European Review for Medical and Pharmacological Sciences 2021; 25: 6164-6166

Letter to the Editor

Decellularization and tissue engineering: viable therapeutic prospects for transplant patients and infertility?

Dear Editor,

The issue of organ availability for transplants can make a life-changing difference for millions of patients all over the world. Research has been showing with a considerable degree of consistency how bioengineering will someday contribute to solving organ shortages and reclaim the lives of patients struggling with countless diseases requiring solid organ transplants (SOT). Patients in need of a transplant generally have considerable hurdles to overcome: from lengthy, and potentially life-threatening, waiting lists to organ compatibility and high rates of failure. The American Transplant Foundation (ATF) has reported that 17 people die every day on average in the United States due to the unavailability of organs for transplants. The process can in fact take years to be completed: a patient awaiting a kidney transplant may have to wait 3 to 5 years before receiving the organ, and over 100,000 patients are on waiting lists for organs in the United States alone[1]. Thankfully, scientific advancements in the field of biotechnologies seem poised to change such dynamics, opening up new prospects that over time could bring about new opportunities, as well as various challenges. The replacement or regeneration of tissues or organs can be achieved through tissue engineering, aimed at restoring organ function while reducing organ specificity and therefore the need for organ donation. That is indeed a potentially invaluable advantage: reliance on tissue and organ scaffolds derived from humans and animals can significantly reduce the donor-patient specificity necessary for successful transplants. Tissue engineering is based on three fundamental pillars: cells, signaling molecules, and scaffold, which complement and interact with each other. Specifically, the scaffold gives structural, biochemical, and biomechanical signaling meant to regulate cell behavior and tissue development, along with integrated signaling molecules. Scaffolds can be obtained by means of synthetic or natural methods. A significant advantage with synthetic scaffolds is that their structural properties can be manipulated and controlled for the purpose of achieving an optimal environment for a given cell type. Decellularization entails the isolation of the extracellular matrix (ECM) of an organ or tissue from its inhabiting cells, whereas the ECM's micro- and macro- anatomy is maintained: decellularized organs contain biologically active molecules fully supporting cell phenotype and function, and are vascularized, thus making tissue generation possible. The remaining ECM scaffold of the original tissue can be used in artificial regeneration of organs and tissues, when the patient-derived cells are used to "repopulate" it. The preservation of the organ's ultrastructure and vasculature is of utmost importance. Essentially, decellularization of donor organs may involve heart, liver, lung among others, in order to obtain an acellular biologic scaffold material that can then be seeded with selected cell populations[2]. Physical, chemical, enzymatic, or combinative methods can be implemented in order to take off cells and DNA from the tissue leaving its structural and regulatory proteins intact[3]. A "custom made" neo-organ can thus be harvested for each individual recipient patient, which, among its advantages, should make immunosuppression unnecessary[4] and stave off rejection. Complexities inherent in such dynamics are worthy of short elaboration, for the sake of thoroughness. Biologic scaffold materials, constituted of mammalian extracellular matrix (ECM) have already been harnessed in order to surgically re-

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construct a broad range of tissues (such as cardio-vascular, gastrointestinal, lower urinary tract, musculotendinous, dermal) in pre-clinical studies, as well as human clinical applications. Such scaffold materials can be generated by ECM harvested from various tissues such as skin[5], small intestinal submucosa[6], and heart valves[7] among others. The ECM materials are harvested and typically processed as two-dimensional scaffolds and do not need direct anastomosis to the recipient vasculature. In order to survive, seeded cell populations need oxygen and nutrients, as the supporting vascular network develops and gradually becomes viable. A different method for *in vivo* organ decellularization, leaving an ECM scaffold fit for grafting exogenous cells, relies on non-thermal irreversible electroporation (NTIRE), a technique used for tissue and tumor ablation through brief, high electric field pulses, to achieve the permeabilization of cell membranes, which leads to cellular death without scar tissue. NTIRE has thus treated the liver of a live mouse and then engrafted exogenous hepatocytes into the cell-ablated region. The procedure ultimately achieved the successful integration of the grafted cells into the host liver parenchyma[8]. Tissue engineering shows potential for fertility treatment as well. Experiments aimed at bioengineering ovaries[9] and even a whole uterus[10] have shown encouraging potential, albeit still far from clinical applications at this time. Patients suffering from ovarian dysfunction arising from congenital malformations, chemotherapy, adhesions, aging and poor lifestyle choices could benefit from tissue engineering relying on a combination of cells, biomaterials and factors aimed at restoring the functional regeneration of the reproductive organ, possibly through ovarian decellularization and repopulation with autologous cells or follicles. As for patients suffering from absolute uterine factor infertility, either arising from congenital factors (e.g., uterine agenesis)[11] or complications from previous pregnancies or procedures[12], uterine transplantation constitutes the only option to restore fertility, although it does entail complications from a technical and ethical perspective[13,14]. Ultimately, we believe there is no denying that tissue engineering and innovations in regenerative medicine hold great potential in terms of solving many of the thorny issues plaguing organ transplants based on human donors. The further development of inducible pluripotent stem cell technology has made it possible to engender personalized cells that are likely to make autologous tissue engineering a reality in the foreseeable future[15,16]. In light of the speed of such progress, legal and ethical responses must not lag behind, given the challenges such new opportunities will pose once they are ready for full-scale mainstream clinical use. It is therefore essential for the scientific community, policy/lawmakers, bioethics committees and the general public to engage in a wide-ranging discussion as to how to regulate such mind-boggling innovations in a well-balanced and ethically tenable fashion, through broadly acknowledged and shared guidelines. Only a concerted effort in that regard can ensure that the public interest and well-being of all are pursued with justice and equality.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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