Acta Biomaterialia 51 (2017) 21–52

Contents lists available at ScienceDirect

Acta Biomaterialia

journal homepage: www.elsevier.com/locate/actabiomat

Review article

Controlling the morphology and outgrowth of nerve and neuroglial cells: The effect of surface topography

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ARTICLE INFO

Article history:
Received 20 July 2016
Received in revised form 23 December 2016
Accepted 5 January 2017
Available online 7 January 2017

Keywords:
Topography
Nerve cells
Neuroglial cells
Micro-/nano-fabrication

ABSTRACT

Unlike other tissue types, like epithelial tissue, which consist of cells with a much more homogeneous structure and function, the nervous tissue spans in a complex multilayer environment whose topographical features display a large spectrum of morphologies and size scales. Traditional cell cultures, which are based on two-dimensional cell-adhesive culture dishes or coverslips, are lacking topographical cues and mainly simulate the biochemical microenvironment of the cells. With the emergence of micro- and nano-fabrication techniques new types of cell culture platforms are developed, where the effect of various topographical cues on cellular morphology, proliferation and differentiation can be studied. Different approaches (regarding the material, fabrication technique, topographical characteristics, etc.) have been implemented. The present review paper aims at reviewing the existing body of literature on the use of artificial micro- and nano-topographical features to control neuronal and neuroglial cells' morphology, outgrowth and neural network topology. The cell responses–from phenomenology to investigation of the underlying mechanisms- on the different topographies, including both deterministic and random ones, are summarized.

Statement of Significance

There is increasing evidence that physical cues, such as topography, can have a significant impact on the neural cell functions. With the aid of micro-and nanofabrication techniques, new types of cell culture platforms are developed and the effect of surface topography on the cells has been studied. The present review article aims at reviewing the existing body of literature reporting on the use of various topographies to study and control the morphology and functions of cells from nervous tissue, i.e. the neuronal and the neuroglial cells. The cell responses–from phenomenology to investigation of the underlying mechanisms- on the different topographies, including both deterministic and random ones, are summarized.

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http://dx.doi.org/10.1016/j.actbio.2017.01.023
1742-7061/

1. Introduction

1.1. The in vitro study of the effect of topography on nerve cells

The role of soluble (bio)chemical signals in cell shape, cell adhesion, differentiation and axon guidance, is well established [1]. In addition to the biochemical signals, there is increasing evidence that the physical parameters (e.g. topography and stiffness) of the complex extracellular milieu, constituted by the extracellular matrix (ECM) components and the surrounding cells, are also important [2]. Recent *in vitro* studies suggest that many neuronal and neuroglial cells respond to stiffness and to other mechanical cues during development (reviewed in [3]). Topography, which can be described as the arrangement of the spatial and structural features (e.g. geometrical architecture, discontinuities motif, contours, etc.) of the extracellular environment, has been also strongly correlated with specific functional characteristics of the cells and the tissues at both physiological (e.g. during development) and pathological states (e.g. wound healing) of nervous tissue [2,4].

The importance of ECM architecture in cells and tissue organization is apparent already from the early developmental stages. Embryonic cells produce their own extracellular scaffolds by secreting many types of molecules in the surrounding space, following a well defined program of differentiation [5,6]. The different spatial organization of these secreted molecules gives rise to a great variety of natural scaffolds where cells continue to proliferate and organize themselves in order to build up tissues and accomplish all their natural functions [7]. The role of ECM organization and distribution on directing neural crest migration has been early understood [8,9]. During glioma progression, i.e. a brain cancer, individual cancer cells have the tendency to migrate along myelinated fibers of white matter tracts [10].

The role of topography on cellular outgrowth *in vitro* has been addressed very early; already in 1914 *R. G. Harrison* cultured embryonic frog spinal neurons in a meshwork of spider web filaments and observed that such cells preferentially extended along the solid support of the filaments. Some years later, in 1934, *P. Weiss* made similar observations with embryonic chicken spinal neurons on grooves generated by brushing clotting blood and established the term "contact guidance", in an attempt to describe the tendency of the cells to orient themselves along anisotropic topographical features of the surface (such as fibers or ridges) [2,11]. The observations that certain physical properties of the substrate can *in vitro* influence cellular outgrowth and functions opened a new promising research field. However, many of these early experimental situations in which contact guidance was demonstrated were quite complex. Indeed, it was difficult to discriminate between the effects resulting from the chemical cues and those resulting from the topographical ones. More specifically, the substrates used, i.e. plasma clots, fish scales, and various grooved surfaces, were anisotropic not only in shape but also in chemistry [12].

Accordingly, there was a need to carefully study the effect of topographical cues *vis-a-vis* (bio)chemical cues in a reproducible way. With the emergence of micro- and nanofabrication techniques, a plethora of approaches to engineering or tailoring surfaces in a controllable manner are now available and specific topographical patterns, at micro and sub-micron scale can be designed and fabricated at a plethora of different materials [13–16]. Patterning of surfaces has triggered the development of new types of cell culture platforms, where the effect of topographical cues on cellular responses can be investigated and/or manipulated, depending on the field of interest.

1.2. Neurons and neuroglial cells: the basic components of the nervous tissue

Unlike other tissues, for example the epithelial tissue, where cells exhibit simple shapes, the nervous tissue is a complex three-dimensional environment whose topographical features span a large spectrum of morphologies and size scales. Nerve cells are the functional units of the nervous tissue which are responsible