At present, patient-derived central nervous system (CNS) tissue is often only available post-mortem. While these tissues can be helpful during autopsy and when confirming a clinical diagnosis, the obvious barriers in accessing primary human CNS tissue in live patients presents an impediment to developing patient-specific personalized approaches in clinical medicine. Furthermore, ideal access to post-mortem tissues is often limited for both clinicians and researchers, and a delayed post-mortem interval can significantly impact tissue and cellular integrity. As a result, animal models of CNS diseases are frequently used in research and are heavily relied upon when studying disease mechanisms and identifying possible treatment strategies. While certain imaging techniques (CT, MRI, PET, etc) can provide valuable clinical information in vivo, their lack of specificity and detailed resolution at the microscopic level is insufficient in providing detailed cellular mechanisms related to pathophysiologial mechanisms of neurodegenerative diseases.

The majority of neurological illnesses rarely occur spontaneously in animals. Researchers have therefore developed animal models that function as extremely valuable tools when attempting to model specific pathophysiological mechanisms related to chronic neurological diseases. Unfortunately, most models do not recapitulate the full spectrum of the human condition and have limited translational potential [1]. For example, experimental autoimmune encephalomyelitis (EAE) is a widely used model and a valuable tool for studying multiple sclerosis (MS). EAE is most commonly induced in rodents and has made a significant impact on understanding how the immune system contributes to the neuropathology observed in MS. Furthermore, the majority of disease modifying therapies that are currently prescribed for MS patients were initially tested and validated in the EAE model [2]. Nevertheless, EAE does not model the entirety of the human condition and the majority of drugs that are successful in EAE often fail in human clinical...
trials, thus limiting the applicability of the model. Non-human primate models of EAE can better recapitulate human disease and carry increased translational potential; however, these models are expensive and difficult to implement [3]. The limited translational potential of animal models of most neurodegenerative disorders has been widely documented [1, 4]. It is important to mention that similar disadvantages are observed in modeling other CNS diseases, including Parkinson’s disease, Alzheimer’s disease, stroke, and ALS. While evidence indicates that many of these failures arise from inadequate internal and external study validity [1], it underscores the unmet need for more optimal models that can help bridge the gap between successful preclinical animal studies and human clinical trials.

The relatively recent discovery that terminally differentiated cells can be reprogrammed to pluripotency, generating induced pluripotent stem cells (iPSCs) [5], provides a novel tool to study the etiology, development, and treatment of disease, including most neurological diseases. Patient-derived iPSCs can be reprogrammed from mature adult cells (often fibroblasts) and selectively differentiated into cells of interest. This not only permits the study of genetic associations with neurodegenerative diseases, but it also allows researchers to study the direct pathological and cellular mechanisms in vitro using patient-specific CNS cells. Importantly, using patient-derived iPSCs can circumvent ethical debates that have plagued allogeneic stem cell trials, eliminate concerns of immune rejection, and provide a format/model that may help to move novel therapies from preclinical animal studies to successful human clinical trials.

Certain challenges remain when studying diseases that arise from the dysregulation and/or mutation of multiple genes or those that are associated with strong gene-environment interactions. Using cells derived from MS patients, stable iPSC-derived lines have been successfully generated [6], and primary patient-derived iPSCs have been successfully differentiated into neurons and oligodendrocytes [7-9]. While no differences in the intrinsic properties of iPSC-derived neurons in patients with MS have been reported, recent evidence indicates that neural precursor cells (NPCs) derived from individuals with a progressive form of MS (primary progressive MS) have inherent defects in their ability to respond to myelin injury compared to cells derived from healthy controls [10]. A second critical finding of Nicaise and colleagues was that NPCs derived from iPSCs of patients with progressive MS exhibited marked individual differences [10]. This finding underscores the significant heterogeneity associated with this disease, which is most often reflected in patients’ clinical trajectories, responsiveness to certain medications and immune cell profiles/activity.

While still in the early stages, the study of patient-derived cell populations has the potential to help us better understand critical pathophysiological mechanisms related to human CNS disorders. For complex and heterogeneous neurodegenerative conditions, like MS, the best hope for appropriate and successful treatment is a personalized approach, where treatment is tailored to the individual. iPSCs may indeed help determine this ‘best course’ of treatment. For example, the genetic predisposition of certain patients might make them unresponsive to certain treatments or even perhaps predispose them to certain risks associated with a particular treatment. Prior screening of potential treatments in vitro using patient-derived iPSCs could reduce these risks and possibly guide optimal treatment strategies for individual patients.

References

