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Commentary: A pile of vital cells is needed to treat myocardial infarction

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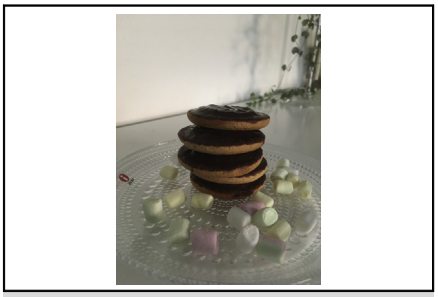

A pile of goodies.

CENTRAL MESSAGE

Successful transplantation of induced autologous pluripotent stem cells requires many challenging technical steps.

It should be simple in theory: if a treatment fails, one only needs to add a missing element, and voilà, recovery continues as ever before. However, it seems that biology is complex and molecular pathways interdependent, and several interventions are often needed to initiate successful healing.

Stem cell research aims at manufacturing products that compensate devitalized myocardium caused by infarction and heart failure. Stem cells are applied to tissue injury, but several risks persist, such as allogeneic tissue rejection, poor cell sustainability, and harmful interaction on vital paracrine functions. Induced autologous pluripotent stem cells (iPSCs) may solve tissue rejection but not necessarily tissue adherence, consequences of genetic mutations, or harmful chemical and molecular mechanisms.[1]

The study by Osada and colleagues[2] investigated whether piles of cardiac cell sheets created from iPSCs together with gelatin hydrogel microspheres would add to cardiomyocyte regeneration, cardiac function, and recovery after experimental myocardial infarction. iPSCs were first differentiated to create potent cells for transplantation using inhibition of the canonical Wnt/β-catenin signaling pathway. Thereafter, gelatin hydrogen microspheres were added to create layers of cell sheets, since relatively poor cell engraftment without a carrying media is evident.[1] The resulting treat was applied to experimentally induced myocardial infarction of rats without a thymus. In conclusion, transplantation of the differentiated iPSCs together with gelatin hydrogen microspheres was feasible and showed signs of functional cardiac recovery and healed myocardial scar area.

The study by Osada and colleagues[2] is technically outstanding and thought-provoking. Exciting details of the study necessitate discussion to plan subsequent research. Wnt/β-catenin signaling is fundamental to many processes, including cell differentiation, proliferation, and tissue regeneration.[3] While the upregulation of Wnt/β-catenin signal is required for mesoderm differentiation, the cardiac specification process requires its inhibition,[3] but only at a specific time window; otherwise, the procedure may be inefficient or even harmful.[3,4] Can manipulation of the cell proliferation pathway exacerbate the risk of cancer and arrhythmia?[4]

The transplanted graft may provide a reservoir of therapeutic cytokines and growth factors that enable the transplanted cells to survive on the hypoxic infarcted area while development of angiogenesis would ensue.[1,2] However, angiogenesis is assumed to initiate from the outer border of the infarction, and the center of the infarction is left without vascular supply for some time. Thick layers of supportive cell sheets may in themselves limit cell oxygenation.[1]

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The use of athymic nude rats as recipients may partly simulate the concept of clinical autologous transplantation, but the use of immunosuppressants is anticipated during any allogeneic transplantation.[5] Would even a graft-versus-host type of disease be possible while using patient cells with genetic mutations?[6]

The combination of preparing all elements of a successful graft is indeed challenging. Many different phases of a manufacturing recipe may increase the risk of undesired outcome; the more cooks, the more complex the output becomes. How much functional cardiac recovery with limited scar and vascular density is required for sufficient clinical recovery after myocardial infarction? When would translational research provide enough technical and ethical evidence to launch stem cell technology into efficient clinical practice?[7]

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