Regenerative Medicine

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Executive Editor

Can Neural Tissue Engineering Lead to New Type of Central Nervous System?

Generation of Biologically Relevant Architecture to Repair Damaged Tissue in the Central Nervous System

Several studies have shown that neural damage is one of the most untreatable causes of long-term disability in patients that have suffered moderate to severe destruction of the tissue architecture in the neural system. This damage in the neural system can occur via slowly progressing neurodegenerative medical conditions such as Alzheimer's disease, which is perceived as the initiator of disorganization of the neural tissue structure [1, 2]. There are several mechanisms that have been studied including the accumulation of extracellular amyloid plaques and the overexpression of laminin. The production of intracellular aggregates of hyperphosphorylated tau protein has also been considered as a factor causing neural tissue damage. Such aggregation of tau protein along with other factors can lead to modulation of the cell function, which eventually results in damage in the surrounding tissue architecture in the central nervous system (CNS) [2, 3].

Researchers have shown the possibility to regenerate large sections of lost or damaged CNS tissue mostly in animal models [4]. However, during regrowth of the CNS tissue, it results in disorganized tissue architecture that does not produce the desired function of the CNS [2]. An alternative route that has been proposed to overcome this limitation of loss of function includes generation of biologically relevant tissue architecture for prime tissue regeneration. This can be done through incorporation of engineered tissue microenvironments [2, 5]. However, to achieve best results, it is suggested to gain the ability to control over the generation as well as delivery of patterned microenvironments into tissues that are targeted for regeneration [2].

It is believed that the ongoing advances in developing cutting-edge biomaterials for regenerative medicine can prove to be a game changer that can pave the way for neuron replacement therapy. It can lead to new types of CNS for effective treatment of neural tissue damage [6]. To this end,

researchers are currently focusing on the development of bio-techniques and processes to create and use multiphase microstructured hydrogels (mostly granular hydrogels or microgels) [2]. This is expected to enable researchers to generate cultures with more biologically relevant architecture. The use of these structured hydrogels is believed to be critical for the development of new types of CNS culture models and therapies [2].

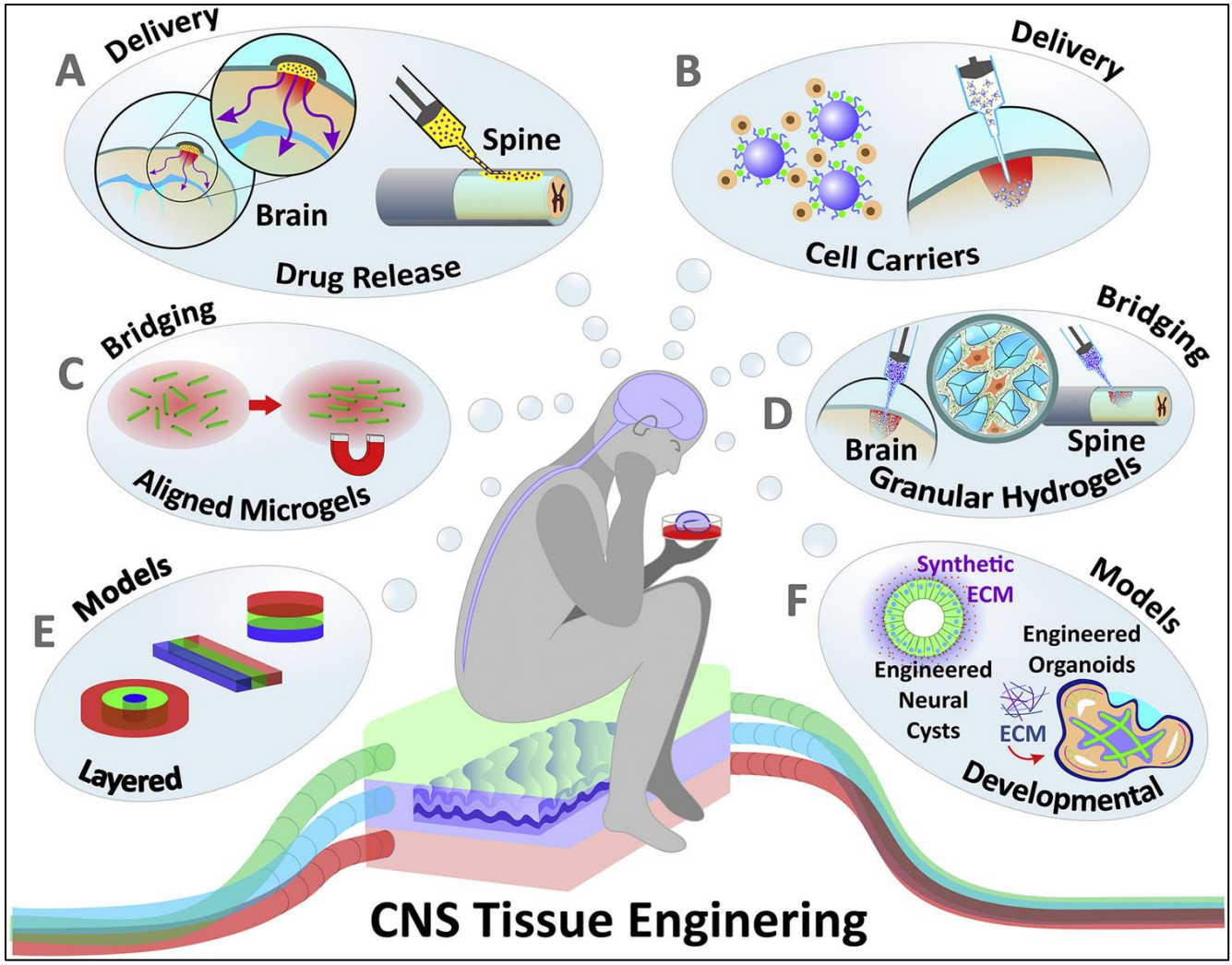

Figure 1: The production and applications of structured hydrogels in CNS models and therapy. (A) Hydrogels for controlled release of soluble factors for drug delivery applications. (B) Drug carriers that support cell transplantation. (C) Production of aligned hydrogels that can guide axon growth and neurite orientation. (D) Applications include bridging scaffolds composed of microgels and granular gels for neuronal growth across damaged tissues. (E) Production of layered hydrogel architectures to spatially confine neurons to mimic in-vivo tissue structure. (F) Hydrogels for the generation of neuroepithelial cysts and CNS organoids [Source: Biotechnology Advances (2019)].

Tissue Engineering of CNS Using Advanced Hydrogels

Cells are the principal agents of tissue function. Other important agents are the dynamically changing extracellular matrix (ECM) and the hierarchically structured arrangement of cells and ECM within the extracellular environment. This structural arrangement of cells and extracellular matrix (ECM) changes constantly throughout the tissue building process [2]. Hence, this poses a significant challenge for in-vitro controlling of the 3D structural arrangement of cells that can replicate natural tissue physiology [2].

The application of hydrogels in tissue engineering has shown a lot of promise to overcome the challenges in controlling 3D structural arrangements of cells. These hydrogels are commonly chosen for their extraordinary functional properties and they are adapted for use as support matrices for neural cultures (Figure 1) [2]. Researchers have employed a number of different techniques to impart the required microstructure to hydrogels for different applications [2]. Some of the approaches include the addition of microscale particles that have anisotropic shape that allows to align with physical force. This helps physical confinement of the hydrogel to create aligned fibrils. Other techniques include applications of magnetic fields to directly modulate the alignment of magnetic particles within a hydrogel or indirectly align hydrogel fibrils [2]. Researchers have also demonstrated the possibility of producing arbitrarily complex microscale patterns within hydrogels [2, 7].

Embryonic Development: Producing CNS Organoids

An embryonic organization as well as tissue function in adulthood can be achieved by gene expression and different stages of patterning. To this end, researchers have conducted investigation of in-vitro models of early development to better understand these principles of replication. In this regard, different organoid models have been highlighted for producing different types of CNS organoids in healthy and disease states [8]. The availability of stem cells and early stage differentiation protocols have facilitated innovation to develop organoids for a new type of CNS [2]. Matrigel that belongs to the family of hydrogels has been leveraged to support the polarization of surface cells into organized cell sheets that form the basis of downstream organoid patterning [2]. Matrigel is known for its structural versatility that is composed of a mixture of biological components. Researchers have investigated synthetic PEG hydrogel in combination with a library of purified proteins that were derived from or related to the constituents of Matrigel. This was aimed to generate neuroepithelial cysts from mouse stem cells encapsulated within the hydrogel (Figure 2A) [2].

Scientists generated the neuroepithelial cysts from an encapsulated population of single cells to produce organoids that were formed from clusters of 2000 or more cells encapsulated within a drop of Matrigel [2]. This approach allowed neural induction that was followed by organization of the neuroepithelial cyst on the surface of the organoid. The surrounding Matrigel coat provided support in a similar way to basement membrane in-vivo (Figure 2B), and the polarized cell sheets replicated the formation of cell sheets within the early

embryo (Figure 2C) [2]. In the more mature organoid, these neuroepithelial-like sheets were shown to undergo developmental patterning similar to early neural tube growth in embryogenesis (Figure 2D) [2]. Further, it was observed that the Matrigel coat weakened with the increase in size of the organoid tissue. Figure 2E shows an early embryo, in which the neural tube is surrounded by a laminin rich basement membrane [2].

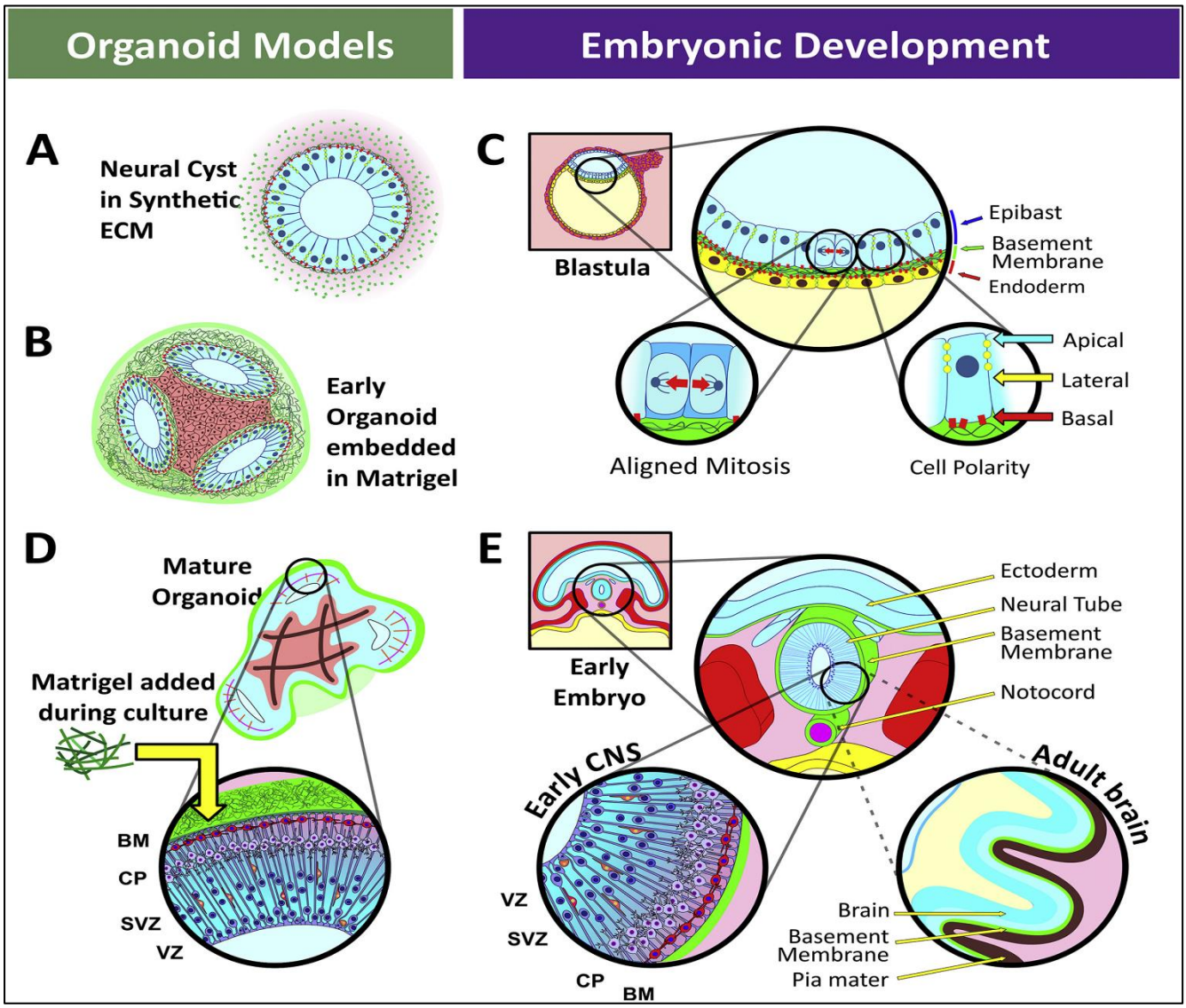

Figure 2: Comparative hydrogel based models for embryonic development [Source: Biotechnology Advances (2019)].

Concluding Remarks

The current research and developments in CNS organoids have shown tremendous promise that could pave the way to the discovery of how of relevant biological patterns needed to replicate and repair the complex tissue microenvironment for

regrowth of a new type of CNS. Such medical breakthroughs in neural tissue engineering could provide solutions to the complex and untreatable problems of CNS tissue damage that results in the loss of neuronal and glial cells.

References for Further Reading

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