Genomic basis of neural regeneration – Week 1

Neural regeneration or neuroregeneration is the process of synthesizing new neurons and connections between them. It's an experimental and up-to-coming field of research interest where its application is being explored in the cases of healing spinal cord injuries, paralysis recovery, brain-cancer rehabilitation, neurodegenerative conditions such as Parkinson's disease, etc. Neural regeneration involves generation of new neurons, glia, axons, myelin and synapses. It differs considerable between the peripheral and central nervous systems by the functional mechanisms involved, especially in the extent and speed of repair. Popular experimental techniques that are being explored in this field include neuronal transplants and replacements and neural stem cell grafting.

Neural regeneration has been studied for centuries, even before the advent of modern scientific techniques. In 1776, William Cruikshank surgically removed a small part of a dog's vagus nerve from one side of the neck and severed the nerve on the other side. While the dog died, the autopsy showed signs or neuronal regeneration as new neuronal growth was seen. Similar phenomenon was seen in salamander nerve tissues in the 19th century. In the beginning of the 20th century, Spanish neuroscientist Santiago Ramón y Cajal discovered that the axons of neurons of the CNS did not regenerate like the axons of PNS nerves. This was the first study that would later on go on to prove that the CNS is not capable of regenerating unlike the PNS, which remains one of the greatest challenges in neuroscience and medicine for the treatment of conditions involving damaged CNS nerves.

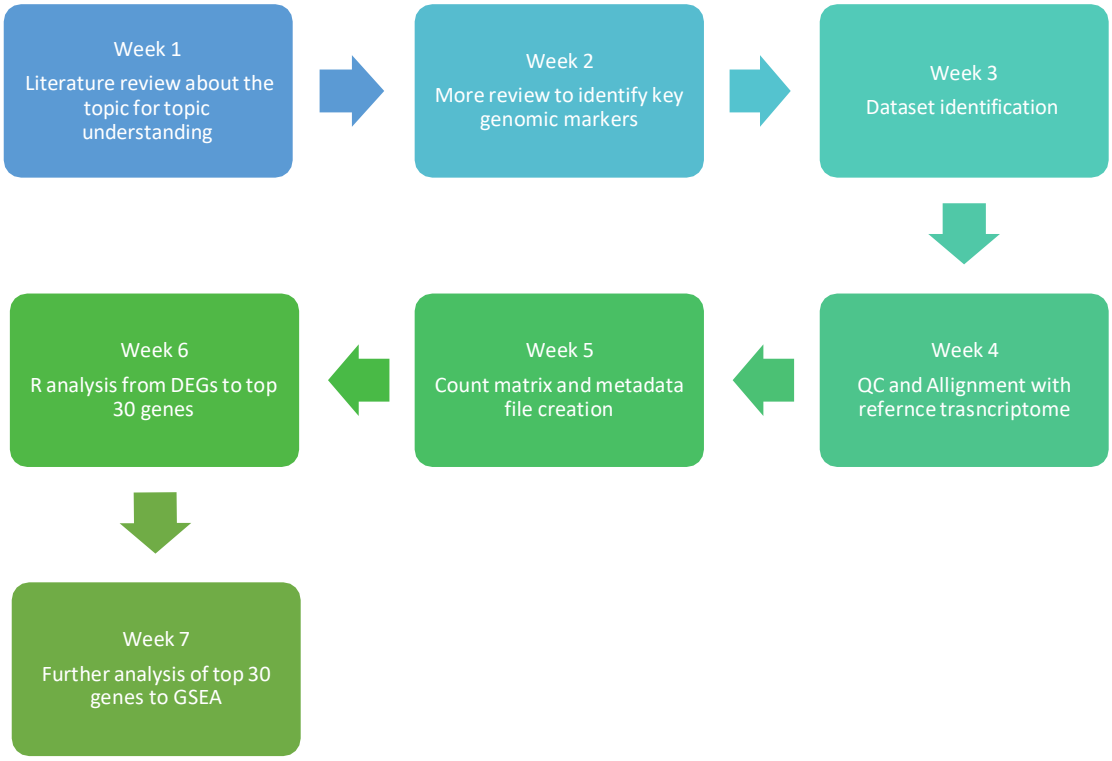
In 1960, stem cells were discovered in the CNS. Joseph Altman's work in the 1960s demonstrated neurogenesis, or the creation of new neurons, in the adult brain. This discovery challenged the long-held belief that the brain stopped producing new neurons after early development. In 1992, a pivotal study by Reynolds and Weiss at the University of Calgary isolated neural stem cells from the adult mammalian brain, specifically from the subventricular zone. These cells were shown to proliferate in vitro and differentiate into neurons and glial cells, providing strong evidence that multipotent neural stem cells exist in the adult CNS. Around the same time, researchers discovered that the hippocampus, a region crucial for learning and memory, also harbours neural progenitor cells capable of neurogenesis. Currently, neural stem cells (NSCs) are being actively investigated for their therapeutic potential in treating a range of neurological conditions, including spinal cord injuries, Parkinson's disease, multiple sclerosis, and stroke. Recent advances have enabled the development of techniques to transplant NSCs into damaged CNS regions, where they can differentiate into neurons, astrocytes, or oligodendrocytes, contributing to tissue repair and functional recovery. In Parkinson's disease, for instance, clinical trials are exploring the transplantation of NSCs programmed to produce dopamine. Breakthroughs in gene editing and biomaterial scaffolds have further enhanced the precision and viability of NSC-based therapies. Moreover, the discovery of in vivo reprogramming—where resident glial cells are converted directly into functional neurons—holds promise for bypassing the need for transplantation altogether, potentially revolutionizing regenerative treatments for degenerative brain diseases.

However, a key challenge that is being presented in this case is the process involved in the isolation of neural stem cells. Despite the incredible promise presented by the field, the process is rather

expensive, making it harder for its application in most clinical cases. As a result, other cells in the body are being explored to check for signatures that can help induce neurogeneration. Blood, bone marrow stem cells, astrocytes and fibroblasts are some popular alternatives being explored. Of these, fibroblast is a type of cell that contributes to the formation of connective tissue, a fibrous cellular material that supports and connects other tissues or organs in the body. Fibroblasts secrete collagen proteins that help maintain the structural framework of tissues. Fibroblasts are being explored as a promising source for generating neurons through a process called direct reprogramming or trans differentiation. By introducing specific neural transcription factors, scientists have successfully converted fibroblasts into induced neurons (iNeurons) without reverting them to a pluripotent state. This approach offers a faster and potentially safer alternative to stem cell-based methods, reducing the risk of tumor formation. Fibroblast-derived neurons are being studied for modeling neurodegenerative diseases, drug screening, and even personalized cell therapy, offering a scalable and accessible avenue for neural regeneration.

Since fibroblasts are comparatively easier to extract and work with, this field presents a promising avenue for neurodegeneration research. This method also shows the potential for successful application as the fibroblasts can be derived from the same person's body, thereby reducing chances of rejection. This miniproject aims to take a look at the process of fibroblast to neuron conversion at a transcriptomic level over a period of time and to look for genes expression patterns that results in the conversion. The project aims establish a transcriptomic basis for this conversion in greater detail and identify novel genes that may contribute to the conversion.

Timeline:



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