¹⁷ Success was facilitated by the presence of host bone marrow that provided a protective environment to nurture the long-term survival of self-renewing stem cell progenitors. This strategy “restores” function by “renewing” the pool of functional progenitor cells to allow differentiation as needed from exogenous stem cells. An intense search is ongoing for tissue-specific, nonhematopoietic stem cells that have the capacity to re-establish lost function when ectopically transplanted into a wide range of diseased tissues, as evident in diabetes, ischemic heart disease, and degenerative neurological diseases.

Rejuvenation

Rejuvenation strategy refers to self-renewal of tissues from endogenous, resident stem cells to maintain tissue homeostasis and promote tissue healing. This natural process of tissue recycling enables cells as they senesce to be replaced with younger cells that are inherently more resilient and equipped to provide adequate stress tolerance for tissue survival.¹⁸ Daughter cells can also be derived from reactivation of the cell cycle within mature cell types in response to (physio) pathological stress. This strategy “renews” tissue structure by “recycling” endogenous stem cells for proactive self-renewal. Rejuvenation ensures continuous production of renewable tissue required for long-term stress tolerance; however, most tissues are able to only partially self-renew. In the context of a massive acute injury, such as myocardial infarction, an inherent repair strategy may be inadequate.¹⁹ A boost in these natural processes, through biologic or pharmacologic treatment, is likely required to stimulate adaptive response and promote adequate biogenesis of functional tissue in the setting of acute or progressive disease.

Conclusion

Regenerative medicine, built on emerging discoveries in stem cell biology, has begun to define the scope of future clinical practice.^{19–22} Regenerative medicine and stem cell biology cross all disciplines of medicine and provide a universal paradigm of curative goals based on scientific discovery and clinical translation. The challenges to realize the full potential of stem cell biology remain substantial and require an integration of multidisciplinary expertise to form a dedicated regenerative medicine community of practice. Building on the foundation of transplant medicine, regenerative medicine will continue to expand and implement technologies to treat diseases at earlier stages with safer and more effective outcomes, not possible with the current therapies. The strategies of *replacement*, *regeneration*, and *rejuvenation*, integrated through the congruent “recycle”, “restore,” and “renew” processes, encompass the “R³” paradigm of therapeutic repair. Progress in this field will proceed with the broad support from the general public and patient advocates, the biotechnology and pharmaceutical industry, governmental agencies and professional (inter)national biomedical

organizations, and the academic/learning institutions, with the pace of which discovery, development, validation, and regulation will impact translation to clinical practice remaining the responsibility of the community at large.

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References

1. Cortese DA. A vision of individualized medicine in the context of global health. *Clin Pharmacol Ther* 2007;82:491–493. [PubMed: 17952101]
2. Waldman SA, Terzic A. Individualized medicine and the imperative of global health. *Clin Pharmacol Ther* 2007;82:479–483. [PubMed: 17952097]
3. Jahangir A, Sagar S, Terzic A. Aging and cardioprotection. *J Appl Physiol* 2007;103:2120–2128. [PubMed: 17717116]
4. Waldman SA, Terzic MR, Terzic A. Molecular medicine hones therapeutic arts to science. *Clin Pharmacol Ther* 2007;82:343–347. [PubMed: 17851568]
5. Rosenthal N. Prometheus's vulture and the stem-cell promise. *N Engl J Med* 2003;349:267–274. [PubMed: 12867611]
6. Daley GQ, Scadden DT. Prospects for stem cell-based therapy. *Cell* 2008;132:544–548. [PubMed: 18295571]
7. Solter D. From teratocarcinomas to embryonic stem cells and beyond: a history of embryonic stem cell research. *Nat Rev Genet* 2006;7:319–327. [PubMed: 16534514]
8. Behfar A, Perez-Terzic C, Faustino RS, Arrell DK, Hodgson DM, Yamada S, Puceat M, Niederländer N, Alekseev AE, Zingman LV, Terzic A. Cardiopoietic programming of embryonic stem cells for tumor-free heart repair. *J Exp Med* 2007;204:405–420. [PubMed: 17283208]
9. Nelson TJ, Faustino RS, Chiriac A, Crespo-Diaz RJ, Behfar A, Terzic A. CXCR4⁺/FLK-1⁺ biomarkers select a cardiopoietic lineage from embryonic stem cells. *Stem Cells* 2008;26:1464–1473. [PubMed: 18369102]
10. Chamberlain G, Fox J, Ashton B, Middleton J. Mesenchymal stem cells: their phenotype, differentiation capacity, immunological features, and potential for homing. *Stem Cells* 2007;25:2739–2749. [PubMed: 17656645]
11. O'Donoghue K, Chan J. Human fetal mesenchymal stem cells. *Curr Stem Cell Res Ther* 2006;3:371–386. [PubMed: 18220881]
12. Jaenisch R, Young R. Stem cells, the molecular circuitry of pluripotency and nuclear reprogramming. *Cell* 2008;132:567–582. [PubMed: 18295576]
13. Klimanskaya I, Rosenthal N, Lanza R. Derive and conquer: sourcing and differentiating stem cells for therapeutic applications. *Nat Rev Drug Discov* 2008;7:131–142. [PubMed: 18079756]
14. Morrison SJ, Spradling AC. Stem cells and niches: mechanisms that promote stem cell maintenance throughout life. *Cell* 2008;132:598–611. [PubMed: 18295578]
15. Waldman SA, Terzic A. Clinical and translational science: at the intersection of molecular and individualized medicine. *Clin Transl Sci* 2008;1:6–8.
16. Atala A. Advances in tissue and organ replacement. *Curr Stem Cell Res Ther* 2008;3:21–31. [PubMed: 18220920]
17. Kørbling M, Estrov Z. Adult stem cells for tissue repair—a new therapeutic concept? *N Engl J Med* 2003;349:570–582. [PubMed: 12904523]
18. Surani MA, McLaren A. Stem cells: a new route to rejuvenation. *Nature* 2006;443:284–285. [PubMed: 16988700]
19. Anversa P, Nadal-Ginard B. Myocyte renewal and ventricular remodeling. *Nature* 2002;415:240–243. [PubMed: 11805849]
20. Segers VF, Lee RT. Stem-cell therapy for cardiac disease. *Nature* 2008;451:937–942. [PubMed: 18288183]

21. Arrell DK, Niederländer NJ, Perez-Terzic C, Chung S, Behfar A, Terzic A. Pharmacoproteomics: advancing the efficacy and safety of regenerative therapeutics. *Clin Pharmacol Ther* 2007;82:316–319. [PubMed: 17671447]
22. Behfar A, Terzic A. Cardioprotective repair through stem cell-based cardiopoiesis. *J Appl Physiol* 2007;103:1438–1440. [PubMed: 17641218]

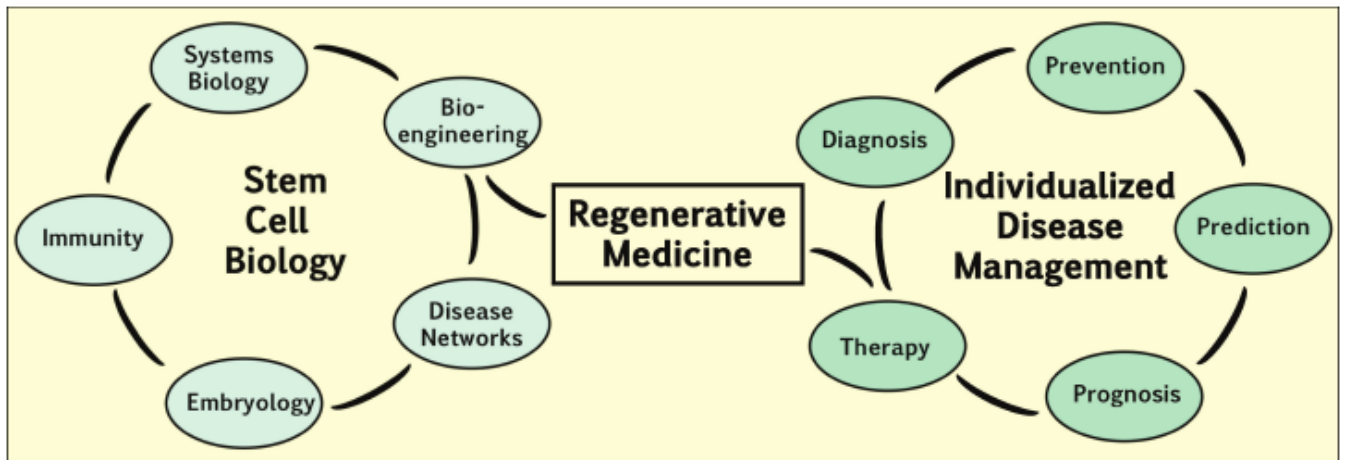


Figure 1. Regenerative medicine bridges advances in stem cell biology with individualized disease management

Progress in stem cell biology has been accelerated through the integration of the fundamental fields of molecular embryology and immunology with the emerging multidisciplinary fields of systems biology, bioengineering, and disease networks. The translation into the clinical applications of regenerative medicine is guided by the opportunities of individualized disease management exploiting personalized prediction, diagnosis, prognosis, prevention, and ultimately, therapy tailored to the specific needs of each patient.

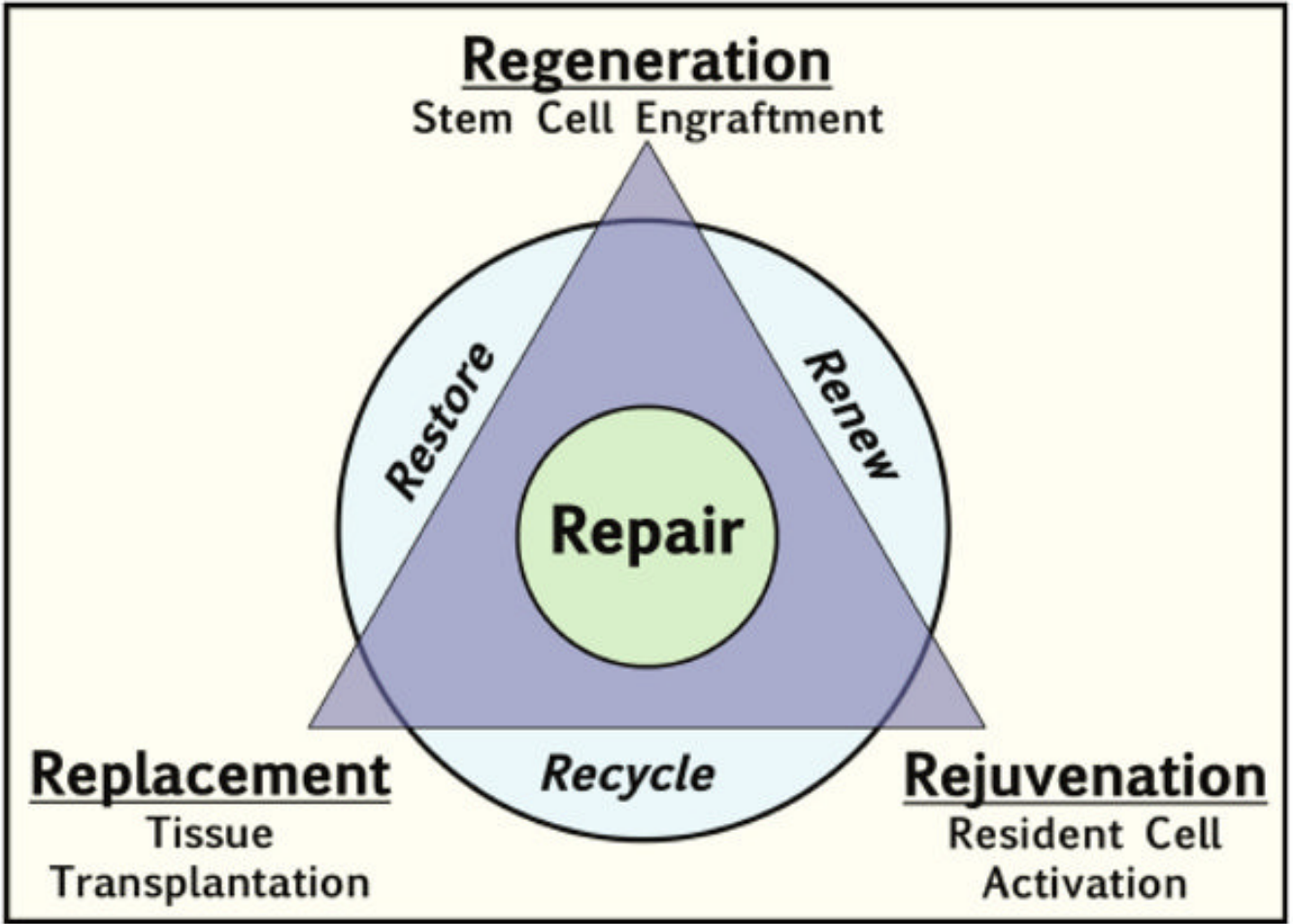


Figure 2. The scope of regenerative medicine

Repair is the central goal of regenerative medicine that encompasses the general strategy triad: replacement, regeneration, and rejuvenation. Replacement is defined as repair of damaged tissue by recycling used parts through tissue/organ transplantation. Regeneration is defined as repair of damaged tissue through differentiation of progenitor cells to replace damaged cells and restore tissue function. Rejuvenation is defined as repair of damaged tissue through activation of endogenous resident stem cells that can stimulate biogenesis and replenish functional tissue. Collectively, therapeutic repair strategies are recognized as the “R³” regenerative medicine paradigm.