EDITORIAL

Regenerative Medicine: On the Vanguard of Health Care

The World Health Organization reports that a staggering 36 million of the 57 million annual global deaths are due to a rampant pandemic of chronic diseases.[1] Success in managing acute conditions has reduced early mortality but has concurrently precipitated a higher incidence of chronic diseases among survivors. Current evidence-based and cost-effective interventions are insufficient to meet the growing challenge posed by noncommunicable chronic conditions, driven in part by the aging of the population and the associated increase in degenerative diseases.[2] Reparative therapies targeting the cause of progressive cell destruction and irreversible loss of tissue function are largely lacking. Transformation of the health care horizon will require unprecedented innovation to extend the reach of clinical practice beyond the current standard of care.

New knowledge on disease causes and cures will enable delivery of high-quality care that more effectively addresses the unmet needs of our patients.

Regenerative Medicine: Transforming Health Care

Advances in the science of regenerative medicine have begun to define a new perspective for the future of health care.[3] Regenerative paradigms offer a "disruptive innovation" poised to transform medicine and surgery by providing the prospect of definitive solutions for our patients. The decisive goal of regenerative medicine is indeed to advance care from palliation to cure.

From pioneering success with bone marrow transplants to recent breakthroughs in neo-organogenesis, regenerative strategies have emerged as a promising core component of medical and surgical practice.[4] Aimed at repair of disease pathobiology and restoration of organ function, forthcoming regenerative applications encompass unparalleled patient-specific diagnostic algorithms and reconstructive treatments for a range of diseases and disabilities. Across a spectrum—from congenital conditions to acquired, age-related pathologies—personalized regenerative medicine products and services promise considerable human health benefit, increased quality of life, and improved patient care.

Repair Paradigms

Decoding the human regenerative map has provided fundamental information on the dynamics of cell turnover in health and disease, demonstrating that self-repair processes contribute to lifelong rejuvenation of our tissues.[5] Typically, innate healing mechanisms are sufficient only for maintenance of tissue homeostasis in health. In the context of large-scale tissue destruction, however, self-renewal is insufficient to ensure adequate repair. To this end, transplant medicine exploits a replacement strategy as a valuable option to restore failing organ function, albeit one that is limited by a shortage of donors.[6] State-of-the-art technologies have enabled next-generation medical therapies aimed at achieving structural and/or functional repair through genuine tissue regeneration. Stem cell–based regenerative strategies refer to engraftment of progenitor cells that, through growth and lineage specification, supplement and recruit resident progenitor pools, promoting reconstruction of damaged tissues. Stem cells are thus a fundamental tool in the rapidly advancing regenerative medicine toolkit.[7] To facilitate the implementation and validation of repair paradigms, the findings of the regenerative medicine vanguard must be rigorously translated from principle to clinical practice.

See also page 634

Stem Cells in our Bodies

The bone marrow, blood, and adipose tissue are among tissues in the human body that naturally harbor readily accessible stem cell pools, broadly known as *adult stem cells*. In contrast to pluripotent embryonic stem cells, which are derived from the inner cell mass of preimplantation blastocysts and are capable of forming all lineages of the body, adult stem cells have a more restricted multipotent differentiation capacity.[7] Clinical experience to date is largely based on adult stem cell use. Beyond established applications in treating multiple myeloma, lymphoma, leukemia, and autoimmune diseases, stem cells derived from adult sources are increasingly considered as a novel treatment for diverse indications, including cardiovascular, musculoskeletal, endocrine, and neurologic disorders.[8,9] Analysis of trial outcomes underscores the feasibility and safety of adult stem cell therapy. However, improvement in functional parameters of recovery has been variable, in part because protocols for optimizing cell isolation and delivery have not been standardized.[10,11] Moreover, transplant of heterogeneous cell populations with varying degrees of reparative capacity has further confounded benefit. In addition, interpatient variability has been increasingly recognized, prompting attempts to identify the most appropriate cell sources and to optimize derived cell types. Furthermore, the selection of patient populations most amenable

Address correspondence to Andre Terzic, MD, Division of Cardiovascular Diseases, Mayo Clinic, 200 First St SW, Rochester, MN 55905 (terzic.andre@mayo.edu).

for cell-based therapy, the targeting of the ideal timing of intervention, and the identification of the most favorable routes of administration have all been singled out as critical translational steps in the application of regenerative medicine.[12,13] Cell therapy is also limited by low rates of cell retention. Advanced patient age, comorbid conditions, and underlying disease all appear to affect the repair aptitude of adult stem cells. Mechanisms underlying improved benefit have implicated, among other variables, a defining role for lineage commitment and preemptive optimization of stem cell fitness to engage host tissue in repair processes.[14] To maximize the potential value of patient-centric cell-based therapy in disease management, individual regenerative profiles need to be established to stratify responders from nonresponders and to personalize treatment regimens.[15]

Redirecting the Fate of Ordinary Cells

In contrast to stem cells, differentiated adult (somatic) cells generally do not spontaneously change fates. However, selective redirection of cells presumed to be in a differentiated state has been reported recently. Redirection is achievable by perturbations in the stoichiometry of transcriptional regulators present in each cell of the human body.[16] In this way, an adult somatic cell (eg, a dermal fibroblast) can be reset, altering its pattern of gene expression and hence its fate. Nuclear reprogramming achieved through introduction of primordial stemness transcription factors induces a regular somatic cell to express gene profiles typical of an embryonic stem cell, returning the cell to an embryonic-like state. Stem cells bioengineered in this way, also known as *induced pluripotent stem cells* (iPS), can in turn differentiate to form genuine tissues of all lineages.[16] Although it is uncertain why a specialized cell would maintain the potential to reactivate gene programs typical of another cell type, the remarkable cellular plasticity has important human health and societal implications.

The Science and Ethics of Induced Pluripotency

In the current issue of *Mayo Clinic Proceedings*, Zacharias et al[17] highlight the science and ethics underlying induced pluripotency and underscore that nuclear reprogramming offers a revolutionary strategy for embryo-independent derivation of pluripotent stem cells from somatic adult sources. Development of reprogramming techniques leading to iPS generation has dramatically changed the landscape of stem cell research and its applications. In particular, Zacharias et al point out that iPS technology avoids the ethical concerns regarding embryo destruction that limit the use of human embryonic stem cells. Moreover, the availability of reprogrammed cells as a possible source for autologous pluripotent stem cell transplant may eliminate, at least in principle, the need for immunosuppression in the context of cell therapy.[17] Of note, derivation of iPS requires a routine punch biopsy and an established methodology for coerced expression of a small number of defined transcription factors to trigger reprogramming, offering a virtually unlimited renewable pool of new tissues obtained from the patient's own cells. In this way, at Mayo Clinic, iPS have been bioengineered for experimental cardiovascular treatments,[18,19] as well as for derivation of glucose-responsive insulin-secreting human cell progeny.[20]

Zacharias et al caution, however, that further advances in iPS technology and improvements in protocols for nuclear reprogramming are needed to improve efficiency and safety. In particular, partial programming can result in transformed or dysplastic progenitor cells, which can contaminate derived stem cell pools.[17] Producing safe and highly purified iPS is paramount for clinical applications. The ultimate value of iPS technology for transplant therapy will depend on ensuring reprogramming fidelity with normal genetic and epigenetic status and defined immunotolerance.

As we await the realization of the therapeutic potential of iPS technology, a more immediate application is in the exploitation of cellular models of disease genetically matched to individual patients.[21] Patient-specific iPS are being rapidly generated for diverse conditions, such as spinal muscular atrophy, familial dysautonomia, dyskeratosis congenita, and long QT syndrome.[22] Such test sites offer, within an unparalleled human context, diagnostic tools for exploration of underlying disease mechanisms, discovery of novel therapeutic targets, examination of the individual response to intervention, and/or screening for drug efficacy and toxicity.[21,22] Reprogrammed somatic tissue samples offer a humanized system for novel discoveries that can directly guide development of individualized molecular diagnostic and therapeutic applications in this new era of regenerative theranostics.[23,24]

Driven by patient needs, progress in regenerative sciences will catalyze the next chapters of medicine and surgery.[25] We must therefore accelerate the pace at which discovery translates into clinical practice to provide solutions and hope for our patients and to speed the arrival of the day when organs will be rebuilt rather than replaced.

Andre Terzic, MD, PhD
Clifford D. Folmes, PhD
Almudena Martinez-Fernandez, PhD
Atta Behfar, MD, PhD
Division of Cardiovascular Diseases
Mayo Clinic
Rochester, MN

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