Tissue Engineering in Disability Management: Fundamentals and Future

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Background

According to CDC (Center for Disease Control and Prevention, USA), one in four adults in the United States struggles with some type of disability. Also, the global increase in the disabled population greatly depends on the next-generation medical sciences including advanced therapeutic interventions, physical therapies, assistive technologies, and psychological well-being, despite the welcoming trend in inclusiveness and awareness. Increased knowledge gap regarding the early-stage detection aggravates the disability sector. Interestingly, the recent advancement in the medical biotechnology is very promising and offers pleasant hope for next generation disability management. Despite the inherent/genetic defects, the physical injuries contribute a lion's share of global disability population. On this juncture, the major focus of this article is to throw insights into the perspectives of tissue engineering (TE), an emerging field of medicine, in addressing the challenges in the management of disabilities with an emphasis on physical injury-driven disabilities including the damages in the internal organs.

Severe injuries due to accidents or diseases often demand immediate surgical removal of organs as a primary life-saving approach. The regeneration or replacement of the lost organ parts largely depend on organ transplantation. Organ transplantation was initially reported by Murray in 1955, as he transplanted kidney between identical twins paving the way to the allogenic transplantation opening the scope of organ transplantation as a life-saving intervention[1]. Importantly, the organ transplantation has saved millions of sufferers from end-stage organ damages and critically severe injuries. However, the postoperative complications in patients, inadequate number of donors, transportation and accessibility, higher chances of post-implantation immune rejection and need of life-long immunosuppressive medication are challenging in organ transplantation approaches.

On considering the disability management, custom designed or engineered organs/prothesis for transplantation is a long-cherished dream in medical research, which is yet to be accomplished. For the last 60 years, diverse groups across the globe have been researching to organ substitutes giving birth to TE. Still, the concept of engineering tissues was introduced in a research proposal submitted by YC Fung to National Science Foundation (NSF) in 1985 *("A Proposal to the National Science Foundation for An Engineering Research Center at UCSD, Center for the Engineering of Living Tissues", UCSD #865023, courtesy of Y.C. Fung, August 23, 2001.)* and the term 'Tissue Engineering' was coined in 1987. The classical and widely accepted definition for TE was given by Robert Langer and Joseph P. Vacanti as '*Tissue engineering is an interdisciplinary field that applies the principles of engineering and the life sciences toward the development of biological substitutes that restore, maintain, or improve tissue function'*, and is the most referred definition[2].

Evolution

The ancient literature/script on the creation of human has been attributed to the Book of Genesis in the Holy Bible where the first women, Eve, was created from the rib bone of the pioneer man, Adam[3]; an ideal concept of whole organism regeneration from the body part. Similarly, the Greek mythology demonstrates multiple occasions regarding the creation of human life without sexual reproduction. For instance, the story of Prometheus narrated during 8th century BC has been prominent illustration of liver regeneration[4] [5]. Ancient Indian literature displays abundant concepts of TE as evident from the skin graft employed by Susruta, the father of surgery during 5200 BC, and the iron leg replacing the amputated leg of Queen Vishpala in Rig Veda (3500 BC–1800 BC)[6, 7]. Interestingly, the Renaissance in Europe has laid a strong foundation to modern science and research which in turn have inspired from the ancient practices, concepts, and culture. Unfortunately, the transition of ancient culture to modern era has not been well documented leaving the knowledge gap regarding the early practices of disability management specialty. Nonetheless, the advancements in the understanding of basic biology and physiochemical and/or biochemical techniques strengthened the field of TE.

Tissue Engineering

TE is an interdisciplinary field that integrates the elements of biology, chemistry, and engineering to generate organ, and/or organ substitute in the laboratory settings. TE aims to create functional tissue constructs for replacing/repairing the damaged tissues/organs. Cells, growth factors, and scaffolds are the inevitable parts of TE which form the "Tissue Engineering Triad". The cells activate tissue formation, and the scaffold offers a platform for the cells to proliferate and function. Growth factors and/or signaling mediators drive the cell differentiation and function according to the tissues of interest[8]. The balance between these components for individual tissue applications, the compatibility of the materials used and understanding regarding their chemistry and biomechanics are critical for successful TE[9]. The cells seeded onto the appropriate scaffolds along with biological programs results in the formation of neo-tissues or engineered tissue construct which upon implantation to the injury site accelerate the healing/regenerative responses.

Cells

The organs/tissues are organized with heterogeneous population of cells with diverse structural and functional features contributing to the specific function. Hence, the choice of appropriate cell phenotypes is primarily critical for the successful engineering of the organs. As the primary cells have low proliferation potential; cell programing or reprograming is necessary for appreciable outcomes. Importantly, the non-proliferating primary cells such as cardiomyocytes, neurons and specialized cells in kidney and lungs are challenging in TE applications warranting additional programing. Translationally, the stem cells are the ideal replacement for the primary cells owing to their potent differentiation capability. In addition, the stem cells can be easily isolated, are superior in proliferation and differentiation to multiple lineages responding to proper stimulation. Major types of stem cells used in TE including embryonic stem cells[10], bone marrow mesenchymal stem cells[11], adipose derived stem cells[12 13], hair follicle-derived stem cells[14], induced pluripotent stem cells[15], and resident stem cells have proven immense success in the engineering of diverse organ constructs. However, increased chances of teratoma formation, and uncontrolled/undesired differentiation are hurdling for the application of stem cells in TE.

Scaffolds

The proliferation and functioning of cells depend on their microenvironment including the substrate/surface for the attachment and homing. Physiologically, the native constituents of ECM in different tissues/organs drive the basic the behavior of cells such as proliferation, adhesion, migration, differentiation, function and apoptosis[16]. Hence, in TE strategies, engineering suitable scaffolds mimicking the native ECM is critical[17]. Ideal scaffolds follow biocompatibility, biodegradability, mechanical properties, architecture simulating the native ECM, and minimal immunogenicity[18]. Biomaterials including synthetic and natural polymers, bioglass, metals and ceramics have been successfully explored for the preparation of scaffolds through solvent casting, particle leaching, freeze-drying, phase separation, gas foaming, electrospinning, and highly advanced 3D, 4D and 5D printing technology[19]. Decellularization of the native ECM is another approach for generating viable scaffolds. Overall, the scaffolds should simulate the native microenvironment and provides the essentials for the cells to perform based on the tissues/organs of interest.

Growth factors

Growth factors facilitate cell-cell interaction and maturation, and the innate developmental process are intimately associated with the versatile growth factors signaling. Hence, introducing essential growth factors and signaling molecules promotes the differentiation of progenitor cells, vascularization and ultimately the maturation of the engineered tissues. Additionally, the chemical modification and biological enrichment of growth factors are possible and can be incorporated into the scaffolds through stable chemical modification or by physical encapsulation[20]. Interestingly, the natural scaffolds and decellularized ECM bear several in build growth factors essential for tissue growth and maturation. On the other hand, synthetic biomaterials warrants functionalization with the growth factors without altering their chemical and biological properties using physical[21] or covalent interactions[22]. Importantly, the release kinetics of the loaded mediators needs to be optimized and controlled for the better performance and long-term sustenance of tissues without any side effects. Hence, the choice of ideal growth factor/signaling mediator based on the intended biological functions and the sustained bioavailability of loaded mediators to the cells in the scaffold and the surviving host cells post implantation is very crucial for successful TE.

Future of TE in disability management

Recent advancements in medical/biological/engineering sciences have revolutionized the field of TE. Also, in the current epoch of personalized medicine, especially in the field of disability management, TE has potential in manipulating the autologous biological mechanisms of the subjects. Interestingly, TE based brain/nervous system manipulation along with musculoskeletal engineering and neuromotor/vascular manipulations offer immense potential in preventing/repairing/repairing the root causes associated with diverse inherent defects associated with disabilities. Additionally, the scaffold technology in TE has been upgraded with the integration of molecular biology and genetics that significantly improves the proposed biological performance of TE based strategies. Importantly, the advent of 3D bioprinting and the upgradation to 4 and 5 dimensions has transformed TE which revolutionized the artificial prothesis technology supporting millions of disabled populations across the globe. Similarly, artificial intelligence (AI) has been integrated with biomedical science and research offering pleasant hope to address the impairments faced by the disability sector. Importantly, nanorobotics, devices designed in nanoscale, are inspired by biological system are capable of finding immense application in disability management. However, the co-evolution of these advanced technologies such as AI, nanorobotics and machine learning along with TE strategies would vividly define the next-generation personalized disability management. As the demand for physical and intellectual disability management continue to grow, TE offers optimistic next-generation patient care approach. Despite addressing the physical disabilities, TE based approaches promise the management of intellectual disabilities and individualized medicine which warrants further research. Nonetheless, TE opens novel next-generation translational avenues in disability management by manipulating the inherent biological mechanisms.

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Endnotes

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