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Maturing From Embryonic to Adult Policy on Stem Cell Therapeutics

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ABSTRACT: The National Institutes of Health (NIH) closure of the agency's Center for Regenerative Medicine (CRM), which focused on therapeutic development of induced pluripotent stem cells (iPS), was caused by the lack of progress in practical development of the iPSs for use in human therapies. As the NIH evaluates priorities in future stem cell therapeutic development, adult stem cell processes in the human body need to be prioritized for a number of key reasons, including (1) adult stem cells release many types of molecules that provide much of the therapeutic benefit of stem cells and (2) adult stem cells and somatic cells exist in a state of dynamic transition between different potency levels and can be naturally driven by the microenvironment to a state of pluripotency. Thus, the study and development of adult stems for therapeutic use can include naturally induced pluripotent stem cells (NiPSs) that lack the problematic genetic and epigenetic reprogramming errors found in iPSs.

Earlier this year, 28 March 2014, the National Institutes of Health (NIH) closed the agency's Center for Regenerative Medicine (CRM), and the center's director Dr. Mahendra Rao, a prominent stem cell biologist, left the NIH. The CRM was established in 2010 to centralize stem cell research activities within the NIH, with the goal to develop therapeutics based on using induced pluripotent stem cells (iPS). The iPS is a mature cell that has been genetically modified, similar to that which is familiar to many people as a genetically modified organism (GMO), to transform the mature cell into a cell with stem cell-like properties. The genetic reprogramming of the mature cell into an iPS means that the newly transformed cell will have properties like an embryonic stem cell whereby the iPS can mature (differentiate) into many types of new cells, whether that new cell type be a nervous system cell or a heart cell or some other cell type, in order to generate that particular tissue in the nervous system or the heart and thus repair the damaged tissue of that particular organ. The importance of the iPS was not only for ethical and religious reasons because an embryo is not destroyed in the making of an iPS, but also because the iSC can be created from somatic cells taken from the same patient that will receive the iPS transplant. Because the iSC comes from the same donor, the possibility of immune mediated implant rejection is obviated or minimized.

The goals of the CRM to focus on the iPS were very ambitious and of great potential importance, but perhaps the goal to focus mainly on iPSs was too narrow. Over the last few year several laboratories have reported reprogramming errors in the iPSs, including epigenetic and genetic errors.[1] The differences (errors) observed between iPSs and embryonic stem cells fall into the categories of gene copy number variation, chromosome duplication, epigenetic variation, and acquired protein coding point mutations. This means that the fundamental nature of the iPS and the constituent parts of the cell being formed contain errors and that the iPS does not have the same characteristics of an embryonic stem cell. Further, this array of errors often occurs in cancer associated regions of the genome and potentially increase the risk of tumor formation where the iPS is to be used as a therapeutic. Thus, while the iPS is of great importance to possible therapeutic development, the efficacy and safety of these cells is still under investigation, and the cells may not yet be warranted for therapeutic use.

In addition to the therapeutic development of embryonic stem cells and iPSs, the use of adult stem cells and the molecules that they release have been intensively investigated and have current therapeutic applications. For example, during the past four decades adult stem cells have been used as a therapeutic in cancer treatment. The adult stem cell procedure can be of three types: (1) autologous, the cells come from the patient; (2) allogeneic, the cells come from a matched related or unrelated donor; and (3) syngeneic, the cells come from the patient's identical twin or triplet. Given the three types of cell acquisition, adult stem cells of many types are abundantly available for therapeutic development. Further, using the stem cell released molecules from adult stem cells, a collection of hundreds of types of molecules leads to a promising area of therapeutic development called "systems therapeutics".[2] Systems therapeutics is based on using multiple molecule types to target multiple pathways, instead of the more traditional, reductionist approach where a small chemical entity is used to target one pathway to ameliorate the condition. Because any function, and hence any dysfunction, involves multiple pathways, the system therapeutic is a potentially more powerful means to cure the ill, and the SRM from adult stem cells and the collective actions of all the molecules are instructive about how to develop systems therapeutics.

As the NIH regroups and discusses plans for future directions in stem cell therapeutic development, short- and long-term strategies need to be considered as to what technologies are available now for development, such as adult stem cell-based technologies, and what technologies offer hope for advances in the coming years, such as iPS technology. My reasoning is not binary; I am not arguing for one or the other, rather I am arguing that our stem cell research and therapeutic development needs to include all stem cell types and consider all of the possible mechanisms through which stem cells provide therapeutic benefit, including not only differentiation into mature tissue but also the very powerful paracrine and

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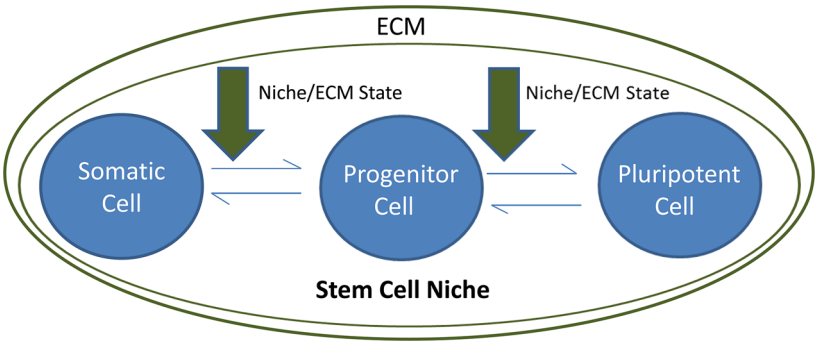

Figure 1. Stem cells, progenitor cells, and somatic cells reside in the stem cell niche and exist in a state of dynamic transition. Not only can pluripotent stem cells and progenitor cells transform into differentiated, mature cells but also recent studies suggest that somatic cells and progenitor cells may revert to a natural stem cell-like phenotype in a stochastic manner. This state of dynamic transition appears to be regulated by natural transcription factors and the physical state of the stem cell niche. Thus, iPSs may be generated in mammals through a naturally occurring set of mechanisms that does not involve artificial genetic reprogramming. Further study of adult stem cells will elucidate the mechanisms for generating naturally occurring iPSs and one day create clinical procedures that allow for the in vitro spontaneous conversion of a patient's own terminally differentiated somatic cells into iPSs that are of therapeutic benefit. ECM = extracellular matrix.

autocrine effects of the stem cell-released molecules (SRM). Often overlooked in view of how stem cells provide therapeutic benefit is the SRM, but as we look more closely at stem cell mechanisms of action, more studies are showing the benefit of SRM.[3]

Considering adult stem cells and their SRM, through reverse engineering of the means that our adult stem cells use to heal the body, we can discover powerful innate mechanisms that may be both mimicked and augmented. The endogenous mechanisms of adult stem cells, and possibly somatic cells in the stem cell niche, seem to include the ability to reprogram themselves into more primordial states that are pluripotent.[4,5] That is, the adult stem cell, and even somatic cells, may exist in a state of dynamic transition between different levels of potency that is dependent on many factors, including paracrine and autocrine factors in the SRM from surrounding cells in the stem cell niche, and by the physical state of the stem cell niche (Figure 1).[6] Beyond transcription factors contained in the SRM,[3] physical manipulation through the cytoskeleton is known to transmit signals to the chromatin and reprogram cells and may represent an additional means for driving cells to varying levels of potency. Reprogramming of differentiated cells to stem-like cells has been described in several tissues[7,8] and is well studied in the epithelial−mesenchymal transition where a differentiated epithelial cell transforms to a mesenchymal cell with a stem cell-like phenotype.[9,10] Thus, by understanding adult stem cell function, we may develop the means to use these cells in many ways to maintain and heal the body, including a means of controlling naturally occurring iPSs.

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Notes

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