New advancements in the use of adult, embryonic stem cells for tissue regeneration

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A major issue in the development of regenerative medicine is the cell sources used to rebuild damaged tissues. In a review of the issue published in *Developmental Dynamics*, researchers state that inducing regeneration in humans from the body's own tissues by chemical means is feasible, though many questions must be answered before the process can reach clinical status.

Regeneration is a regulative developmental process ubiquitous across all species. It functions throughout the life cycle to maintain or restore the normal form and function of cells, tissues and, in some cases organs, appendages and whole organisms. The roots, stems and leaves of plants, for example, have extensive regenerative capacity, and entire plants can grow from single cells or small cuttings.

The regenerative capability of most vertebrate animals, however, is restricted to certain tissues. In the absence of injury, many cell types such as epithelia and blood cells turn over rapidly, while others such as hepatocytes, myofibers, osteocytes, and most neurons, have low turnover rates or do not turn over at all. In organisms that grow throughout life, such as fish, the total number of cells in various tissues increases continuously, indicating that the number of new cells produced is higher than the number of cells lost.

By contrast, the loss of normal tissue mass and/or architecture to acute injury or disease in humans requires a more intense and qualitatively different regenerative response that restores the tissue to its original

state. This response is called injury-induced regeneration.

A major issue for cell transplant therapies is the source of the cells to be used. Three sources of cells can be tapped for transplant: differentiated tissues, adult stem cells (ASCs) and derivatives of embryonic stem cells (ESCs). Adult stem cells regenerate epithelia, brain tissue, muscle, blood and bone. They have also been found in other tissues that normally scar after injury, such as myocardium, spinal cord and retina tissues.

"Adult stem cell therapy has real potential to regenerate at least muscle and bone damaged by injury or genetic disease, and cardiac stem cells may be a way to regenerate new cardiomyocytes after myocardial infarction," says David L. Stocum, co-author of the paper.

Progress is also being made toward the use of ESCs to derive functional cells for treatment of diabetes and muscular dystrophy.

A procedure has been developed to direct the differentiation of human ESCs to pancreatic islet cells, including insulin producing cells. When implanted into mice, the cells produce human insulin in response to glucose stimulation and protect against hyperglycemia.

"ESCs show great promise as a cell source for the regeneration of new tissue, due to their high growth and self-renewal capacity, and their ability to differentiate into a myriad of precursor or differentiated cell types when directed by the appropriate set of environmental factors," says co-author Günther K.H. Zupanc.

The recently acquired ability to reprogram adult somatic cells to ESCs in culture ("induced pluripotent stem cells") has solved bioethical concerns surrounding the destruction of somatic cell nuclear transfer embryos to make personal embryonic stem cells that will not be immunorejected. The authors state, however, that induced pluripotent stem cells raise their

own biological and bioethical issues. Biological issues include the differentiation and survival time of reprogrammed somatic cells, and the need to develop methods to reprogram cells without introducing exogenous DNA. Ethical issues, including cost, the ease of reprogramming for the purpose of conducting unethical experiments, like the derivation of human offspring, have yet to be resolved.

The ability to reprogram adult somatic cells to ESCs in culture has led the authors to the concept that it may be possible to use natural or synthetic molecules to reprogram adult somatic cells in vivo to adult stem cells that will recapitulate the development of a tissue, organ or appendage, or to stimulate resident adult stem cells to do so. They argue that strong regenerators, such as fish and amphibians know how to do this naturally, and should be studied to learn what molecules are required for such stimulation or reprogramming. The counterparts of these molecules, or synthetic small molecules that mimic their action, could then be applied to regeneration-deficient mammalian tissues.

Source: Wiley