Neuroscience 320 (2016) 105–121

REVIEW

HUMAN DERMAL FIBROBLASTS IN PSYCHIATRY RESEARCH

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Abstract—In order to decipher the disease etiology, progression and treatment of multifactorial human brain diseases we utilize a host of different experimental models. Recently, patient-derived human dermal fibroblast (HDF) cultures have re-emerged as promising *in vitro* functional system for examining various cellular, molecular, metabolic and (patho)physiological states and traits of psychiatric disorders. HDF studies serve as a powerful complement to postmortem and animal studies, and often appear to be informative about the altered homeostasis in neural tissue. Studies of HDFs from patients with schizophrenia (SZ), depression, bipolar disorder (BD), autism, attention deficit and hyperactivity disorder and other psychiatric disorders have significantly advanced our understanding of these devastating diseases. These reports unequivocally prove that signal transduction, redox homeostasis, circadian rhythms and gene*environment (G*E) interactions are all amenable for assessment by the HDF model. Furthermore, the reported findings suggest that this underutilized patient biomaterial, combined with modern molecular biology techniques, may have both diagnostic and prognostic value, including prediction of response to therapeutic agents.

Key words: dermal fibroblasts, schizophrenia, major depression, bipolar disorder, *in vitro* model, gene*environment interaction.

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THE NEED FOR MULTIPLE MODEL SYSTEMS

Models simplify complex processes, isolate critical pathophysiological components and allow experimentation. In order to study a system, the model has to be able to test cause–and–effect relationships. Yet, compromise is unavoidable: we select a model for its desired features, and the presumably "less relevant" variables are sacrificed for the sake of simplicity. Obviously, the choice of the model should always be guided by the tested hypothesis, as the combination of various models should result in conclusive data and gain of new knowledge.

Considering that the brain pathophysiology of psychiatric disorders can be only analyzed in humans by non-invasive methods, animal models are the preferred choice to examine behavioral disturbances and associated structural and functional brain alterations that arise from genetic manipulations (Schmidt and Mirnics, 2012; Schmidt et al., 2014; Brown et al., 2015). Although these experiments are essential, psychiatric disorders are uniquely human conditions, and cannot be interpreted in the disease context without understanding the events in the diseased tissue (Nestler and Hyman, 2010).

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Abbreviations: BD, bipolar disorder; BDNF, brain-derived neurotrophic factor; CREB, cAMP-response element-binding protein; ECM, extracellular matrix; G*E, gene*environment interaction; GCL, glutamate cystein ligase; GSH, glutathione; HDF, human dermal fibroblast; iNCs, induced neuronal cells; iPCSs, induced pluripotent stem cells; MD, major depression; NGF, nerve growth factor; PKA, protein kinase A; PKB, protein kinase B; PLC, phospholipase C; SZ, schizophrenia.

http://dx.doi.org/10.1016/j.neuroscience.2016.01.067
0306-4522/

Brain biopsies from psychiatric patients are very rarely justified, and even when brain biopsy tissue is obtained, keeping mature neurons alive is extremely challenging (Hayashi-Takagi et al., 2014). As a result, postmortem studies are the preferred choice to study disease-related transcriptome, proteome and metabolome changes. However, these tissue samples have limited utility for the most critical functional assays, such as evaluating gene*environment (G*E) interactions, stress resilience or drug effects (Horváth et al., 2011; Horváth and Mirnics, 2015). Additionally, as this is a sample of opportunity, the interpretation of findings is greatly complicated by confounds such as individual lifestyle differences, comorbidity, drug abuse, medication use, postmortem interval, hormonal status, cause of death and many other factors (Mirnics et al., 2006; Schmitt et al., 2008). Furthermore, perhaps the greatest intrinsic limitation of postmortem tissue is its limited utility in establishing diagnosis and aiding therapeutic approaches.

PATIENT BIOMATERIAL MODELS, ADVANTAGES AND LIMITATIONS

Psychiatric disorders are multifactorial and multidimensional diseases: the pathology and pathophysiology encompass biological events that span genetic, molecular, cellular, neurochemical, systemic, psychological and social domains (Schmitt et al., 2014). As a result, all human-based *in vitro* experimental systems have limitations, but also offer significant advantages: they allow mechanistic experimentation on patient biomaterial, and this is especially important as none of the *in vivo* rodent models of psychiatric disorders can fully recapitulate human genetic diversity and overall disease phenotype (Sarnyai et al., 2011; Kaiser and Feng, 2015).

There is a strong need for patient-derived biospecimens that can be propagated, preferably without altering the genetic makeup of the patients. Importantly, the pathophysiological mechanisms associated with psychiatric disorders such as schizophrenia (SZ) can be investigated in cell cultures as (1) they show high heritability, suggesting a significant genetic contribution to the disease, which would be preserved in an *in vitro* model (Brennand et al., 2012); (2) psychiatric disorders appear to be a disease of the whole body (and not only the brain), therefore many of the disease-associated immune, endocrine and metabolic dysregulations should be detectable in peripheral cells as well (Penninx et al., 2013; Shivakumar et al., 2014); (3) the molecular anomalies which contribute to the neural dysfunction (e.g. altered oxidative and energy homeostasis, mitochondrial changes, metabolic disruptions, signal transduction disturbances) are also present in patient-derived peripheral tissues.

Investigators have been testing meaningful patient-derived functional experimental models for decades. To date, the most commonly used patient-derived models include (1) peripheral blood leukocytes; (2) immortalized peripheral lymphocytes; (3) olfactory epithelium, (4) induced pluripotent stem cells (iPCSs), (5) induced neural progenitor cells (iNPCs) and induced neuronal

Table 1. Suitability of commonly used patient-derived *in vitro* models for studying psychiatric disorders (+ + + + high; + low)

	Availability/Ease of harvest	Renewability and propagation	Uniformity of cell types	Similarity to human brain tissue	Genetic stability	Cost effective generation – maintenance	Throughput	Ease of maintenance
Peripheral leukocytes	+ + +	+	+	+	+	+ + +	+	+
Immortalized lymphocytes	+ + +	+ + +	+ + +	+	+ + +	+ + +	+ + +	+ + +
Olfactory epithelium	+ +	+ + +	+ + +	+ +	+ +	+ +	+ +	+ +
iPSC	+ +	+ + +	+ +	+ +	+ +	+ +	+ +	+ +
iNC	+ +	+ +	+ +	+ +	+ +	+ +	+ +	+ +
HDF	+ + +	+ + +	+ + +	+ +	+ +	+ +	+ +	+ +

HDF: human dermal fibroblast; iPSC: induced pluripotent stem cell, iNC: neural cell induced from iPSC or directly from postmitotic somatic cell.