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Topical Issues of Bioprinting Technology

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Abstract

Brief analysis of positive and negative aspects of bioprinting was performed. Bioprinting has technical deficiencies and a range of unresolved issues, including the absence of bioprinting protocol strategy. It is necessary to develop bioprinting protocols as well as technologies of 4D production of biological tissues and techniques of formed organs and tissues combination with tissues of living organism to successfully resolve biocompatibility issues.

Keywords: Brain Structure; Brain Functions; Brain Plasticity; Brain Reparation; Bioprinting Prospects

Abbreviations: 2D: Two-Dimensional Space; 3D: Three-Dimensional Space; 4D: Four-Dimensional Space; BBB: Blood-Brain Barrier

Introduction

Recovery of violated structure and functions of tissues and organs of living organisms still remains a complicated problem. It is especially hard to perform reparation of central nervous system fragments as it integrates all structures and functions of the organism into a whole. That is why ideas of bioprinting of tissues and organs appeared. Ideas appeared, but they were not followed by reliable fundamental substantiation and finally resulted in plenty of deficiencies in bioprinting technology; sometimes bioprinting attempts to fill in certain applied clinical fields paying zero attention to fundamental state of development. Despite of ambitious scientific and popular articles of various levels, clinicians didn't come close to successful total recovery of impaired brain functions after destruction of its separate regions. This is because scientists focus on recovery of brain plasticity, its structure and functions and don't consider plenty of structural and functional elements of brain which are vital for nerve tissue effective functioning - even for a short period of time. For example, only several articles pay attention on functional role of blood-brain barrier (BBB), which protects brain cells from circulating microorganisms, toxins, cellular and humoral factors of immune system - those who detect brain tissue as allogeneic [1]. Damage or moreover absence of BBB is one of the main reasons for development of autoimmune brain diseases, such as multiple sclerosis. However, for example, outstanding study by Maoz BM et al. [2] about microfluidic organ chips mention only one BBB element - the barrier between microvascular bed and brain tissue [2]. But this model doesn't take into account BBB role in relationships between brain surface with surrounding liquor. Also, nothing is said [2] about role of BBB in protection of brain from harmful factors when cranial nerves directly contact brain tissue.

Prospects for Tissue Engineering

Cellular and bioprinting technologies have been implemented recently along with classis techniques of recovery of impaired brain and spinal cord functions. Cellular technologies are promising because they allow using lessons learnt by nature during phylo- and ontogenesis in reconstruction of neural networks with stem cells and other biological materials of organs and tissues [3-5]. Existing technologies are focused mainly on creation of artificial elements of organs and tissues or technique of donor material transplantation [6]. Therefore, tissue engineering becomes humane alternative to methods aimed at organ transplantation [6,7].

Printing of organs looks like fantastic step forward, because such technology is aimed at complete recovery of impaired functions of organs and tissues. Brilliant idea, but hard to realize due to known drawbacks of such promising technology. Authors of the article suggest that bioprinting should be combined with techniques of stem cells implantation. This will lead to combination of natural reparative function of stem cells with technology of substrate bioprinting, when neural networks with specific neuroglial and neurovascular relationships will form in 3D or 4D space.

The situation with bioprinting in scientific literature was analyzed: the search for "bioprinting" in PubMed revealed 1050 articles on December 06, 2018; "bioprinter" - 69 articles; the search for "bioprinting neural network" and "bioprinter neural network" resulted in 4 and 0 articles, respectively. Such paradox with unsuccessful bioprinting of nerve tissue is quite explainable: it is hard to reproduce such complicated structure in 3D and time, as nerve tissue - besides various types of neurons - has at least three types of glial cells, synaptic contacts, intercellular matrix, neuropil, axons' endings, blood vessels, liquor, stem cells and various biomolecules and microstructures [8-12]. Also, it is necessary to comply with conditions for effective oxygen supply to all regions of 3D brain space and carbon dioxide elimination, harmonization of hydrogen ions balance, as well as other ions and signaling molecules. There is still no solution for stable oxygenation of bioprinted brain object and for creation of other life-sustaining environment, besides respiratory homeostasis, for optimal functioning of all printed elements.

Unresolved Issues of Additive Manufacturing Techniques

It is necessary to mention that such robotic approach is very promising. But this layered reproduction of 3D biological tissues and organs in biological substrates should be updated with another one technology based on implantation of stem cells or spheroids as structure elements [9,10]. Existing idea of bioprinting, unfortunately, does not take into account very complex heterogeneity of tissue structure - say nothing of the organ or living organism. Heterogeneity in this case means plenty of various elements which are present in different 3D layers at the same time [13]. Therefore, elements for bioprinting should be distributed not only by layers. Technologies should be proposed to distribute elements of nerve tissue in time in all or several gel layers. This task seems quite technically complicated. Three-dimensional structure should be formed in consistent time intervals; the structure should penetrate each gel layer and 3D bioprinted object should be sequentially formed in each 2D layer [14].

Specification of time intervals during formation and conjugation of printed object is another unresolved problem. In fact, completely new field of science should be formed just to answer questions about time and space during formation of organs and systems of living organism.

Conclusion

Therefore, there are a lot of unresolved issues in bioprinting. The idea aimed at search for solution of ethical problems in transplantation of organs and tissues looks positive in bioprinting. Taking into account complexity of organs and tissues composition, authors reached a common ground that existing bioprinting technologies are not completely biocompatible. There are also other than technical drawbacks. There is no bioprinting protocol strategy based on fundamental postulates of structure and functions of nature [15,16].

Scientists should develop bioprinting protocols as well as technologies of 4D production of biological tissues and techniques of formed organs and tissues combination with tissues of living organism to successfully resolve biocompatibility issues. Authors tried to bear in mind drawbacks of modern bioprinters and built new model. It has technologies which allow combining sequential formation of layers in 3D of 4D space with controlled distribution of stem cells in time and space [17,18].

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