Induced Cell Turnover: A proposed modality for in situ tissue regeneration & repair

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Credit: Biogerontology Research Foundation, Feinberg School of Medicine & Swammerdam Institute for Life Sciences

Thursday, July 15, 2017, London, UK: Scientists at the Biogerontology Research Foundation, Feinberg School of Medicine at Northwestern University and Swammerdam Institute of Life Sciences at the University of Amsterdam have published a paper on a proposed method of in situ tissue regeneration called Induced Cell Turnover (ICT) in the journal *Human Gene Therapy*. The proposed therapeutic modality would aim to coordinate the targeted ablation of endogenous cells with the administration of minimally-differentiated, hPSC-derived cells in a gradual and multi-phasic manner so as to extrinsically mediate the turnover and replacement of whole tissues and organs with stem-cell derived cells.

"One of the major hurdles limiting traditional cell therapies is low levels of engraftment and retention, which is caused in part by cells only being able to engraft at locations of existing cell loss, and by the fact that many of those vacancies have already become occupied by ECM and fibroblasts (i.e. scar tissue) by the time the cells are administered, long after the actual occurrence of cell loss. The crux underlying ICT is to coordinate endogenous cell ablation (i.e. induced apoptosis) with replacement cell administration so as to manually vacate niches for new cells to engraft, coordinating these two events in space and time so as to minimize the ability for sites of cell loss to become occupied by ECM and fibroblasts. This would be done in a gradual and multi-phasic manner so as to avoid acute tissue failure resulting from the transient absence of too many cells at any one time. While the notion of endogenous cell clearance prior to replacement cell administration has become routine for bone marrow transplants, it isn't really on the horizon of researchers and clinicians working with solid tissues, and this is something we'd like to change." said Franco Cortese, Deputy Director and Trustee of the Biogerontology Research Foundation, and lead author on the paper.

Cell-type and tissue-specific rates of induced turnover could be achieved

using cell-type specific pro-apoptotic small molecule cocktails, peptide mimetics, and/or tissue-tropic AAV-delivered suicide genes driven by cell-type specific promoters. Because these sites of ablation would still be "fresh" when replacement cells are administered, the presumption is that the patterns of ablation will make administered cells more likely to engraft where they should, in freshly vacated niches where the signals promoting cell migration and engraftment are still active. By varying the dose of cell-type targeted ablative agents, cell type and tissue-specific rates of induced turnover could be achieved, allowing for the rate and spatial distribution of turnover to be tuned to the size of the tissue in order to avoid ablating too many cells at once and inadvertently inducing acute tissue failure.

"Cell therapies are limited by low levels of engraftment, and in principal their ability to improve clinical outcomes is limited by the fact that they can only engraft at locations of existing cell loss. Conversely, therapeutic tissue and organ engineering requires surgery, is more likely to introduce biochemical and mechanical abnormalities to tissue ultrastructure through the decellularization process, and is fundamentally incapable of replacing distributed tissues and structures with a high degree of interconnectivity to other tissues in the body. The aim of ICT is to form a bridge between these two main pillars to regenerative medicine, extending the efficacy of cell therapies beyond a patch for existing cell loss and accomplishing the aim of tissue and organ engineering (i.e. the replacement and regeneration of whole tissues and organs) while potentially remaining free of some of their present limitations." said Giovanni Santostasi, co-author on the paper and a researcher at the Feinberg School of Medicine, Northwestern University.

While future iterations of the therapy could use patient-derived cells, such as ESCs derived via somatic cell nuclear transfer (SCNT) or iPSCs derived from nuclear reprogramming, shorter-term applications would likely use existing stem cell lines immunologically matched to the patient

via HLA matching. The authors contend that the cloning of adult organisms with normal lifespans from adult somatic cells testifies to the fact that adult cells can be rejuvenated and used to produce a sufficient quantity of daughter cells to replace the sum of cells constituting adult organisms, and that serial cloning experiments (in which this process is done iteratively, using an adult cell of each subsequent generation to derive the next) attests to this fact even more strongly.

"ICT could theoretically enable the controlled turnover and rejuvenation of aged tissues. The technique is particularly applicable to tissues that are not amenable to growth ex vivo and implantation (as with solid organs)—such as the vascular, lymphatic, and nervous systems. The method relies upon targeted ablation of old, damaged and/or senescent cells, coupled with a titrated replacement with patient-derived semi-differentiated stem and progenitor cells. By gradually replacing the old cells with new cells, entire tissues can be replaced in situ. The body naturally turns over tissues, but not all tissues and perhaps not optimally. I am reminded of the quote attributed to Heraclitus: 'No man ever steps in the same river twice, for it's not the same river and he's not the same man.'" said Sebastian Aguiar, a coauthor on the paper and researcher at the Swammerdam Institute of Life Sciences, University of Amsterdam.

"Reversing aging in humans will require a multi-step approach at multiple levels of the organismal organization. In situ targeted ablation of the senescent cells and regeneration will be an important component of comprehensive anti-aging therapies." said Alex Zhavoronkov, Chief Science Officer of the Biogerontology Research Foundation.

The researchers originally proposed ICT in 2016 in the context of biomedical gerontology as a possible means of preventing and/or negating age-related phenotypic deviation for the purposes of healthspan extension, and in this new paper they refine the methodological underpinnings of the approach, take a closer look at potential

complications and strategies for their deterrence, and analyze ICT in the context of regenerative medicine as an intervention for a broader range of conditions based on disease or dysfunction at the cellular and intercellular level, with potential utilities absent from traditional cell therapies and tissue/organ engineering, the two main pillars of regenerative medicine. The intervention is still very much conceptual, and any potential utilities over other therapeutic modalities within regenerative medicine would need to be verified via preclinical studies, but their hope is to stimulate further research at this interface between geroscience and regenerative medicine.

More information: Francesco Albert Bosco Cortese et al, Induced Cell Turnover: A novel therapeutic modality for in situ tissue regeneration, *Human Gene Therapy* (2017). DOI: 10.1089/hum.2016.167

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