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Human Dermal Fibroblasts in Psychiatry Research

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Summary

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, depression, bipolar disorder, 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 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.

Graphical abstract

Keywords

Dermal fibroblasts; schizophrenia; major depression; bipolar disorder; *in vitro* model; gene*environment interaction

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1. 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 (Brown et al., 2015; Schmidt et al., 2014; Schmidt and Mirmics, 2012). 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).

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 and Mirmics, 2015; Horváth et al., 2011). 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 (Mirmics 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.

2. 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 (iPSCs), (5) induced neural progenitor cells (iNPCs) and induced neuronal cells (iNCs) and (6) human dermal fibroblasts (HDFs) (Hayashi-Takagi et al., 2014). Each of these cellular models have advantages and shortcomings, described below and summarized in Table 1.

In addition to the inherent differences between all cellular models, they all share a common limitation: the cells are maintained in an artificial environment. The biology of all cells (including, but not limited to proliferation, migration, and function) is highly dependent on the microenvironment. Unfortunately, we have limited understanding of *in vivo* spatiotemporal relationships and microenvironments (Tatullo et al., 2015; Lu et al., 2011). We cannot recreate them in our *in vitro* culturing environments, and the physiological niche of the dissociated cells is certainly far from ideal. For example, we know that self-maintenance and renewal of cell cultures is highly dependent on the extracellular matrix (ECM) remodeling in a cell type specific fashion (Przybyla et al., 2013): it appears that some cells grown *in vitro* are capable of modifying their microenvironment by producing ECM-proteins, glycopeptides and proteases (e.g. cultured astroglia or HDFs) (Fullár et al., 2015; Biran et al. 1999), while other cell types (e.g. pluripotent stem cells and neurons) require support in niche-modulation from feeder cells such as mouse embryonic fibroblasts or astroglia (Moore et al., 2009; Przybyla et al., 2013).

2.1. Peripheral leukocytes

Peripheral leukocytes, and particularly peripheral blood derived mononuclear cells have a long history of use in psychiatric research, assuming a bidirectional communication between the immune and nervous systems (Khandaker and Dantzer, 2015; Naydenov et al., 2007). It has been argued that peripheral leukocytes and brain cells share considerable similarities in their proteome, signaling signature, and hormone and drug response (Gladkevich et al., 2004; Iga et al., 2008). Several studies revealed peripheral leukocyte number and functional alterations in psychiatric diseases, establishing it as a useful *ex vivo* model (reviewed in Gladkevich et al., 2004 and Iga et al., 2008). The main advantages of the peripheral leukocyte/mononuclear cell model are that 1) they can be easily and repeatedly harvested during the course of the illness, and 2) they are reactive to external and internal stimuli, allowing monitoring of the disease state. In contrast, the main drawbacks of the peripheral blood cell models are the considerable individual variability and sensitivity to factors that are independent of the course of the neuropsychiatric disorders (e.g. lifestyle, hormonal

status, circadian rhythm, exposure to pathogens) (Druzd et al., 2014; Gladkevich et al., 2004). In addition, the number and function of circulating leukocytes are affected by the psychopharmacological treatment (Munzer et al., 2013; Tourjman et al., 2013). All these factors are a considerable source of “biological noise” that results in a considerable variability among subjects, often preventing discovery of small effect sizes or discerning clear causality (Krieger et al., 1998). However, peripheral blood cells are still quite useful for performing one-generation-long *ex vivo* functional assays (Naydenov et al., 2007).

2.2. Immortalized lymphocytes

In contrast to natively harvested, unmodified leukocytes, immortalized lymphocytes have self-renewal capacity and represent a virtually unlimited source of experimental material. However, immortalization (which introduces foreign genetic material into the cells) is a time and resource consuming process which might erase the majority of epigenetic modifications, and alters the DNA makeup of the cell lines to the degree that the responses might not properly mimic the cellular response found in unmodified cells (Fridman and Tainsky, 2008). In addition, immortalized cell lines exhibit significant karyotypic instability and disturbed DNA damage response (Toouli et al., 2002). Hence, these cells are more appropriate for addressing narrow focused questions in the context of the donor’s genetic background (e.g. the BDNF-induced serotonin receptor changes) (Mössner et al., 2000), but less practical for the investigation of the broad spectrum of cellular functions (e.g. transcriptome and proteome signatures).

2.3. Olfactory epithelium

Olfactory epithelium derived cell cultures are promising models in neuropsychiatric research (Borgmann-Winter et al., 2015). Biopsies or exfoliated tissue samples yield a mixture of multipotent stem cells, mature and developing neurons and glia (Huard et al., 1998). Consequently, *ex vivo* and *in vitro* experiments (reviewed by Borgmann-Winter et al., 2015) can be performed on cells which closely reflect the donor’s neurobiology without compromising the self-renewal capacity. Unfortunately, these cell cultures remain quite diverse even after culturing (Huard et al., 1998), and represent a mixture of different cell types at various stages of differentiation, which can change based on culturing conditions (Féron et al., 2013), presented co-factors (Greiner et al., 2011), number of passages and site of the biopsy (Borgmann-Winter et al., 2015). During culturing some cells maintain proliferative capacity, others progress to replicative senescence, while the highly differentiated cells respond to odorants in the primary cultures (Gomez et al., 2008). Thus, these experiments require standardized methodology, careful identification of the examined cells *via* molecular phenotyping, and conservative interpretation of findings. In summary, olfactory epithelium cell cultures present a unique, very valuable experimental system, with drawbacks related to the complexity of biomaterial harvest and subsequent culturing challenges.

2.4. Induced pluripotent stem cells (iPSC)

In the last decade induced pluripotent stem cells (iPSCs) emerged as an exciting, disease-relevant experimental model (Tang et al., 2015). iPSCs, re-programmed from somatic cells

can differentiate into virtually any adult cell type, resulting in an unlimited source of patient-specific biomaterial (Takahashi et al., 2007). The technology is rapidly developing, and several protocols exist for reprogramming and differentiation with varying efficacy and results (Singh et al., 2015). Disease- and patient-specific iPSC lines have been created for several disorders, including Parkinson's disease (Park et al., 2008 and Soldner et al., 2011), amyotrophic lateral sclerosis (Dimos et al., 2008), spinal muscular atrophy (Ebert et al., 2009), Alzheimer's disease (Israel et al., 2012), Huntington's disease (Park et al., 2008), and schizophrenia (Brennand et al., 2012). Still, it is worth noting that during reprogramming, unforeseen DNA mutations may occur and significant part of the epigenome becomes rearranged (Martins-Taylor and Xu, 2012). This (epi)genetic instability of iPSCs could result in great heterogeneity within cultures, often necessitating performing the experiments on multiple cell lines from the same individuals (Brennand et al., 2014). Additionally, creating and maintaining iPSCs is a labor-intensive, and a time- and resource-consuming endeavor.

2.5. Induced neural cells (iNCs)

Currently, neural cells can be derived from somatic cells *via* iPSC differentiation (Hu et al., 2010) or *via* lineage conversion (direct transdifferentiation) (Pang et al., 2011). The reprogramming and differentiation of iPSCs into neural progenitor cells (NPCs) and mature neurons is achieved by forced expression or exogenous addition of growth factors and small molecules (reviewed by Kim et al., 2014). The obtained cells are thought to undergo the neuronal developmental pathways observed in the brain, and can be easily cultured and stored (Song et al., 2013; Hu et al., 2010). Technical challenges associated with iPSC research (i.e. generation time and resource demands, (epi)genetic changes, population heterogeneity and oncogenesis) motivated the development of alternative iNC generation methods, i.e. cell lineage conversion (Pang et al., 2011). Remarkably, the expression of only two microRNAs or a single transcription factor might be sufficient to induce neural cell fate in human postmitotic somatic cells and produce functional neurons (Chanda et al., 2014; Yoo et al., 2011).

Both iPSC-derived and transdifferentiated iNCs form functional synapses and resemble the receptor expression and electrophysiologic profile of neurons in the brain (Belinsky et al., 2014; Chanda et al., 2014). Moreover, iNCs with different neurotransmitter- and region-specific identity can be generated, such as GABAergic cortical interneurons (Liu et al., 2013), glutamatergic pyramidal neurons, dopaminergic midbrain neurons, or spinal motor neurons (Zeng et al., 2010). However, the iNC models need comprehensive validation by genetic, electrophysiologic and pharmacologic approaches due to the following reasons: (1) *de novo* copy number variations (CNVs) are likely to happen through the somatic cell – iPSC – iNC transitions (Corrales et al., 2012); (2) the maturation of neurons requires 6–12 weeks. During this time window there are virtually thousands of gene expression changes (Dage et al., 2014; Fathi et al., 2011) and the extended culture period often results in heterogeneous, asynchronous cell populations consisting of progenitors, glial cells, mature and immature neurons (Belinsky et al., 2014). (3) iPSCs “reset” in their epigenetics, telomere processing and mitochondrial organization (Rohani et al., 2014) while transdifferentiated neurons retain the donor's age-related signature (Mertens et al., 2015).

2.6. Human dermal fibroblasts

Notably, the HDF model excels in many of the important experimental considerations listed above: (1) they are relatively easy to obtain from ambulatory skin biopsies (Vangipuram et al., 2013, Wang et al., 2004), (2) their maintenance does not require significant equipment, chemical or human resources; (3) they can be easily propagated for long periods of time without genetic manipulation or external growth factors and stored in liquid nitrogen for years (Auburger et al., 2012;); and (4) HDF cultures consist of mitotic and post-mitotic, uniform fibroblast cells (Bayreuther et al., 1991) and retain genetic stability for 15–20 passages (Hänzelmann et al., 2015), making a single biopsy sufficient for hundreds of experiments. All these considerations make HDF cultures an appealing, cost-effective experimental model.

There are several drawbacks that should be considered when using the HDF experimental model. First, *in vivo* and *in vitro* cellular aging-related changes in HDFs must be considered, as several experiments examined the effects of donor's age on cell viability and senescence based on multiple parameters (e.g. life span, replicative life span, growth rate, replicative potential, proliferation rate). These publications reveal that mRNA, miRNA and protein levels (Waldera-Lupa et al., 2014), DNA methylation (Koch et al., 2011), intracellular calcium levels, mitochondrial function and cell size (Peterson et al., 1986) are all influenced by the age of the HDF donor. These findings necessitate careful case-control age matching and/or use of senescence markers. Furthermore, to avoid consequences of *in vitro* cellular ageing, matching of HDF passage is equally important, as multiple studies reveal that the mitotic rate (Maier et al., 2007), telomere length, DNA methylation (Hänzelmann et al., 2015), proteome and protein phosphorylation (Sprenger et al., 2010) change after the 15th passage in HDF cultures and the cells enter replicative senescence between passage 21 and 40 (Hänzelmann et al., 2015). Additionally, it is also noteworthy that using early HDF passages might be also less than ideal: during the first 3 divisions HDF cultures are not yet homogeneous (Auburger et al., 2012) and are undergoing adaptation to the culturing conditions that result in both transcriptome and epigenome remodeling (Antequera et al., 1990; Nestor et al., 2015b). Similarly, Akin et al. (2004) suggest that patients' dietary, hormonal and medication effects disappear after the 5th HDF passage. Other, consistent reports suggest that body mass index (BMI), smoking and medication use of the biopsy donor do not influence the metabolome of HDF cultures past several passages (Fournier et al., 2014). Therefore, it appears that case-control HDF experiments produce the most consistent and reproducible findings when performed on HDFs between passages 5 and 15.

In addition, HDFs are as variable as the human beings they originate from. HDF signal transduction (Gaspar et al., 2014), mitochondrial function, circadian period length (Brown et al., 2005) and cell size (Huang et al., 2005) all show individual variability, necessitating careful consideration of experimental and control group size. However, as much as this individual variability represents an experimental challenge in case-control studies, it also allows assessment of individual, patient-specific responses, opening the door to future personalized/precision medicine approaches.

Lastly and obviously, HDF cells are not brain cells, and being aware of the differences between HDFs and neurons is essential when considering the usefulness of the HDF model for a specific experimental purpose: (1) HDFs are much more robust and stress-resilient (Auburger et al., 2012); (2) Unlike post-mitotic neurons, HDFs can proliferate or enter into a reversible quiescent state and then spontaneously regain proliferating capacity (Lemons et al., 2010). (3) HDFs are self-sufficient, while neurons live in a symbiotic relationship with glial cells (Lundgaard et al., 2014); (4) Neuronal energy homeostasis relies almost exclusively on lactate oxidation (Lundgaard et al., 2014) while HDFs utilize a much broader range of substrates for metabolic activity (Lemons et al., 2010). (5) There is an undeniable divergence in functional specializations between HDFs and neurons. Neurons are built to be excitable and rapidly convey cell-to-cell signals, while HDFs are primarily stromal cells with a prominent role in immune response and regeneration (Glaros et al., 2009). The advantages and drawbacks of the HDF model are summarized in Table 2.

3. Utility of fibroblasts in psychiatric research

In summary, the selection of the right *in vitro* experimental system should always depend on both the characteristic features of the model and the experimental questions asked. In the absence of human neural tissue, HDFs are useful for examining genetically encoded and conserved cellular functions and molecular pathways (e.g. cycle, apoptosis, secretory and intracellular signaling). HDF cultures are easily obtained using minimally invasive skin biopsies; primary cell lines can be established within 24 hours and maintained for more than 20 passages without genetic or chemical manipulation (Akin et al., 2004). Hence, the investigator can perform controlled, reproducible, ‘personalized’ experiments without a need to alter the individual patient’s genetic background. Such a functional model can be used to perform both state and trait experiments, focusing either on the endophenotype at rest, and/or assess resilience or maladaptation to various challenges (and compare the response to that seen in HDF samples obtained from matched controls) (Figure 1).

Fibroblasts have been traditionally used to study neurodegenerative disorders to investigate mitochondrial dysfunction (Moreira et al., 2007), calcium dynamics (Palotás et al., 2002), membrane composition (Evangelisti et al., 2014), autophagy and lysosomal activation (Coffey et al., 2014), redox homeostasis (Naderi et al., 2006), and amyloid precursor protein or hyperphosphorylated tau (Shahpasand et al., 2012) related cell damage. In psychiatric research, the late 1980s were the golden age of HDF culture experiments, followed by an extended period of decline in the utilization of this model. This trend is recently changing: in the last 5 years HDFs have been rediscovered as useful patient-derived models for studying CNS dysfunction (Figure 2).

To better understand this trend and to define the areas where HDFs can contribute most to understanding brain disorders, we performed a critical review of the published HDF literature to date. We searched the PubMed database for publications from 1966 until October 2015 using the following keywords: “fibroblast AND schizophrenia” (221 items), “fibroblast AND major depression” (110 items), “fibroblast AND bipolar disorder” (81 items), “fibroblast AND autism” (123 items), “fibroblast AND attention deficit” (27 items), “fibroblast AND alcohol dependency” (66 items). Case reports and animal studies were

excluded. We also excluded articles when the abstracts did not contain information on study subjects, measured parameters and main findings. It is noteworthy that by design we limited our search to psychiatric disorders and the HDF model – due to the extent of the literature, our review cannot encompass other models and diagnoses (Table 3).

4. Understanding pathophysiological processes using HDFs

4.1. Signaling pathway studies

Understanding neurotransmitter systems enabled the development of symptom-alleviating drugs in psychiatry, yet it did not elucidate the full pathophysiology of these disorders. This resulted in a shift from studies of neurotransmitter levels to studies of intracellular dysregulations underlying the neurochemical and pathological changes. These studies were quite fruitful and suggest that signal transduction disturbances can lead to altered states of neuronal function and predispose to cognitive and affective disorders (Akin et al., 2005; Dwivedi et al., 2002; Zhan et al., 2011).

The cell-type specific response to stimuli depends on a cascade of intracellular events, and encompasses receptor and effector expression, the presence of co-regulatory factors, epigenetic modifications and final effectors (most commonly a transcription factor). However, it should be noted that second messenger systems and intracellular signal transduction cascades are highly conserved among many different cell types. Importantly, Rieske et al. (2005) proved that HDF expressed transcription factors, signaling molecules and receptors that are highly similar to cells of neuro-ectodermal origin (Rieske et al., 2005).

The work of *Shelton et al.* is a good example of taking advantage of the cellular/molecular similarity between HDFs and neuronal cells. Studying signal transduction following adrenoreceptor stimulation in HDFs revealed that cAMP-response element binding-protein (CREB) can be activated both through the cAMP/protein kinase-A (PKA) and phospholipase-C/protein kinase C (PLC/PKC) pathways (Manier et al., 2001). Furthermore, HDFs from melancholic MD patients had decreased PKA and PKC activity and reduced serotonin 2A receptor specific PLC response, confirming previous *post mortem* and platelet findings in MD patients (Akin et al., 2005 and 2004; Shelton et al., 1999).

This PKA/PKC-deficit of CREB activation in MD deserves more attention, considering that CREB plays an essential role in activity-driven functional and structural neural changes (Benito and Barco, 2015) and that monoamines, stress hormones and antidepressants affect the CREB/BDNF pro-survival pathway (for a comprehensive review see Dwivedi et al., 2008). Notably, some CREB-mediated cellular functions are neuron-specific, but others – like the circadian rhythm regulation – are also present in peripheral cells (Druz et al., 2014; Gaspar et al., 2014; McCarthy et al., 2013a).

4.2. Circadian rhythm studies

Disruption of the circadian rhythm is a well-known pathogenic factor for psychiatric disorders such as MD, BD and SZ (Jagannath et al., 2013). During the last decade HDFs have been established as a valid model for studying molecular oscillators, as: (1) cultured HDFs have cell-autonomous circadian rhythm (average length of 24.5 h) that depends on the

same clock genes found in the pacemaker cells of the suprachiasmatic nuclei (Nagoshi et al., 2004); (2) the circadian rhythm in HDFs is stable, and donor-specific differences are preserved even after multiple cell divisions (Brown et al., 2005; Pagani et al., 2010); and (3) the HDF cellular clock can be re-synchronized with a serum shock (50% serum treatment) (Yagita et al., 2001).

In more recent experiments, *Gaspar et al.* examined the differences in the cAMP/CREB pathway in fibroblast cultures from BD patients and healthy subjects (Gaspar et al., 2014). They found that the cAMP induced CREB response was inversely correlated with light-stimulated melatonin changes in the donors, and concluded that light-induced melatonin suppression and resetting of the circadian rhythm (Lonze and Ginty, 2002) is present in HDFs. Importantly, BD cells showed approximately 3.3 fold higher CREB induction than control cells, suggesting an increased sensitivity to phase-resetting in BD patients (Gaspar et al., 2014).

Similarly, McCarthy et al. (2013a) found longer circadian period length in HDF cultures from BD patients. Furthermore, lithium treatment augmented the resynchronization of the circadian clock, with BD responding more prominently to drug-induced resynchronization than the matched control HDFs. Additionally, it was determined that genotype can predict the lithium-induced rhythm changes: increased period length in HDFs was associated with SNPs in the *RORA* and *PER3* genes in a diagnosis-independent fashion. Importantly, SNPs in both of these genes have been previously identified as potential BD, anti-depressant response and post-traumatic stress disorder associated alleles (Benedetti et al., 2008; Smith et al., 2009; Garriock et al., 2010 and Logue et al., 2013).

These experiments suggest that HDFs can be used in studies bridging genetics and disease-associated endophenotypes (i.e. the inherited sensitivity to light-induced circadian rhythm disruption) (Saini et al., 2015). Furthermore, such assays could sub-stratify affective patients based on circadian rhythm status, and thus open the door for basic and clinical studies that specifically target subgroups of patients.

4.3. Studies of stress and adaptation

Stressful life events contribute to the development of psychiatric disorders (Musliner et al., 2015; Walker et al., 2008). Maladaptive stress response can lead to systemic immune, hormonal and metabolic dysregulation in the body and affective, behavioral and cognitive disturbances in the brain. According to the stress–diathesis or G*E model of MD, the hereditary risk factors will manifest in clinical symptoms when the environmental challenges exceed the individual's adaptation potential (Santarelli et al., 2014).

In our recent studies, we used HDF cultures from MD patients and matched controls to determine the genetically encoded stress vulnerability to metabolic stimuli (Garbett et al., 2015; Kálmán et al., 2014). mRNA and microRNA profiling analyses after metabolic stress exposure revealed profound transcriptional differences between the MD and control HDFs: the mRNA signature of MD patients consisted of cell cycle, apoptosis and immune function related gene sets. Furthermore, the metabolic stressors affected MD HDFs differently than controls, as 81–90% of the microRNA changes were detected only in the MD biomaterial.

These findings also suggest that different metabolic stressors lead to different transcriptome changes, thus culturing conditions and stressors for HDFs have to be selected carefully in order to appropriately study the pathophysiology of interest (Garbett et al, 2015; Kálmán et al., 2014).

4.4. Redox state studies

Oxidative stress related disturbances in SZ, BD and MD are an integral part of these diseases, yet our understanding of the underlying pathophysiology is quite limited (Bajpai et al., 2014; Reyazuddin et al., 2014). As free radicals are found in very low concentrations in human biomaterials and have short half-life (Reyazuddin et al., 2014), the majority of past experiments relied on indirect measures of oxidative stress such as DNA damage, lipid peroxidation, levels of antioxidants and enzyme sets in the blood or the brain tissue (Reyazuddin et al., 2014). Reliable, direct and meaningful measurements of oxidative stress markers are challenging even in freshly prepared plasma due to large differences between intra- and extracellular concentrations and rapid molecular transformations (e.g. rapid oxidation, disulfide exchange and redistribution) (Gysin et al., 2011). Thus, functional peripheral assays in HDFs are better suited to assess both the oxidative status and the anti-oxidative reserve capacities of the cells.

A good example of this is the research performed by *Do et al.* who studied the redox homeostasis in SZ patients by combining neuroimaging, blood and cerebrospinal fluid assessment, genetic testing and HDF functional assays (Gysin et al., 2007; Tosic et al., 2006; Do et al., 2000). Their study, using patient HDFs expanded on previously reported findings that 1) glutamate-cysteine ligase (GCL) is the rate-limiting enzyme of reduced glutathione (GSH) synthesis, which is one of the main antioxidant mechanism across various tissues (Meister, 1995), 2) genetic variants of the GCLM-subunit appear to be associated with greater risk to SZ (Tosic et al., 2006), and 3) *in vivo* and postmortem studies reported decreased GSH levels in the SZ brain (Yao et al., 2006; Do et al, 2000). The redox homeostasis of SZ HDFs (measured by GSH and GCL levels) was suboptimal even under standard culturing conditions and, when exposed to oxidative stress, HDFs from SZ patients were unable to appropriately adapt and increase GCL activity in response to the environmental challenges (Gysin et al., 2007). Notably, this antioxidant deficit had widespread consequences under stress (Gysin et al., 2009; Fournier et al, 2014) and could also be observed in the blood of patients carrying a high-risk GCL genotype who also had plasma thiol alterations (Gysin et al., 2011).

4.5. Age-related studies

The combined data argue that oxidative stress and inflammation, elevated stress hormones, subsequent insulin resistance, dyslipidemia, premature telomere shortening, mitochondrial dysfunction and multiple other factors contribute to enhanced systemic and brain ageing (Liu et al., 2014; Wolkowitz et al., 2010). At a cellular level, aging is associated with a loss of division potential (replicative senescence) and increased apoptotic rate. Unlike immortal and genetically modified cell line systems the dividing HDFs show natural aging and reflect the biological age of donors, providing a platform to study the effects of genetic and environmental factors on cellular senescence (Tigges et al., 2014).

Although the term ‘dementia praecox’ is no longer in use (McGlashan, 2011), there are indications that SZ is at least partially a systemic disorder accompanied by accelerated molecular aging (Shivakumar et al., 2014). During the course of the illness, the premature onset of age-related pathophysiological changes mentioned above appear to affect both the brain and the peripheral tissues (reviewed in Kirkpatrick et al., 2008 and Shivakumar et al., 2014). Previous results demonstrated accelerated aging-related processes in HDF cultures from SZ patients, which encompassed reduced growth and proliferation rate (Wang et al., 2010), decreased adhesiveness (Mahadik et al., 1994b), relative predominance of sub-G0 cells (Catts et al., 2006), increased apoptotic susceptibility, elevated pro-apoptotic caspase-3 reactivity and lower anti-apoptotic *Bcl-2* expression (Gassó et al., 2014). These combined findings indicate that the observed molecular similarities between SZ and aging could and should be investigated in HDF cultures, as they may be an important part of the disease pathophysiology (Batalla et al., 2015).

4.6. Data-driven studies

Psychiatric disorders arise as an interplay between the individual’s genetic makeup and environmental influences. “Hypothesis-generating” or “data-driven” approaches allow new, unanticipated discoveries, potentially revealing the consequences of known and unknown genetic factors and identifying the most affected pathways and cellular functions.

One example of HDFs used for this purpose is the study by *Garbett et al.*, which provided a detailed description of the transcriptome alterations in HDFs from patients with MD (Garbett et al., 2015). Molecular pathway analysis both on mRNA and microRNA levels revealed that apoptosis, cell-cell communication, adhesion and immune function related transcripts were significantly altered in the MD samples. These results were consistent with the previous postmortem and *in vivo* findings (Shelton et al., 2011, Hung et al., 2014), and provided further validation of transcriptome similarities between the brain and peripheral tissue of patients with MD.

The utility of HDFs in data-driven discovery efforts is not solely limited to studies of pathophysiological mechanisms in MD. In a recent analysis, Cattane et al. (2015) performed transcriptome profiling of HDFs from SZ patients and controls using DNA microarrays and RT-qPCR. The study identified 6 differentially expressed genes (*Egr1*, *Fos*, *Fosb*, *Hist2h2be*, *Jun* and *Tcf4*), 5 of which have been previously implicated in the pathophysiology of schizophrenia in postmortem brain, peripheral blood and genetic studies (Forrest et al., 2014; Kurian et al., 2011; Kyosseva, 2004). It is also notable that this study found that *EGR1* levels were correlated in the peripheral blood cells and HDFs from the same donors.

4.7. Studies of pharmacological agents

To date, the majority of studies of psychotropic drugs effects utilized control, immortalized or non-human fibroblasts (e.g. Lauth et al., 2010; Sugden et al., 2010; De Filippi et al., 2007). However, patient HDFs deserve a much greater consideration as models for testing pharmacological agents and responses: (1) In the context of precision/personalized medicine, patient-derived HDF lines could be successfully used to predict treatment

response to lithium in BP patients (McCarthy 2013a). (2) Self-sustaining HDF cell lines provide virtually unlimited source of experimental material, enabling high-throughput screening assays for identification of novel therapeutic compounds (Bae et al., 2015; Kubben et al., 2015). 3) This *in vitro* model system is also useful for identifying unwanted side effects and toxicity of known psychotropic drugs, such as antidepressant-caused cellular damage (Cordero et al., 2009), lithium and valproic acid-caused circadian clock alterations (Johansson et al., 2011a), or antipsychotic agent modulated aminoacid transport (Bongiovanni et al., 2013).

5. Similarities between HDF and CNS cells

Neurons and glia are both affected in psychiatric disorders and both can be considered valid therapeutic targets (Eroglu et al., 2010; Sanacora and Banasr, 2013). Interestingly, glia and HDF show striking similarities in several aspects.

1. Glia generate extracellular matrix (ECM) consisting of hyaluronic acids, glycoproteins and proteoglycans (Faissner et al., 2010). Although ECM is tissue specific, the main components and the cell-matrix dynamics show high similarity throughout various tissues (Naba et al., 2015). The roles of ECM are many: ECM determines structural plasticity and adaptation, modulates inter- and intracellular signaling, ion levels and transmits survival or death/survival signals (Gundelfinger et al., 2010). Postmortem, neuroimaging and genetic studies of SZ, MD and BD all suggest neurodevelopmental disturbances, which might be highly dependent on the extracellular environment (Berretta et al., 2015; Gong and He, 2015; Gurung and Prata, 2015). It has been also suggested that both the composition and the turnover of ECM are likely contributors to the development and progression of psychiatric disorders (Lubbers et al., 2014). For example, the reelin/Dab1 molecular pathway, which is triggered in the ECM, is implicated in corticogenesis and the neurobiology of SZ and BD (Iafrafi et al., 2014; Ovadia and Shifman, 2011). Clearly, HDFs can provide valuable information about reelin-induced signal transduction (Leeb et al., 2014), and the similar ECM-generating potential of HDFs and glia might allow mechanistic ECM studies on HDF systems that might provide important disease insights.
2. Glia provide antioxidant defense in the CNS and closely cooperate with neurons for GSH synthesis (Bélanger et al., 2011). Postmortem and peripheral biomarker studies reveal a diminished ability to maintain redox homeostasis in psychiatric disorders (Bajpai et al., 2014; Reyazuddin et al., 2014). In addition, HDF cultures obtained from SZ and MD patients show impaired GSH regeneration (Gysin et al., 2007; 2009; Tosic et al., 2006; Cohen et al., 1986; Gibson et al., 2012; Ranjekar et al., 2003). Therefore, the decreased oxidative resilience in HDFs is potentially mimicking a dysfunction that occurs in glial cells in the brains of patients with SZ and MD.
3. Neurons have a narrow metabolic spectrum and rely on glia in almost every metabolic process (Brown et al., 2014; Lundgaard et al., 2014). Energy storage and supply and lipid homeostasis of the brain (fatty acid oxidation, cholesterol

biosynthesis and trafficking) is primarily driven by astrocytes (Bélanger et al., 2011; Dietschy and Turley, 2004). Recent study of HDF from patients with MD revealed a disease-specific response to lipid deprivation (Garbett et al., 2015b), suggesting that this molecular endophenotype might be related to glial cell deficits in subjects with MD.

4. In addition to microglia, astrocytes also actively participate in the inflammatory and immune response, and they contribute to these processes by secretion of many auto- and paracrine factors (reviewed by Lee and MacLean, 2015). Prolonged neuroinflammation with glial involvement is a key step in the progression of multiple psychiatric diseases (Leonard, 2007; Müller et al., 2012). Consequently, altered expression of immune and cell-cell communication molecular pathways in HDFs from subjects with MD and SZ (Cattane et al., 2015; Garbett et al., 2015b), as well as BD specific changes in the basal and cytokine-induced tryptophan-kynurenine metabolism (Brown et al., 2014; Johansson et al., 2013a) may reflect disrupted glial inflammatory functions in the brains of diseased individuals.
5. Growth factors coordinate cell proliferation, migration, survival and apoptosis, synapse formation and axonal guidance (Terwisscha et al., 2013). Additionally, two recent meta-analyses showed that serum BDNF is decreased in first episodic psychotic patients (Toll and Mané, 2015) and serum NGF is lowered in MD patients (Chen et al., 2015). Importantly, recent HDF studies by Palazzo et al. (2012) revealed that HDF express BDNF, NGF, neurotrophin-3 (NTF3) and NTF4 and their respective receptors. Thus, HDF experiments might allow testing for how genetic variants of growth factors contribute to acquired vulnerability to psychiatric disorders.

6. Conclusions

The expanding literature during the last several decades suggests that the patient-derived HDF model is a valuable platform for developing novel molecular biology methods and represents a useful cellular system for studying the molecular basis of psychiatric disorders. The value of HDFs is based on ease of acquiring/establishing of the cell lines from patients, sharing molecular similarities with cells from the CNS, and the ability to be propagated without additional genetic manipulations. HDFs also facilitate our understanding of brain disorders by allowing us to examine similarities between the *in vitro* observations and pathophysiology of the CNS, and by providing the arena for investigating G*E interactions, signal transduction and metabolic dysfunctions. Additionally, the HDF model can be instrumental in identifying brain disease biomarkers and thus emphasize the organic aspects of neuropsychiatric disorders. Due to these characteristics, in the near future HDFs might provide seminal contribution to pharmacogenetics and individual therapeutic strategies used in precision/personalized medicine.

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Abbreviations

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

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HIGHLIGHTS

- Patient derived human dermal fibroblasts (HDFs) are a widely used *in vitro* model for multifactorial psychiatric disorders.
- HDF model provides an invaluable platform for *in vitro* experimentation with living patient biomaterial.
- HDFs greatly contribute to the understanding of the disease related cell function abnormalities.
- HGFs reveal deviations in signal transduction, redox homeostasis, circadian rhythms, gene*environment interaction, etc.
- HDF studies uncover disease traits and biomarkers and contribute to developing potential therapeutic strategies.

“OMICS” STUDIES

- epigenome
- transcriptome
- proteome
- metabolome

DRUG RESPONSE STUDIES

- case-control studies
- personalized medicine (individual response)

FUNCTIONAL STUDIES

- viability
- aging
- stress response
- interactome
- gene regulation
- signal transduction
- metabolism
- G*E interaction
- ECM studies
- iPSC, iNC generation

Figure 1.

Utility of human dermal fibroblasts in neuropsychiatric research (iPSC – induced pluripotent stem cell; iNC – induced neural cell; ECM – extracellular matrix; G*E – gene * environment interaction)

Figure 2.

Number of publications utilizing human dermal fibroblast cultures for studies of psychiatric disorders between 1970 and October 2015. Note the increased number of publications within the last five years.

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

Table 2

The advantages and limitations of human dermal fibroblast (HDF) cultures as *in vitro* model of psychiatric disorders (based on Auburger et al., 2012 and Connolly, 1998)

<p>Advantages</p> <ul style="list-style-type: none"> • easy to obtain, transport, culture and store • high sample volume • feasibility of well-matched case–control and within subject control studies • trophic factors or genetic modification are not necessary to maintain the cell line • primary cell cultures with functional and genetic homogeneity (better signal/noise ratio) • enables personalized/precision medicine studies and allows testing personalized drug treatment response • express many of the same receptors and signaling pathways as neurons • synthesize and respond to multiple auto-, para- and endocrine factors • model amenable to stimulation and genetic manipulation • lose epigenetic modifications and <i>in vivo</i> effects after 5 passages • show natural <i>in vivo</i> and <i>in vitro</i> ageing • can be used for generation of iPSCs and iNCs
<p>Limitations</p> <ul style="list-style-type: none"> • cultures are a mixture of keratinocytes/fibroblasts in early passages (before P5) and proliferating/postmitotic cells in late passages (after P20) • proliferation rate, confluent growing and cell senescent might bias inter- and intragroup variability • susceptible to environmental influences • cultured cells grow on artificial surfaces • lack the variety of physiological, <i>in vivo</i> signals • the age of the donor might affect cell viability • HDFs differ from neurons in multiple relevant features, including synapse formation, division, ion channel expression, excitability, neurotransmitter release and glial interaction.

iPSC: induced pluripotent stem cell; iNC: neural cell induced from iPSC or directly from postmitotic somatic cell

Table 3

Supplemental Material

Human dermal fibroblast studies in psychiatric disorders

Research Focus	Psychiatric Disorder	Findings	Reference
Receptor Profile and Signaling Pathway			
muscarinic cholinergic receptors	affective disorders	increased density of binding sites in patients and their affected or healthy relatives	Nadi et al., 1984
	ADHD	decreased B _{max}	Johansson et al., 2013
serotonin 2A receptor	MD	decreased receptor coupled phosphoinositide response in melancholic MDD	Akin et al., 2004
β2 receptor signaling	BD	NSD in receptor coupled cAMP synthesis	Berettini et al., 1987
	MD	decreased cAMP induced PKA activity	Shelton et al., 1996
cAMP/PKA signaling	MD	decreased basal and cAMP-stimulated PKA activity, especially in melancholic subgroup	Shelton et al., 1999
	MD	reduction in the B _{max} of cAMP binding to PKA	Manier et al., 2000
	MD	reduced PKC dependent CREB phosphorylation; decreased PKA activity correlated with Hamilton-D score	Akin et al., 2005
	BD	increased cAMP induced CREB response	Gaspar et al., 2014
glucocorticoid receptor	MD	NSD in glucocorticoid binding	Wassef et al., 1992
Enzyme Activity			
transketolase	AUD and their offspring	increased K _m	Mukherjee et al., 1987
kynurenine pathway	SZ, BD	increased KYNA and 3-HK production; increased 3-HK/KYNA ratio after cytokine; NSD in enzyme levels	Johansson et al., 2013
monoamine oxidase -A, -B and catechol-O-methyl transferase activity	SZ	NSD	Groshong et al., 1978 Ramchand et al., 1995
	BD	NSD	Breakefield et al., 1980
	ASD Tourette syndrome	NSD	Giller et al., 1980
	AUD	NSD	Giller et al., 1984
Metabolism			
carbohydrate metabolism	SZ	increased glucose oxidation	Ramchand et al., 1995
	episodic schizoaffective disorder	NSD in one-carbon metabolism enzymes	Bruinvels et al., 1988
	episodic psychotic patients	NSD in serine-folate metabolism enzyme set	Fekkes et al., 1986
cell membrane phospholipid composition	SZ	lower phospholipids, phosphatidylserine,	Mahadik et al., 1994a

Research Focus	Psychiatric Disorder	Findings	Reference
		phosphatidylinositol, phosphatidylethanolamine, cholesterol fraction	
	SZ	increase in polyamines	Ramchand et al., 1994
	SZ	decreased total n-3 fatty acid; NSD in arachidonic acid	Mahadik et al., 1996a
	SZ, BD	decreased eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA); NSD in arachidonic acid	Ranjekar et al., 2003
	BD	NSD in total n-3 fatty acids and arachidonic acid	Mahadik et al., 1996a
utilization of essential fatty acids	SZ	NSD	Mahadik et al., 1996b
Mitochondria			
mitochondrial morphology and distribution	BD	altered mitochondrial morphology and distribution; abnormal cytochrome C distribution; NSD in cytochrome C level and ATP production	Cataldo et al., 2010
Membrane Transport			
tyrosine	SZ	decreased $V_{\max}$; NSD in K_m	Hagenfeldt et al., 1987 Bongiovanni et al., 2013
	SZ	decreased $V_{\max}$ and K_m	Ramchand et al., 1996 Flyckt et al., 2001
	SZ	decreased transport due to the L-system	Olsson et al., 2006
	BD	decreased $V_{\max}$; NSD in K_m	Persson et al., 2009
	ADHD	NSD	Johansson et al., 2011
	ASD	increased K_m	Fernell et al., 2007
tryptophan	ADHD	decreased $V_{\max}$ and K_m	Johansson et al., 2011
	BD	NSC	Persson et al., 2009
serine, folate	psychotic patients	NSD in $V_{\max}$ and K_m	Fekkes et al., 1986
alanine	ADHD	increased $V_{\max}$	Johansson et al., 2011
	AD	increased $V_{\max}$	Fernell et al., 2007
lithium	BD, SZ	NSD	Hitzemann et al., 1988 Breslow et al., 1985
Cell Growth, Proliferation and Apoptosis			
apoptotic susceptibility	SZ	increased apoptotic susceptibility; higher caspase-3 activity; decreased BCL2	Gassó et al., 2014
	SZ	increased apoptotic susceptibility; <i>in vitro</i> apoptotic markers correlate with volumetric and metabolic brain measures	Batalla et al., 2015
	SZ	more sub-G0 cells;	Catts et al., 2006

Research Focus	Psychiatric Disorder	Findings	Reference
cell viability, proliferation and growth		attenuated caspase-3 response	
	BD	NSD in apoptotic rate	Cataldo et al., 2010
	SZ	NSD	Cohen et al., 1987 Gassó et al., 2014
	SZ	reduced growth rate	Mahadik et al., 1991
	SZ	cell-cycle associated transcriptome and proteome changes; decreased proliferation rate	Wang et al., 2010
	SZ	decreased adhesiveness and fibronectin synthesis	Mahadik et al., 1994b
cytoskeleton	BD	NSD in actin or tubulin cytoskeleton	Cataldo et al., 2010
Stress Resilience and Adaptation			
sensitivity to oxidative stress	SZ	impaired capacity to synthesize GSH	Gysin et al., 2007 Tosic et al., 2006 Gysin et al., 2009
	SZ	9 protein is affected by the impaired antioxidative protection in genetically predisposed SCZ patients	Gysin et al., 2009
	SZ	NSD in SOD activity	Cohen et al., 1986
	MD	increased GS reductase; decreased antioxidant reserve capacity; NSD in GSH	Gibson et al., 2012
	SZ	decreased SOD, CAT and GSH peroxidase; NSD in membrane lipid peroxidation	Ranjekar et al., 2003
	BD	decreased SOD, CAT; NSD in GP	Ranjekar et al., 2003
metabolic stress response	MD	26–33% of the mRNA and 81–90% of the microRNA stress response were MDD specific	Garbett et al., 2015a
metabolome after oxidative stress	acute psychosis	extracellular matrix, arginine metabolism, plasma membrane alterations; deficit of lysolipid response	Fournier et al., 2014
sensitivity to DNA-damaging agents	SZ, MD, BD	NSD	Cohen et al., 1989
Transcriptome			
transcriptome	SZ	434 differentially expressed transcripts, NSD after multiple comparison test	Matigian et al., 2008
	SZ	6 genes upregulated	Cattane et al., 2015
	MD	139 genes affected (114 downregulated); 38 microRNAs changed	Garbett et al., 2015b
	Fragile X syndrome	disease specific protein synthesis and phosphorylation profile	Kumari et al., 2014
Circadian Rhythm			
period length	BD	NSD in period length and clock gene expression rhythmicity	Yang et al., 2009
	BD	NSD	Bamne et al., 2013
	BD	longer period length; NSD in amplitude genotype-determined lithium response	McCarthy et al., 2013a

Research Focus	Psychiatric Disorder	Findings	Reference
	AUD	period correlates inversely with symptom severity; NSD in contrast with CNT	McCarthy et al., 2013b
lithium- response	BD	calcium channel genes modulate the effect of lithium on the circadian rhythm	McCarthy et al., 2015

Abbreviations used: 3-hydroxy-kynurenine (3-HK), attention deficit hyperactivity disorder (ADHD), autism spectrum disorder (ASD), alcohol use disorder (AUD), maximal binding capacity ($B_{\max}$), bipolar disorder (BD), cyclic adenosyl monophosphate (cAMP), catalase (CAT), glutathione peroxidase (GP), control, healthy subjects (CNT), glutathione (GSH), substrate affinity (K_m), kynurenic acid (KYNA), major depressive disorder (MD), no significant difference (NSD), protein kinase A (PKA), schizophrenia (SZ), superoxide dismutase (SOD), maximal transport velocity ($V_{\max}$).