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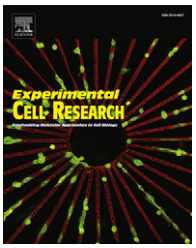

Pluripotent stem cell for modeling neurological diseases

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ABSTRACT

The availability of human pluriopotent stem cells, embryonic (ESC) and induced pluriopotent (iPSC) stem cells, not only can be a renewable source for investigating the early human development, etiology and progression of different diseases but also recapitulating the disease with the same genomic materials of the patient. In particular, specific neuronal subtypes generated from the patient ESC/iPSCs has become a source for studying disease mechanisms underlying different neurological disorders and allowed drug discovery. In this review, we summarize the recent advances in establishing patient ESC/iPSC to model various neurological diseases. We will also discuss the challenges and limitations of the current disease models and their potential future applications for untangling the unknowns in neurological disorders.

Contents

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Introduction

From Parkinson's diseases to autism, the devastating truth about neurological diseases lies within the idiopathic and often progressively fatal nature of the diseases, due to the loss of specific types of neurons. Yet no effective prevention or cure of the diseases is currently available. Owing to the inaccessibility to the susceptible neuronal subtypes, the establishment of a biologically relevant disease model remains critical in the field. Animal models, especially rodents, have irrefutably provided some valuable information on the disease etiology and allowed researchers to pinpoint the crucial mutations contributing to many neurodevelopmental and neurodegenerative diseases. However, the fundamental genetic and anatomical difference between animals and human make them struggle to fully recapitulate human diseases. It is particularly hesitant when translating animal experimental data to clinical settings failed repetitively. Ideally, a patient-specific model prevailed over these limitations, but invasive human biopsy sampling from living patients is rarely available and often impotent for long-term culturing while postmortem samples usually represent only the end-stage of the diseases. Apart from the paucity, the study of neurogenesis in early embryos also arises many ethical issues. Lack of a relevant human model for in vitro examination therefore stumbled the progress of systematic analysis of disease pathogenesis, making the development of effective therapeutics particularly slow.

Until recent years, human pluripotent stem cells, embryonic stem cells (ESCs) and induce pluripotent stem cells (iPSCs), emerge and offer exciting and unprecedented opportunities to improve the human models for the unresolved. The self-renewal properties of the pluripotent cells provide an inexhaustible source to generate various neuronal subtypes. While a more amenable and well-defined way for the use of ESC/iPSCs is gradually emerging, the potential for ESC/iPSCs to decipher the molecular and cellular mechanisms underlying the defects in specific neuronal subtypes becomes solid. Here, we review the recent advances in using ESC/iPSCs for neurological disease modeling and also highlight some of the major concerns and focuses within the field.

ESC/iPSC based neural differentiation

Embryonic stem cells (ESCs) are derived from the inner cell mass of the mammalian blastocysts, whereas induced pluriopotent stem cells (iPSCs) are generated by reprogramming the somatic cells (e.g. skin fibroblast) back to a pluripotent status with the ectopic expression of Yamanaka's factors (OCT4, SOX2, KLF4 and c-MYC) [1,2]. Both ESCs and iPSCs are endowed with high self-renewability and pluripotency, making them promising sources in various fields of human research. Initial studies involving the generation of diverse neuronal subtypes in the central nervous system (CNS) from ESCs have allowed the direct mimicking of the developmental process *in vitro* for more than a decade. ESCs spontaneously aggregates into embryoid bodies were directed to form neural stem cells by supplementing a combination of extrinsic factors which are vital in the actual neural tube development. Early studies were dependent on the presence of stromal feeder cells for neural induction yielded a small amount of neuronal cells. Although conventional techniques such as the hanging drop and rotary orbital culture were developed to allow a more controllable production of embryoid bodies, the heterogeneous nature and patterns of embryoid bodies resulted a low yield of targeted neurons. This has urged a more specific and efficient neural differentiation protocol. Later studies directed ESCs to the neuroectodermal lineage and subsequent neuronal precursor specification in a feeder-free and adherent culture system which bypassed the embryoid body formation and reduced the variables [3,4]. Particularly, during neural differentiation, ESC derived neuroepithelial cells were radially organized as neural rosettes. These neural rosette cells exhibited board differentiation potential toward both the CNS and PNS (peripheral nervous system) fates [5]. In response to appropriate patterning cues such as bone morphogenetic protein (BMP), Sonic Hedgehog (Shh) and Notch, neural rosette cells directly differentiated to varied region-specific CNS neurons including the midbrain and hindbrain neurons [6,7], Purkinje and granule cells of the cerebellum [8,9], hypothalamus [10], the cortical neurons [11] and spinal cord interneurons [12]. These studies have established a precious platform to delineate the mechanisms underlying generation and specification of complex neuronal network in the brain. Subsequent transcriptome and epigenome analyses using these platforms further defined the molecular events taken place during neuralization of human ESC. For instance, global gene expression study has been performed on human ESCs and ESC-derived floor plate, in which the role of SHH underlies floor plate versus anterior neurectoderm commitment during neural development have been established [7]. In parallel, genome-wide epigenome analyses comparing ESC versus ESC-derived neural precursors also revealed that histone modifiers such as JARID1b, LSD1 and CBX7 are essential for ESC differentiation along the neural lineage [13–15].

The rapid development of cellular reprogramming technologies allows the establishment of a catalog of patient specific iPSC lines for the study of disease etiologies and offers opportunities for therapeutic interventions. Thus, tremendous effort has been put on generating a more relevant diseased neuronal subtype using ESCs and iPSCs. Recent studies aimed to drive the ESC/iPSCs towards a more specific subtype of mature neurons in a more coordinated and well-defined way, making them more relevant in providing insights correlating the molecular to the functional defects in neurodegenerative diseases. The emergence of SMAD dual inhibition by supplementing Noggin and small molecule SB431542, respectively inhibit BMP and transforming growth factor beta (TGFβ) signaling, improved the purity and efficacy of obtaining neuroepithelial cells up to 80% in a much shorter period of time (9 days) and converting human ESC/iPSCs to the specific CNS or PNS neuronal lineages [16]. This has also brought the availability of ESC/iPSCs to model PNS under the spotlight where its applications to PNS neuropathies and the neural crest-associated lineages were addressed. More recently, Studer's group has made use of small molecules to further improve the neuronal fate acquisition process. Use of a combination of five small molecules significantly accelerated the neural conversion process and yielded functional nociceptive neurons of 75% efficiency within 10 days, where the neurons not only expressed nociceptors, but also responded to stimuli recapitulating sensory neurons in response to pain [17]. All these studies have built a solid foundation for the subsequent use of human ESC/iPSC to model various neurological disorders.