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3D Neural Tissue Engineering: A Review

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Abstract

Human CNS is a very vital component of body and any damage or injury to it can cause serious lethal and fatal consequences. So there is thus need to regenerate this system incase of injury and is currently the most challenging task due to difficult system and restricted regenerative capacity. 3D bioprinting has outgrowth as an advanced field in field of neural tissue engineering. Which has enabled researchers to develop novel 3D scaffolds with complicated architecture in an effort to alleviate challenges defining neural tissue engineering. Amongst all the possible treatment of neuro-regenerative treatment available, 3D scaffolds had gained immense potential due to the advantage of being highly alterable, promoting complete similarity to the native biological architecture. This high architectural similarity between printed constructs and *in vivo* structures is known to promote a greater capacity for repair of damaged nerve tissues. This article consists of advancements in several 3D bioprinting approaches in accordance with the emergence of 4D printing, which adds a dimension of transformation over time to traditional 3D printing.

Keywords: Neural tissue engineering • 3D printing • Nerve scaffolds • Cell tissue engineering • 3D bio printing • Biomaterials

Introduction

Tissue engineering comprises of principles and techniques of cell biology, material science, and engineering to fabricate tissue substitutes that mimic the structural and physiological nature of native tissue with the fundamental aim to regenerate the functional properties of an injured or diseased tissue [1].

Restorement of functions of both CNS and PNS are important challenge in the arena of tissue engineering due to complex functions and limited regeneration capability.

This highlights the need of use of any such alternatives which can restore this functions as well as providing a firm platform for the development of healthy tissues [2].

Impairments to the CNS can occur in multiple ways, such as fall trauma and car accidents which are the leading causes of long-term disability in both urban and rural population worldwide (Figure 1).

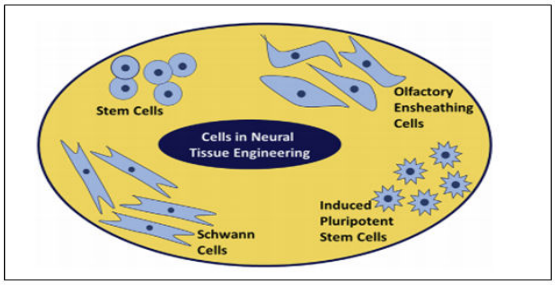

Figure 1. Types of cells for neural tissue engineering.

Literature Review

In addition, the PNS is also prone to different kinds of traumatic injuries because of the extensive presence of nerves throughout the body. The most common types of traumatic peripheral nerve injuries are penetrating injury, crush injury, traction injury, ischemia, laceration, compression, and radiation injuries [3]. With the drawback of limited therapeutic approaches for CNS and PNS injuries, significant work has been oriented towards the development of novel neural tissue engineering approach as a potential treatment for tissue regeneration [4].

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Some promising set of neural tissue engineering has the ability to cater these challenges in neural tissue engineering and has regeneration of neural tissue. The development of 3D nerve scaffolds has been broadly researched to imitate the neighbouring extracellular matrix to provide structural and biochemical indication to enhance nerve regeneration. Certain biomaterials have the capacity of being regenerating the neural tissue by providing them a firm surface over which they can progress and differentiate at the site of injury [5]. When making a nerve scaffold, 3D bioprinting in accordance with advanced biomaterials is a promising strategy to create a complex 3D structure with controlled geometry of the pores. 3D bioprinting allows fabrication and indication of complex structures of micrometer scale. Advanced biomaterials such as carbon nanomaterials and conductive polymers are currently used as bioink in many printing systems. These biomaterials includes both natural as well as synthetic, which has the capability of mimicking the native architecture of the extracellular matrix [6]. Incorporation of conductive polymers and carbon nanomaterials in neural tissue engineering has drastically been growing due to their excellent electrical and physical properties. 3D bioprinting allows configurational modification of cells and biomaterials, a method which is called as “bioink”, which permits the interaction between the cells and materials [7,8]. Due to 3D bioprinting, it has been possible to generate functional tissues and cells in advancements in field of science, genetic engineering, printing technology, etc., and hence, is also called as ‘Adaptive Bio fabrication’. Bioprinting enables diversification of extracellular tissues for model development and disease, transplantation therapy etc. It is 3D bioprinting which made possible for stem cell regeneration; bitterly recapitulate natural cell environment and cell-to-cell interaction. Key features of a printed construct include porosity for diffusion of oxygen and nutrients, and correct mechanochemistry of biomaterials to promote cell adhesion, survival, and function [9,10]. A novel and well-defined method making 3D neural Mini-Tissue Construct (nMTC) by micro extrusion bio printing frontal cortical human Neural Stem Cells (hNSCs) with a support of bioink followed by in situ differentiation of functional neurons and providing a supporting neuroglia. The bioink is composed of polysaccharides Alginate (Al), Carboxymethyl Chitosan (CMC), and Agarose (Ag), which forms a gel by chemical cross-linking followed by extrusion with hNSC encapsulation. Al and Ag providing a structural support for the biomaterial [11,12].

Physicochemical properties of 3D collagen-CS scaffolds for use in neural tissue engineering

The design and selection of an appropriate scaffold is an important feature of neural tissue engineering. The key task for science is creation of *in vitro* scaffolds with an appropriate composition of stem cells. Stem cells are multipotent cells, which has potential of self-renewal, differentiation in suitable medium. They can be differentiated into three main cell types of CNS: neurons, astrocytes, and oligodendrocytes. The ideal scaffold is one, which is capable of mimicking the natural Extracellular Matrix (ECM) of brain/spinal cord. A new three-dimensional (3D) scaffold consisting of more than one component, Chondroitin Sulphate (CS) and Collagen (Col) was produced [13]. The CS-CoL is not novel, it has been utilized to regenerate skin, bone, conjunctiva, cartilage, etc., but has been rarely been utilized for CNS regeneration. Collage type-I is not the principal component of ECM of brain, the studies in past years has showed that collagen hydrogels or sponges can be used to grow and culture of many cell types found in the nervous system. This ability is a distinctive feature of this protein [14-17]. This collagen is biocompatible, provokes weak immune reaction and provides better attachment, migration, differentiation and/or proliferation to the cell. CS molecules that contain sulphated N-galactosamine and D-glucuronate units are an important component of brain (Figure 2). However, CS alone is not used to construct scaffolds due to its relatively weak physical and mechanical properties (Table 1) [18].

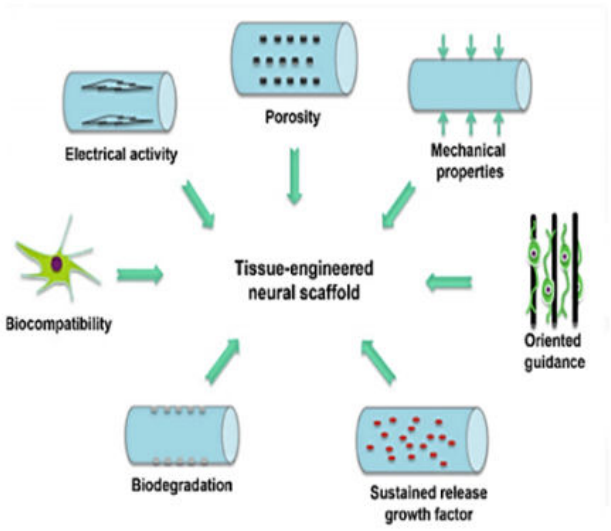

Figure 2. Physico-mechanical properties of tissue engineered scaffold.

Methodology

Author	Technology adopted	Methodology	Findings
Wei Zhu, et al., 2015	Nanotechnology	--	--
Haixing Xu, et al., 2013	Image J software (NIH)	*In-vivo* synthesize of a conducting composite nerve conduit with PPY and poly (D, L-lactic acid) (PDLLA), assess its ability to support the differentiation of rat pheochromocytoma 12 (PC 12) cells	--
Tao Xua, et al., 2006	--	Inkjet printing method	--
Fu-Yu Hsieh, et al., 2015	--	The conventional 3D scaffold fabrication by novel 3D Bio printing	--

Zin Z. Khainga, et al., 2012	Micro fabrication techniques using different biomaterials	Use of natural biomaterials	--
Raj Kumara, et al., 2020	Nanotechnology with Confocal microscopy	Use of organic and inorganic nanomaterials	--
Nic D. Leipzig, et al., 2010	--	AviTag recombinant IFN-g purification, denaturation and biotynilation	--
Christian Mandrycky, et al., 2015	3D Bio printing	--	--
Amit Panwar, et al., 2016	3D Bio printing	Micro-extrusion-based	--
Roger Y Tam, et al., 2013	Electro spinning	use of biomaterials to enhance graft survival and integration	--
Pei Zhuang, et al., 2017	3D bio printing in-vitro	Use of microfluidic platform	--
Krystyna Pietrucha, 2015	Nova NanoSEM 230 scanning electron microscope	Use of Collagen-based composite scaffolds	--
Lin Qi, et al., 2013	--	Engineered topographical manipulation	--
Geoffrey Potjewyd, et al., 2018	Binding of fluidic pumps to a vascular channel	Bio fabrication strategies using bio printing and bio-assembly used to develop 3D NVU models.	--
Qi Gu, et al., 2016	EZ-S mechanical tester (Shimadzu)- for modulus and bioink consistency measurement	Direct-write printing of stem cells in the biomaterials	Describing the first example of direct-write printing of hNSC-laden bioink to engineer a novel functional 3D nMTC.
Tzu-Yun Cheng, et al., 2012	--	Specifically linking the lamina-derived IKVAV motif on C-terminal to enrich self-assembling peptide RADA16 as a functional peptide-based scaffold.	samples of RADA16 and RADA16-IKVAV depicted typical b-sheet structure
Haoqing Cao, et al., 2009	--	Two fiber-fabrication methods	--
Andreas Blaeser, et al., 2016	Rotary rheometer	regulating shear stress and alleviating its impact in balancing cell integrity and printing resolution	--
Christine E. Schmidt, et.al., 003	--	Use of different biomaterials and neutrophic factors to promote regeneration	--
Waeljumah Aljohani, et al., 2017	--	Bio printing of three-dimensional constructs	Together with tissue engineering, bio printing technology as the potential to serve as a strong fabrication tool for the development of micro- and macro-scale biomedical systems
Emily Abelseth, et al., 2018	Steriflip vacuum driven filtration system	Human induced Pluripotent Stem Cells (hiPSCs) serve as an important drive when engineering neural tissues.	hiPSC-derived NAs support the cell viability throughout the culture period
Silvia Panseri, et al., 2008	--	Electro spinning technique	Proved that electrospun tubes, with no additional biological coating or drug loading treatment, are potential scaffolds for functional nervous regeneration.
Ulises A Aregueta-Robles, et al., 2018	Epifluorescent Microscope	Systematic evaluation of the capacity of a biosynthetic poly(vinyl alcohol) (PVA) hydrogel to support growth and differentiation of co-encapsulated neurons and glia	SCs dynamically respond to PVA-SG stiffness, with changes in ECM expression that were dependant on the mechanical moduli of the degrading hydrogel
Dong Nyoung Heo, et al., 2019	3D structure was printed using a Solidoodle 3D printer platform	ELECTRICAL STIMULATION (conductive hydrogel crystallized with PEDOT:PSS for neural tissue engineering)	Successfully employed a 3D printing system directing to the fabrication of patternable conductive hydrogels for the systematic delivery of ES for enhanced neural differentiation.
Laura de la Vega, et al., 2019	--	3D printing using different types of biomaterials	Tissue engineered model of the BBB was generated that possesses a high degree of complexity ratio.

Table 1. The given table is discussing about the technology adopted and methodology.

Many printing approaches such as Stereo Litho Graphy (SLA), Selective Laser Sintering (SLS) of polymeric and metallic powders, and Fused Deposition Modelling (FDM) of synthetic thermoplastics, inkjet printing and direct extrusion have been employed for scaffold printing. Amongst all this printing technologies, inkjet and extrusion printing are the two important printing technologies which can print cell-laden constructs under native physiological conditions. Micro-extrusion printing provides a diversity to print this cell-laden constructs efficiently and in a controlled fashion under physiological conditions (Table 1).

In micro-extrusion printing, desired biomaterial constructs could be printed by dispersing biomaterial through a nozzle attached with a cartridge loaded with ink. For bioprinting of cell laden constructs, cells are diversified with bioink. Bioink is a material which is used to encapsulate cells to provide a supportive Extracellular Matrix (ECM) environment and safeguarding cells from the stresses a cell has to undergo during printing. But before bioprinting, some parameters such as printing speed, dispensing pressure, distance, etc are to be checked properly. These parameters depend upon the type of cell line and bioink properties (Figure 3).

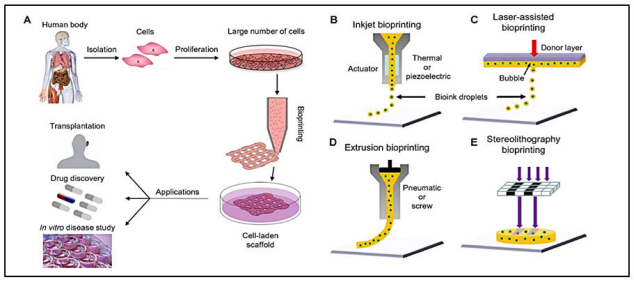

Figure 3. 3D Bioprinting techniques for neural tissue engineering, (A) Basic process of cell regeneration by isolation from human body; (B) Inkjet bioprinting; (C) Laser-assisted bioprinting; (D) Extrusion bioprinting; (E) Stereo lithography bioprinting.

In an ideal situation, the viscidity is also an important factor. The viscidity of bioink supporting a particular cell type should be quite close to that of bioink viscosity suitable for printability. Following are some types of bioinks particularly used-

Naturally-Derived Bioinks-

1. Alginate-based bioinks
2. Gelatin-based bioinks
3. Collagen-based bioinks
4. Fibrin-based bioinks
5. Hyaluronic acid-based bioinks
6. Decellularized extracellular matrix
7. Silk based bioinks
8. Chitosan-based bioinks

Bynthetic bioinks-

- PEG-based bioinks
- Pluronic acid-based bioinks
- Synthetic nanostructured bioinks
- Self-assembled bioinks

3D bioprinting techniques for neural tissue engineering

Inkjet bioprinting: Its name itself suggests, "ink expulsion with a jet". In inkjet bioprinting, an electrically heated print-head produces pressurized pulses of air that force the droplets of bioink from the nozzle. This technique is totally inexpensive and capable of dispensing biological polymers and materials in a highly controlled manner through the extension of commercially available inkjet printers. Recent studies have focused on hybridized bioprinting technique using a combination of cell suspension and a printing bioink. The resultant cell-embedded 3D structure can improve cell proliferation.

Viability and electrophysiology of neural cell structures generated by the inkjet printing method

Many complex cellular patterns and structures are fabricated by automated and direct inkjet printing method. Rapid fabrication of tissue is an important challenge in tissue engineering. Inkjet printing nowadays is of great interest as it is providing tools for dispensing and handling of biological materials to generate cell tissues, organ analogues, etc., Previously, a tow-step process was applied in which cell-adhesive molecules, such as collagen, collagen/poly D-lysine, or laminin, were initially printed, onto substrates with cell background and then seeded and formed cellular pattern by attaching with this cell adhesive molecules. Though these steps have high flexibility and are less expensive, they are limited only to 2D printing due to the use of thin coating of cell adhesive molecules.

So, to overcome this problem, inkjet printing forms the basis of printing. To understand whether the basic printing process affects the neural cell properties or not, primary hippocampus and cortical neuronal cells were used. This cell were tested by following steps-

- Cell preparation and cell print suspension, which were obtained through enzymatic dispersion of day-18 fetal tissue from pregnant Sprague–Dawley rats.
- Fabrication of monolayer of primary hippocampus and cortical cells
- Immunostaining of printed primary embryonic hippocampal and cortical neurons- the primary basis of this method was like Radio-Immuno assay (RIA) in which, primary cortical and hippocampus cell were first exposed to mouse antibody and then with fluorescence labelled secondary antibody and then observed using a Zeiss LSM-510 confocal microscope.
- Electrophysiology was checked
- Fabrication of 3D neural sheets with fibrin gels
- DAPI staining of the printed 3D neural sheets
- SEM of 3D printed neural sheets
- Tensile strength testing

The inferences thus obtained with the above methodologies were-

- Cells differentiated
- Showed high immune reaction and emitted specific fluorescence (axons showed red fluorescence whereas dendrites and cell body showed green fluorescence)
- Printed cortical cells matured into developed neurons and showed voltage-gated Na and K channels on their membrane and then repetitive firing on this cells shows excitability.

Laser bioprinting

In laser-assisted printing, a laser light is used as a source to evaporate a portion in the donor layer (top layer) producing a bubble that propels a suspended bioink falling on the substrate. The donor layer usually consists a 'ribbon' structure containing an energy-absorbing layer (e.g., titanium or gold) on the top and a layer of bioink solution suspended on the bottom. As compare to inkjet bioprinting, laser-assisted printing avoid direct contact with the dispenser and the bioinks. This non-contact printing method does not cause mechanical stress to the cells, which results in high cell viability (usually higher than 95%).

Bioplotting

In this printing technique, a pressurized syringe allows expulsion of a viscous liquid drop wise onto a gel-like material. The resultant hydrogel material can be solidified in time dependent manner using a crosslinking agent or laser light. One warning of this technique is the matching density of viscous plotting material into a liquid medium. As a result of this buoyancy compensation, architectures can be fabricated without temporary support structures.

Electrospinning

This technique produces fibres of several micrometres to nanometres size, which can be induced at the site of lesions by implantation. This fibres are usually formed from various natural, synthetic polymers, ceramics and composites. Many parameters relating to these polymers such as polymeric solution concentration and viscidity, and polymer solution dispersion rate may be controlled during fabrication so as to modify the dimensions of the fibre.

Due to versatility of electro spinning technique, electro spun has found applications in various fields of tissue engineering such as neural tissue engineering. Differentiation between substrates made out of polymer films versus electro spun fibres have been tested both *in vitro* and *in vivo* to demonstrate the efficacy of these fibres in enhancing nerve regeneration. *In-vivo* extension of axon with electro spun biomaterials has been identified suggesting them as a potential approach for nerve tissue regeneration.

Extrusion- based bioprinting

This technique utilizes pneumatics or manual force to continuously extrude a liquid cell–hydrogel solution. It is an alteration of inkjet-printing, in order to print the viscous materials which inkjet printers are not able to deposit, extrusion printing applies either an air-force pump or a mechanical screw plunger to disperse bioinks. It can print unperturbed cylindrical lines rather a single droplet using continuous force.

Self-assembly

Self-assembly refers to wherein an individual biological component (including viruses, RNA, DNA, peptides, etc) organize themselves impulsively into nanostructures such as nanofibers, nanotubes, vesicles, helical ribbons, etc., This process of self-assembling is influenced by environmental alterations such as pH, temperature, ionic strength, presence of specific solutes. It is another approach to fabricate nanofibers. In self-assembly technique, fibres having diameters of tenth of nanometers can be injected into CNS repair. Self-assembly is actually a spontaneous process of organization of molecules into patterns or structures by using covalent bonding such as van der waals forces, hydrogen bonds and electrostatic forces without human intervention. Moreover, these peptide molecules can break down into natural L-amino acids which are nontoxic and could potentially be used by nearby cells for growth and repair. It is also believed that self-assembly can provide 3D microenvironment that is very similar to natural extracellular matrix. This advantage suggests it as a potential approach towards the nerve tissue regeneration.

Cell viability and proliferation ratio in 3D peptide culture

Live/Dead assay is used to determine cell viability. The results obtained showed only few red fluorescence-stained cells, which were both in 3D RADA16 and RADA16-IKVAV at day 14 after seeding. The quantitative analysis of the total viable cell population was conducted with the MTS assay. The results showed that cell numbers of NSCs drastically rises in both RADA16 and RADA16-IKVAV 3D peptide hydrogel in 2 weeks. At day 7, the amount of proliferative cells in RADA16-IKVAV hydrogel was less than those in RADA16, denoting a time delay in proliferation. At day 14, the encapsulated cells in RADA16 and RADA16-IKVAV proliferated dramatically to about 30 times when compared to the initial cell density in 3D peptide hydrogel cultured at day 1, suggesting the 3D SAP hydrogel a non-cytotoxic supporting matrix for NSCs growth and with good viability of encapsulated cells. Adhesive gene expression analysis was done by the extension of IKVAV motifs for improving neural cells attachment, qPCR analysis was conducted with NCam2, Fbln1, and Lamb2 as target genes. And to study the survival and organization of implanted Neural Stem Cells (NSCs), GFP-labelled NSCs were transplanted in order to trace the existence of implanted donor neural stem cells and then this tissue were also stained with Nissl stain (red) to define host neural tissue. And the results stated that accumulated GFP positively labelled NSCs were easily seen and located around the boundary of cavity at the first week and still can be discovered 3 weeks after the transplantation.

Trends in natural biomaterials for nerve tissue repair

Naturally-derived biomaterials for use in the Central Nervous System (CNS) and in the Peripheral Nervous System (PNS) have many advantages over synthetic biomaterials; although synthetic biomaterials are more flexible in their design, naturally derived biomaterial has greater possible achievement because of their biocompatibility which plays a vital role in wound healing.

Noncellular tissue grafts as scaffolds

The application of decellularized tissues had become a foremost option in search of scaffold to restore nervous system. The use of intact natural tissue ECM scaffolds such as acellular peripheral nerve grafts appear to be highly successful for repairing peripheral nerves. Their advantages are-

- Contains appropriate concentrations of proteins relative to the tissue
- Has an appropriate microarchitecture for the host tissue

Collagen based biomaterials

This class of biomaterials usually represents the biomaterials which promotes the regeneration of axons both in CNS and PNS.

They had also been utilized in drug delivery to deliver multiple-cell types in brain after injury. Collagen is the principle component of ECM of different variety of cell in the body and allows good cell fixation sites, and is generally non-immunogenic. There are many types of natural collagens (at least 28 forms) in various tissue types but the most abundant form in the body is type I collagen. Collagen monomers can also construct fibres and 3D hydrogels under the right pH and temperature.

Discussion

Multiple collagen based biomaterials have also been formed to repair nerve injuries in the PNS. Previously, collagen conduits containing collagen glycosaminoglycan matrix have been shown to support excellent axonal regeneration after a sciatic nerve injury in rats, and the level of regeneration was similar to that of a nerve graft [19-21]. Thus, collagen based biomaterials have been shown to aid axonal regeneration [22-24].

Conclusion

This review highlights the most promising solution to the problems of CNS and PNS damage by 3D approach for neural tissue engineering as they have the capability for the formation and regeneration of neural networks which are characteristics of cytoarchitecture of cortical tissue. We depicted the importance and characteristics of Bioprinting and their various techniques and 3D approaches in tissue engineering especially that of neural tissue engineering. 3D bioprinting has come-up as an important approach for fabrication of artificial biomimetic tissue constructs with precise control over their architectural accuracy and spatial distributions. The approach has exhibited some striking advantages over its conventional methods, but is remaining to be exploited to its full capacity for use in neural tissue engineering. The complicated environment of neural tissues owes us the potential of 3D bioprinting but the need of bioink is one of the challenges for faster progression of this field of research. So, here in this review importance of such bioink and various approaches to bioprinting has been explained, which with contribution of 3D approach can help faster development in the field of neural tissue engineering.

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