INFLUENCING NEURONAL GROWTH USING BIOMIMETIC SUBSTRATES

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Curriculum: Ingegneria dei Materiali e delle Strutture

The brain possesses a remarkable ability to adapt to new information and continually rewire its neural circuitry to process that information. The neurons in these circuits, “talk” to each other via a junction between two neurons called synapse. Upon receiving an action potential, the pre-synaptic neuron releases neurotransmitters which are absorbed by receptors of the post-synaptic neuron. When the same neuronal circuitry is fired repeatedly, the brain tries to increase its efficiency by modifying the synapse; the more two neurons “talk” to each other, the stronger their synapse becomes. Neuropsychologist Donald Hebb famously summarized this by stating “Neurons that fire together, wire together". Biologically, this means that there are functional (increase in neurotransmitter release and post-synaptic receptor density) and structural changes in the synapse (anatomic spine clustering, addition of new spines to existing circuits, and synapse formations) which are triggered upon constant neuronal firing. Before elucidating the changes that occur at the synapse, it is imperative to understand the basic critical factors responsible for these changes.

Synaptogenesis, progression through developmental stages, neuron migration and neurite outgrowth, all rely on a highly organized crosstalk amongst neurons and their extracellular matrix (ECM). While making important growth and developmental decisions, neurons sense their surroundings through certain processes called growth cones. During axonal growth, these microscale processes guide the axon by searching for potential post-synaptic dendritic spines. d. The multitude of cues it senses include biochemical, physical, mechanical and topographic properties. Based on these cues, neuronal polarity and fate of neurites is decided as to which protrusion progresses as an axon and which form dendrites. . [1]Preliminary studies show that micro and nanoscale structures influence cell fate and ultimately affect formation of neural circuits. This area of research remains largely unexplored due to the inability to recreate precise and uniform micro and nano scaled topographies in neuronal cultures. With recent developments of novel material fabrication techniques like ion beam etching and photolithography, this barrier has been overcome opening up new lines of research. [2]

When cells are exposed to new topographies, they engulf it by wrapping their cell membrane around the substrate. The new curvatures induced in the cell membrane are responsible for recruiting curvature sensitive proteins. [3] These proteins trigger intracellular signaling pathways, which in turn affect cell function and may also alter gene expression. Some proteins which are recruited during membrane curvatures are also responsible for synaptic plasticity indicating that the interplay between topography, plasma membrane curvature and plasticity is a potential arena for research. [4]

In this project, I aim to characterize the basic cellular and molecular mechanisms of pre and post synaptic crosstalk to understand the fundamental principles of influence of cell fate and then recapitulate this *in vitro* with biomimetic substrates. I plan to use mature and immature microfabricated biomimetic dendritic spines to replicate in vivo environment [5] of the brain. In the presence of such a biomimetic environment, I aim to understand events leading to axon initiation and maintenance by exploring key biochemical

pathways. The goal is to replicate cell signaling pathways which are triggered in native synaptic and neuronal crosstalk.

Experimentally, my work includes interfacing neuronal cells with pseudo-3D biomimetic substrates and growing them in such pseudo-3D cultures. Thereafter, I explore the extent of neuronal signaling cascades that are triggered with these biomimetic dendritic spines. I study them using a wide variety of biological assays, and to visualize their interactions at a cellular scale by means of optical and electron microscopy. [6]

With this knowledge, new areas of research studying cognitive decline due to synapse degeneration can be explored. Axon degeneration is a leading cause of synaptic shrinkage. The fundamental mechanisms of synaptic formation, learning and memory will be understood. Therapeutic approaches to prevent synaptic degeneration can be developed and regeneration can be triggered. This can finally, also be used to prevent and treat neurodegenerative diseases due to cognitive decline.

References:

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