Extended Abstract Journal of Alzheimer's & Dementia 2021 Vol.4 No.1

Parkinsons Congress 2019: Derivation of dopaminergic neurons from embryonic stem cells using a silk nanofibrous scaffold

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The limited capacity of the central nervous system in repairmen of neuronal population such as dopaminergic neuron cells suggests stem cell therapy for neurogenesis in Parkinson's disease. Also, stem cell therapy accompanied with scaffolds, is a promising treatment in neural tissue engineering to induce neural differentiation in damaged tissue of brain. Here we fabricated and used a silk Nano fibrous scaffold for differentiation of embryonic stem like cells in to dopaminergic neuron cells. Embryonic stem cells were cultured on fabricated Silk scaffolds. The neural differentiation was induced using a modified technique includes; culturing in the presence of Retinoic acid and neurobasal medium with 10 ng/ml epidermal growth factor, 20 ng/ml basic fibroblastic growth factor for 10 days. The neural differentiation was investigated using the evaluation of specific markers via immunocytochemistry and real-time technique. Our dates proved that silk scaffold support the differentiation of embryonic stem cells cells in to dopaminergic neuron. The expression of neural specific markers were significantly higher in the cells were cultured on fabricated Silk scaffolds in compare to monolayer control group. Electro spun silk Nano fibrous scaffold is considered as biological substitutes for neural differentiation of stem cells that is a crucial step in tissue engineering for neural tissue repair and regeneration.

The nervous system is composed of specialized cells organized in complex networks with the ability to integrate and adopt signals from different tissues and organs. The nervous system receives sensorial inputs from the outside environment and sends signals to the periphery cells and muscles to execute simple and complex motor commands. In the brain, variable distribution of neural networks that have not yet been completely deciphered supports cognitive abilities such as verbal, visual learning, and memory. Like other tissues the neural tissue is subjective to senescence, degeneration, and occasional damage. However, the nervous system shows a poor regeneration potential, which is still a motive of controversy. Many efforts of regenerative medicine focus on providing "fresh" cells to structurally and functionally replace neural cells lost after degeneration or trauma. Stem cell (SC) delivery is a popular therapy due to their pluripotency and multipotency ability for direct differentiation into neural lineages and/or the release of specific factors that can stimulate endogenous neurogenesis and self-repairing mechanisms. For example, the implantations of Embryonic Stem Cells (ESC) and Neural Stem Cells (NSC) have been used in very different contexts such as spinal cord injury or Parkinson's disease. Mesenchyme stem cells (MSC) are also commonly used since they can overcome specific limitations usually found with other stem cell cells; namely the difficulty of isolation and expansion and ethical and safety (i.e., tumorigenesis) issues. To restore the functionality lost, the transplanted cells should not be just mere spectators in the evolution of the pathological process, and their differentiated progeny should be able to structurally and functionally integrate with the remaining non-damaged host tissue.However, cell therapy is faced with the strong decline in survival observed for the majority of transplanted cells. This fact is even more accentuated in the nervous tissue, a very hostile environment for donor cells, independently of their germinal origin. For example, MSC show poor survival after brain transplantation into the brain as soon as one week post-transplantation. MSC viability is even lower in the injured brain. Similar circumstances occur with other stem cell phenotypes.. Due to these limitations, current research aims to develop strategies for increasing cell content and engraftment. However, grafted cell content must be strictly controlled, since beyond therapeutics, excessive in vivo expansion might lead to uncontrolled division and tumor formation. An interesting opportunity in this context emerges from the use of matrices (or scaffolds) to favor cell engraftment in specific desired locations. In addition to cells, the direct delivery of stimulating factors from these scaffolds is also possible. Suitable scaffolds should satisfy several criteria such as appropriate bioactivity, biomechanical properties, and biocompatibility to mimic the anatomical and physiological environment of the target tissue.

Matrices for tissue engineering have a diverse origin. Natural matrices are obtained from extracellular matrix (ECM) components produced by living organisms. Biological materials such as collagen, fibronectin, and laminin can provide molecular cues such as the Arginine-Glycine-Aspartic (RGD) motif and, in addition, provide structural support to the scaffold. In contrast, their structure and reproducibility are not as well defined as that of synthetic biomaterials, an artificial route to mimic ECM properties. Thus, synthetic biomaterials such as polycaprolactone (PCL) and poly-D, L-lactide (PLA), provide a well-defined structure at different levels of observation with controllable and repetitive properties, though showing limited biocompatibility. The lack of biological sequences in synthetic biomaterials is a challenge that can be partially addressed by further chemical or physical modifications. Some studies have reported the drawbacks of these approaches, such as those relying on graphene or carbon nanotubes.

In an attempt to combine the advantages of natural and synthetic sources ECM-derived matrices have been proposed. ECM-derived matrices are obtained from the decellularization of organs and tissues and can provide a solution for the accurate reproduction of the anatomical and physiological environment. Nevertheless, several steps in the processing of these scaffolds (i.e., the usage of different solvents) might modify their biomechanical and biological properties. In addition, special attention needs to be paid to the decellularization process and RNA/DNA decontamination, which should be done without changing the biochemical and biomechanical properties of the tissue while removing any trace of cellular and immunogenic material from donated tissues. During decellularization, the biomechanical properties can be impaired and many extracellular matrix proteins and signaling molecules are usually lost. A main limitation of matrices based on decellularized tissues is the rate of cell repopulation, which is usually inefficient and random. Additionally, decellularized matrices can be subjective to safety and ethical problems for clinical use.

Foot Note: This work is partly presented at Joint Event on 5th World Congress on Parkinson's & Huntington Disease & 5th International Conference on Epilepsy & Treatment, August 29-31, 2019 Vienna, Austria