Human Dermal Fibroblast: A Promising Cellular Model to Study Biological Mechanisms of Major Depression and Antidepressant Drug Response

Pierre Mesdom¹, Romain Colle¹,², Elise Lebigot³, Séverine Trabado⁴,⁵, Eric Deflesselle¹,⁶, Bruno Fève⁷, Laurent Becquemont¹,⁵, Emmanuelle Corruble¹,² and Céline Verstuyft¹,⁵,*

¹Université Paris-Saclay, UVSQ, Inserm, CESP, Team MOODS, 94270, Le Kremlin-Bicêtre, France; ²Service Hospitalo-Universitaire de Psychiatrie de Bicêtre, Hôpitaux Universitaires Paris-Sud, Assistance Publique-Hôpitaux de Paris, Hôpital de Bicêtre, Le Kremlin Bicêtre, F-94275, France; ³Service de Biochimie Pharmaco-Toxicologie, APHP, Hôpitaux Universitaires Paris-Sud, Hôpital de Bicêtre, Le Kremlin Bicêtre, F-94275, France; ⁴Université Paris Saclay, Faculté de Médecine Paris Saclay, Le Kremlin Bicêtre, F-94276, France; ⁵Institut National de la Santé et de la Recherche Médicale UMR-S U1185, Le Kremlin Bicêtre, F-94276, France; ⁶Service de Génétique moléculaire, Pharmacogénétique et Hormonologie, Assistance Publique-Hôpitaux de Paris, Hôpitaux Universitaires Paris-Sud, Hôpital de Bicêtre, Le Kremlin Bicêtre, F-94275, France; ⁷Département de Médecine Générale, Université Paris Saclay, Faculté de Médecine Paris-Sud, Le Kremlin Bicêtre, F-94276, France; ⁸Sorbonne University-Saint-Antoine Research Center, UMR-S938, Hospitalo-Universitary Institute of Cardiometabolism ICAN, Department of Endocrinology, Sant-Antoine Hospital, APHP, F-75012, Paris, France

Abstract: Background: Human dermal fibroblasts (HDF) can be used as a cellular model relatively easily and without genetic engineering. Therefore, HDF represent an interesting tool to study several human diseases including psychiatric disorders. Despite major depressive disorder (MDD) being the second cause of disability in the world, the efficacy of antidepressant drug (AD) treatment is not sufficient and the underlying mechanisms of MDD and the mechanisms of action of AD are poorly understood.

Objective: The aim of this review is to highlight the potential of HDF in the study of cellular mechanisms involved in MDD pathophysiology and in the action of AD response.

Methods: The first part is a systematic review following PRISMA guidelines on the use of HDF in MDD research. The second part reports the mechanisms and molecules both present in HDF and relevant regarding MDD pathophysiology and AD mechanisms of action.

Results: HDFs from MDD patients have been investigated in a relatively small number of works and most of them focused on the adrenergic pathway and metabolism-related gene expression as compared to HDF from healthy controls. The second part listed an important number of papers demonstrating the presence of many molecular processes in HDF, involved in MDD and AD mechanisms of action.

Conclusion: The imbalance in the number of papers between the two parts highlights the great and still underused potential of HDF, which stands out as a very promising tool in our understanding of MDD and AD mechanisms of action.

Keywords: Human dermal fibroblasts, human skin fibroblasts, major depression, major depressive episode, antidepressant drug, cellular model.

1. INTRODUCTION

Human dermal fibroblasts (HDF) originate from mesenchymal cells. They are located in particular, in the dermis and are the main actors of extracellular matrix (ECM) production and homeostasis. In response to skin injury, HDF acquire myofibroblast phenotype characterized by increased proliferation, migration and ECM synthesis activity. Thereby, HDF plays a central role in skin wound healing [1, 2].

After a poorly invasive skin biopsy, in vitro cultured HDF adhere to the bottom of the culture dish and proliferate. Isolation and culture of these cells have been well described [3], and can lead to a cell bank of about 15 to 20 million cells from a 4 mm² skin biopsy after 3 passages (about 35
days of culture). Interestingly, HDF do not need immortalization steps before the culture, maintaining the native genetic background of the patient [4-6]. Moreover, after several passages, HDF loose the epigenetic signature related to hormonal, nutritional and treatment state of the patient [7-9]. Thus, HDF represent an interesting tool to relate genetics to pathophysiology and to study in vitro therapeutic response [10-12]. Moreover, this model served for the diagnosis and investigation of diseases. For instance, HDF were used to study impairments in the wound healing process [13], skin fibrosis propensity in response to radiotherapy [14], oxidative phosphorylation impairment [15], and evaluation of the presence or the risk of metabolic diseases in patients [16, 17]. HDF were also used to study neurodegenerative diseases such as Parkinsons [18] and Alzheimers [19, 20].

In a recent review [9], the different human primary celllar models used in the study of mental disorders were compared according to their ability to mirror brain cells and their efficiency for research. These characteristics underlined the high potential of HDF in psychiatry research [9]. When compared to the other main in vitro human models which are leukocytes, immortalized human lymphocytes (lymphoblastoid cells), olfactory epithelium, induced pluripotent stem cells and induced neural cells, HDF are a good compromise to study brain-related diseases [9]. Several investigations of HDF from patients with mental disorders (bipolar disorder, major depression disorder and schizophrenia) have evidenced biological impairments such as oxidative homeostasis dysfunctions [21-23], inflammation [24] and modified metabolic activities [25]. In the context of mental disorders studies, HDF have been used as a sensor of these peripheral biological impairments [9], as well as a reflection of brain cell biological mechanisms (circadian rhythms, response to psychotropic drugs, pathways such as serotoninergic and adrenergic signaling) [26-29]. However, until now, only few neurobiological and biological mechanisms of Major Depressive Disorder (MDD) have been assessed in HDF.

Considering potential models for MDD study is of major interest, because this mental disorder is the second cause of disabilities worldwide [30], and biological mechanisms implicated in this disorder remain unclear [31]. Furthermore, the efficacy of antidepressant drug (AD) is still insufficient with only one-third of patients in remission after 3 months of treatment [32], and considering the delayed action after initiating treatment [33]. Therefore, biological understanding of AD treatment mechanisms of action is needed, to identify biomarkers that may help choose the best treatment in a personalized medicine approach [34-36].

The use of HDF as a cellular model from patients with a major depressive episode (MDE patients) has already been described in two reviews from 2000 and 2016 [9, 29]. However, the first one is not systematic and only reviewed the papers before 2000, and the second one did not focus on MDD but also reviewed papers related to other mental disorders. Also, these two reviews did not present the potential of HDF in the MDD study. This potential is defined as the presence of many molecules and compounds of interest regarding MDD pathophysiology and AD mechanisms of action, described in HDF but not yet investigated in MDE patients’ HDF.

2. OBJECTIVES

The first part is a systematic comprehensive literature review listing works that used HDF from MDE patients as a model to study MDD, and works that used HDF from AD non-responder patients as compared to responders. The second part highlights the great potential of HDF as a tool to study MDD and AD mechanisms. To demonstrate this potential, we assessed biological mechanisms both present in HDF and relevant regarding biology and neurobiology of MDD and AD treatment mechanisms of action and AD response, which have not yet been studied in HDF from MDE patients or in the context of depression. This part highlights the potential of HDF as a human cellular, non-invasive and relevant model for studying MDD pathophysiology, AD treatment response, and AD treatment mechanisms of action.

3. METHODS

A systematic Pubmed search following PRISMA guidelines was conducted. For the first part of our review, MeSH criteria were used with the following key words: “depressive disorder OR major depressive disorder OR depression AND fibroblast AND human” and a classical PubMed search with the following key words: “MDD OR MDE OR major depression OR depression AND human skin fibroblast”. Papers that compared HDF from MDD patients and controls were assessed. A paper was found in the references from our selected articles (referred as “cross-reference” in Fig. 1). We referred to PRISMA guidelines to establish the chart (Fig. 1).

For the second part of the review, reference was given to the relevant biological pathways regarding neurobiology of AD mechanisms. Therefore, several Pubmed searches were performed by the key words listed in Table 1. Only articles that dealt with human AND dermal AND fibroblasts AND the presence of at least one protein belonging to the studied pathways (illustrated by column 4 of Table 1) were retained. Through this methodology, papers in which HDF were treated with an antidepressant were also selected. These papers are cited in paragraph 2.2.

4. RESULTS

4.1. HDF: A Model Already used to Study MDD Pathophysiology and AD Response

HDF cellular model has already shown successful results in the research on MDD. 16 from the 18 referenced studies identified differences between HDF from MDE patients and healthy controls. Among these studies, the oldest used HDF to reflect CNS cells in accordance with the central pathophyslogic hypothesis of MDD. However, more recently, the expansion of high-throughput screening technologies (transcriptomic and metabolomic) resulted in a regain of HDF as a peripheral sensor of metabolic changes associated with MDD (Table 1).

4.1.1. HDF: A Human Cellular Model for MDD

4.1.1.1. Monoamine Pathways

Monoamine pathways are among the most studied in the MDD research field. Most of the studies focusing on monoamine pathways in MDE patients’ HDF were performed by
Fig. (1). Systemic research methodology for the first part. Legend: Papers published from no limit in the past until December 2018 were selected.

Table 1. Systemic research methodology for the second part.

| System           | Research | Keywords                                                                 | Available Papers | Retained Papers |
|------------------|----------|--------------------------------------------------------------------------|------------------|-----------------|
| Serotonin        | PubMed   | Human skin fibroblast AND serotonin                                      | 53 papers        | 14 papers        |
| Norepinephrine   | PubMed   | ("Skin" AND "Humans"[Mesh] AND "Fibroblasts"[Mesh]) AND ("Adrenergic Agents"[Mesh] OR "Adrenergic beta-Antagonists"[Mesh] OR "Adrenergic alpha-Antagonists"[Mesh] OR "Receptors, Adrenergic, beta"[Mesh] OR "Receptors, Adrenergic, alpha"[Mesh] OR "Receptors, Adrenergic"[Mesh]) | 24 papers        | 18 papers        |
| Dopamine         | PubMed   | Human skin fibroblast AND dopamine                                        | 40 papers        | 6 papers         |
| Acetylcholine    | PubMed   | ("Skin"[Mesh] AND "Humans"[Mesh] AND "Fibroblasts"[Mesh]) AND ("Cholinergic Agonists"[Mesh] OR "Receptors, Cholinergic"[Mesh] OR "Muscarinic Agonists"[Mesh] OR "Nicotinic Agonists"[Mesh] OR "Receptors, Nicotinic"[Mesh] OR "Receptors, Muscarinic"[Mesh]) | 17 papers        | 15 papers        |
| Glutamate        | PubMed   | "Fibroblasts"[Mesh] AND "Humans"[Mesh] AND ( "Glutamate"[Mesh] OR "Receptors, Metabotropic Glutamate"[Mesh] OR "Glutamate Plasma Membrane Transport Proteins"[Mesh] OR "Receptors, Glutamate"[Mesh] OR "Glutamate Synthase"[Mesh] OR "Glutamate Dehydrogenase"[Mesh] OR "Receptors, Ionotropic Glutamate"[Mesh]) | (463 papers)     | (8 papers)       |
| GABA             | PubMed   | "Human skin fibroblast AND GABA"                                         | 18 papers        | 6 papers         |
| Neurotrophins    | PubMed   | "Human dermal fibroblast AND neurotrophins"                              | 46 papers        | 5 papers         |
| HPA axis         | PubMed   | ((("Humans"[Mesh]) AND "Skin"[Mesh]) AND "Fibroblasts"[Mesh]) AND ("Hypothalamic Hormones"[Mesh] OR "Pituitary Hormone-Releasing Hormones"[Mesh] OR "Receptors, Pituitary Hormone-Regulating Hormone"[Mesh] OR "Hypothalamo-Hypophyseal System"[Mesh]) | 46 papers        | 19 papers        |
| HPA axis         | PubMed   | "human skin fibroblast AND hypothalamic pituitary adrenal axis"           | 16 papers        | 2 papers         |
| Circadian rhythm | PubMed   | "human dermal fibroblast AND clock gene"                                 | 8 papers         | 2 papers         |

Abbreviations: We selected papers published from no limit in the past until December 2018.
the same team from the Vanderbilt University School of Medicine. They demonstrated that HDF responds to beta-2-adrenoceptor stimulation following isoproterenol treatment [29]. They also pointed out that the beta-2-adrenoceptor-dependent cAMP / PKA (cyclic adenosine monophosphate; protein kinase A) activation and cAMP response element-binding protein (CREB) phosphorylation were weak in MDE patients [38], and more specifically in melancholic patients [39, 41]. Then, they identified a blunted serotonin 2A (5-HT2A) activation after serotonin treatment, in HDF from melancholic MDE patient [7]. This pathway involves several proteins such as protein kinases A and C and the phosphorylation of CREB, which are reduced in melancholic MDE patients. However, these were preliminary results from one study and relatively small sample size (10 controls, 10 MDE patients without melancholic features and 8 MDE patients with melancholic features) (Table 2).

4.1.1.2. HDF as a Tool to Assess the Functionality of MDD-associated Genetic Modifications

To the best of our knowledge, only one study used HDF to assess the functionality of genetic polymorphisms. In this study, the Catechol-O-methyltransferase (COMT) Val158Met genetic polymorphism and its potential effect on COMT functionality were investigated in HDF from MDD patients [43].

4.1.1.3. miRNA Brain Regulation and Cellular Plasticity

A recent study [47] highlighted differential micro RNA (miRNA) expression between MDE patients and healthy controls. Among miRNA differentially expressed, miR22 regulates serotonin 5-HT2C receptor [47], and miR22 and miR132 are involved in the regulation of the pro-neurogenic neurotrophin brain-derived neurotrophic factor (BDNF).
miR132 upregulates BDNF in a CREB-dependent manner and is upregulated in MDE patients whereas miR22 represses this neurotrophin [51-53]. CREB is a transcriptional factor controlling several genes encoding proteins involved in brain cellular plasticity, including the neurotrophin BDNF. It has already been established that CREB phosphorylation and activation are reduced in the hippocampus and prefrontal cortex of depressed patients who committed suicide [54]. CREB phosphorylation and activation pathway have been studied in HDF from melancholic MDE patients and are decreased as compared to healthy controls [41]. According to the previously cited study [47], miR22 is down-regulated and miR132 is upregulated in HDF from MDE patients as compared to healthy controls. These results argue toward increased plasticity in MDE HDF. Would this represent a compensatory mechanism to face the lack of plasticity and neurogenesis associated with MDD? Further studies will be necessary to refine the understanding of the mechanisms controlling cellular plasticity and involved in the pathophysiology of MDD.

### 4.1.1.4. Oxidative Stress

In HDF, miRNA and mRNA signature in response to oxidative stress conditions have been compared between 16 MDE patients and 16 matched healthy controls [25]. The results show that HDF from MDE patients present a different response to \textit{in vitro} oxidative stress conditions as compared to controls [25]. The difference is characterized by an increase in the expression of genes regulating the cell cycle, apoptosis, migration and proliferation pathways in patients’ HDF, interpreted as a defective adaptive response regulation.

In another paper [22], in response to \textit{in vitro} oxidative stress conditions (by \textit{in vitro} galactose treatment), HDF from MDE patients were less able to adapt as compared to those from healthy controls [22]. Increased oxidative stress in MDE patients was independent of glutathione reductase and glutathione concentration [22], meaning that the observed difference in oxidative stress is not related to diminished antioxidant enzyme activity. It is assumed that it is rather linked to other metabolic dysregulations, which can be studied in HDF such as mitochondrial activity, oxidative and nitrostative stress (O&N stress) production and the nitric oxide synthase (NOS) activity. The NOS is an interesting target which is known to be at the crossroad of several mechanisms such as inflammation, oxidative stress and cellular plasticity [55] (Fig. 2). This enzyme has not yet been studied in HDF from MDE or MDD patients but represents a study potential detailed in the 4.2 section.

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**Fig. (2).** HDF potential in the study of MDD related Inflammation, O&N stress and CNS molecular and cellular dysregulations. Legend: Fig. 2 illustrates the great potential of HDF as a model to study MDD related brain and peripheral impairment such as oxidative stress, inflammation, genetic related functionality and pathways dysfunctions of CNS cells. (A higher resolution / colour version of this figure is available in the electronic copy of the article).
4.1.1.5. Inflammation

Pro-inflammatory cytokines such as interleukin-6 and -1 beta (IL-6 and IL1-β) and tumor necrosis factor-alpha (TNF-α) are expressed by HDF and these cells are sensitive to extracellular inflammatory signals [56]. One study investigated HDF after in vitro treatment with the pro-inflammatory cytokine IL-6, reporting a blunted response (calculated on the expression of a set of genes usually increased by IL-6 treatment) in HDF from MDE patients as compared to healthy controls [24]. The same group identified a diminished pentraxin-3 mRNA expression in HDF from MDE patients as compared to healthy controls HDF. Pentraxin-3, a protein involved in inflammatory transduction signal, is highly expressed in response to inflammatory cytokines such as TNF-alpha, IL1-β or activation of toll-like receptors. Therefore, this study illustrated how MDE patients’ HDF investigation can contribute to the understanding of MDD pathophysiology [48].

4.1.2. HDF: A Model for the Study of AD Response Variability

To the best of our knowledge, only one study deals with AD response in HDF from AD-responder patients as compared to AD-resistant patients (defined as the failure to respond to two or more different classes of ADs and to a tricyclic AD drugs) [50]. They used HDF from a subpopulation of their cohort to study the link between PSMD13 (gene encoding a key protein in the ubiquitin-proteasome complex) polymorphism (rs3817629) and the cognate mRNA expression. They showed that the double homozygous recessive GG carrier gene patients (4%) present a greater risk of AD resistance and have a diminished PSMD13 mRNA expression in HDF [50].

4.2. HDF is a Unique and Potent Human Cellular Model for Studying MDD and AD Treatment

As highlighted by the previous chapter, HDF is a good model to study MDD pathophysiology comparing HDF from MDE patients and healthy controls. It allowed the study of transduction pathway impairments in MDE patients as well as functional investigation of genetic polymorphisms associated with depression. HDF have also been used, in one study, to explore treatment response mechanisms through the study of cells from AD responder patients as compared to those from AD resistant patients [50]. However, it is worthy to note that the first chapter of this review described a relatively small number of studies as compared to the strong interest of HDF as a cellular model for the research on MDD. Indeed, HDF present many features shared with central nervous system (CNS) cells, they express molecules that are relevant for MDD pathophysiology, together with the advantage to conserve the initial genetic background. Therefore, the second chapter reviews mechanisms or proteins present in HDF, relevant to biology and neurobiology of MDD but not yet investigated in MDE. This will highlight the great potential of HDF for understanding MDD pathophysiology and the mechanisms underlying AD response.

4.2.1. HDF as an Underused Model Regarding its Potential for the Research on MDD

HDF express many molecules (receptors, enzymes, transcription factors, …) that belong to relevant pathways regarding neurobiology and biology of MDD. These relevant pathways have already been reviewed [57], and mainly involve the monoaminergic pathway [58-60], cholinergic pathway [61-63], the gaba-ergic/glutamatergic pathway [64], the hypothalamo-pituitary-adrenal axis [65-67], the cellular plasticity [68], the circadian rhythm [57], inflammation pathways [69], and oxidative stress pathways [70] (Table 3).

4.2.1.1. Monoaminergic Pathways

Serotonin and catecholamines (dopamine, adrenaline and noradrenaline) are monoaminergic neurotransmitters. Their dysregulation has been associated with MDD [127, 128] and interestingly, several molecules belonging to monoaminergic-related pathways are present in HDF (Table 3).

An altered 5HT2A receptor signal transduction has already been shown [7] in HDF from melancholic MDE patients as compared to healthy controls. However, HDF also express other serotoninergic pathway components such as 5-HT1A, 5-HT1B, 5-HT2B, 5-HT2C and 5-HT7 receptors, the tryptophan hydroxylase (TPH) (the rate-limiting enzyme of serotonin biosynthesis) [72, 74, 129] and the monoamine oxidase-A (MAO-A) [75, 130], all identified in HDF but not yet investigated in MDE patients.

HDF express the same tryptophan transporter (L-type amino acid transporter 1 (LAT1) [131]) than the blood-brain barrier cells. It has been used to study blood-brain barrier impairment in tyrosine and amino acid transport related with mental disorder such as attention-deficit hyperactivity disorders (ADHD) [132], schizophrenia [133], bipolar disorder [134] and autism [135]. This HDF characteristic represents a potential interest in studying serotonin metabolism from tryptophan.

Alpha-1, beta-2 and beta-3 adrenoceptors are expressed in HDF (Table 2) and play a role in wound healing mechanisms [80]. Beta-2-adrenoceptors are related to neurotrophin expression via kinases and CREB activation, are present in HDF and have been investigated in only 2 studies with relatively small cohorts of MDE patients [29, 38].

Dopamine pathway has never been studied in HDF from MDE patients. However, tyrosine transport related to dopamine metabolism has been investigated in HDF from patients with other psychiatric diseases such as schizophrenia [133], bipolar disorder [134], and autism [135], as mentioned above. HDF express D1 and D2 dopaminergic receptors and tyrosine transporter (tyrosine being the dopamine precursor) [85-87] (Table 3). Moreover, HDF express several important proteins characteristic of the dopaminergic pathway such as the COMT [43], one of the main enzymes involved in catecholamine catabolism, which has been related to MDD pathophysiology [136]. Therefore, HDF represent a relevant model to study the dopaminergic pathway involvement in MDD pathophysiology.

4.2.1.2. Cholinergic Pathway

As illustrated in Table 3, HDF expressed several proteins from the cholinergic pathway, such as acetylcholine receptors (nicotinic and muscarinic) [73, 89, 137, 138] and acetylcholinesterase [92]. HDF respond to nicotinic and muscarinic agonists [90, 139]. Moreover, muscarinic binding sites seem
Table 3.  Biological mechanisms described in fibroblasts and involved in major depressive disorder and antidepressant treatment response.

| The Systems Involved in MDD and/or Antidepressant Treatment Response | Involved in Depression and Antidepressant Response | Identified in HDF | Studied in MDD HDF | Reference in HDF |
|-------------------------------------------------------------|-----------------------------------------------------|------------------|-------------------|-----------------|
| **Main System** | **Involved Proteins** | **5-HT transporter (SERT)** | **5-HT1A** | **5-HT1B** | **5-HT2C** | **5-HT2B** | **5-HT2A** | **5-HT4** | **5-HT7** | **TPH1-2** | **MAO-A** |           |
| **Catecholamines** | | | | | | | | | | | | | |
| | | | | | | | | | | | | | |
| **Serotonin** | | 5-HT transporter (SERT) | 5-HT1A | 5-HT1B | 5-HT2C | 5-HT2B | 5-HT2A | 5-HT4 | 5-HT7 | TPH1-2 | MAO-A |           |
| | | - | V' | V' | V' | V' | V' | V' | V' | V' | V' | V' | [71] |
| **Dopamine** | | Receptor D1 and D2 | COMT | Tyrosine transporter | Muscarinic receptor | Nicotinic receptor | acetylcholinesterase | AMPA | NMDA | GluR6 | EAAT1, EAAT2, and EAAT3 | Glutamate dehydrogenase | [29, 38, 79-84] |
| | | 5-HT1A | 5-HT1B | 5-HT2C | 5-HT2B | 5-HT2A | 5-HT4 | 5-HT7 | TPH1-2 | MAO-A |           | | |
| | | - | V' | V' | V' | V' | V' | V' | V' | V' | V' | V' | [71] |
| **Glutamatergic system** | | | | | | | | | | | | | |
| | | | | | | | | | | | | | |
| **Acetylcholine** | | beta-2-adrenoceptor | NET | Receptor D1 and D2 | COMT | Tyrosine transporter | Muscarinic receptor | Nicotinic receptor | acetylcholinesterase | AMPA | NMDA | GluR6 | EAAT1, EAAT2, and EAAT3 | Glutamate dehydrogenase | [29, 38, 79-84] |
| | | - | - | - | - | - | - | - | - | - | - | - | - | [71] |
| | | | | | | | | | | | | | |
| **GABAergic system** | | GAD67 | GABA transporter 1 | BDNF | NGF | NT 3,4 and 5 | P75NTR | TrkB | CRH / ACTH / POMC / α-MSH and cognate receptors | Corticotropic functionality | [106-116] |
| | | - | - | - | - | - | - | - | V' | V' | - | - | [106-116] |
| | | | | | | | | | | | | | |
| **Neurotrophins** | | | | | | | | | | | | | |
| | | | | | | | | | | | | | |
| **HPA axis** | | | | | | | | | | | | | |
| | | | | | | | | | | | | | |
| **Inflammation-metabolism** | | | | | | | | | | | | | |
| | | | | | | | | | | | | | |
| **Oxidative stress** | | | | | | | | | | | | | |
| | | | | | | | | | | | | | |
| **Circadian rhythm** | | | | | | | | | | | | | |

**Abbreviations**: V' = already published, - = not shown yet. Serotonin (5-HT), serotonin receptor (5-HTR), tryptophan hydroxylase 1 (TPH1), monoamine oxidase A (MAO-A), norepinephrine transporter (NET), Catechol-O-methyltransferase (COMT), dopamine receptor 1 and 2 (receptor D1, D2), α-amino-3-hydroxy-5-methylisoxazole-4-propionate (AMPA), N-Methyl-D-aspartic Acid (NMDA), glutamate receptor 6 (GluR6), Excitatory Amino Acid Transporter (EAAT), glutamate decarboxylase (GAD67), gamma-aminobutyric acid (GABA), brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), neurotrophin (NT), neurotrophin receptor P75 (P75NTR), P75NTR, cytokine receptor B (TrkB), corticotropin releasing hormone (CRH), adreno-corticotropic hormone (ACTH), proopiomeLANOCORTIN (POMC), alpha-melanocyte stimulating hormone (α-MSH), γ-AMP element-binding protein (CREB), glycogen synthase kinase 3 (GSK3), fibroblast growth factor 2 (FGF2), NOD-like receptor family pyrin domain containing 3 (NLRP3), period circadian regulator 2 (PER2).
to decrease in HDF from patients with affective disorders (Table 3) in comparison to controls [42]. Interestingly, HDF from the MDD patient (only one patient in the study) presents the lowest muscarinic binding capacities but further studies are needed to confirm and elucidate this phenomenon.

4.2.1.3. GABA-ergic/glutamatergic Pathway

HDF have several features of GABAAergic system. HDF respond to GABA stimulation [140, 141], but the receptors involved have not been identified yet. Another study reported the presence of GABA transporter 1 (GAT1), also known as Na- and Cl-dependent GABA transporter in HDF [142]. Moreover, the glutamic acid decarboxylase 67 (GAD67) (GABA production catalyzer enzyme) has been identified in HDF and plays a role in extracellular matrix homeostasis (hyaluronic acid and collagen production) [101]. This protein has also been related to MDD. Indeed, a study identified a decreased expression of GAD67 in the prefrontal cortex of untreated MDD patients as compared to controls [143]. At last, GABA synthesis has been investigated in HDF to relate central impairment in Huntington disease context [144], and increased GABA neurotransmission has already been reported in the brain of a preclinical model of Huntington disease [145], suggesting that GABA metabolism impairment in HDF could reflect central dysfunctions.

HDF also express glutamate pathway molecules such as glutamate dehydrogenase [100] as well as several glutamate brain transporters excitatory amino acid transporter 1, 2 and 3 (EAAT1, 2 and 3) [146, 147]. To the best of our knowledge, glutamatergic signaling impairment in HDF has not yet been studied in the MDD context. However, glutamate transport impairment in HDF served as central dysfunction sensor in the context of Alzheimer’s disease [148]. Moreover, HDF were also used as a tool to study glutamate dysfunction-related apoptosis, and could represent a marker of neuroanatomical change due to glutamate impairment in the first-episode schizophrenia [149].

4.2.1.4. Proliferation and Cellular Plasticity

Neurotrophins are key regulators of neurogenesis, neuronal survival, function and brain plasticity, which are all relevant mechanisms in neurobiology of MDD [150]. The six neurotrophins: neuronal growth factor (NGF), BDNF, neurotrophins (NT) 3, 4, 6 and 7, and their receptors: (neurotrophin receptor P75 (P75NTR) and tropomyosin receptor kinase (Trk) A, B and C are expressed in HDF [28] (Table 3).

Other key proteins in pathways involved in MDD-related cellular plasticity impairment, such as glycogen synthase kinase 3 (GSK3), CREB, Pi3K-Akt, ROS-ERK, cAMP-PKA and NOS-NO [54], are present in HDF [104, 121, 151], and some have already been studied in HDF of MDE patients [29].

4.2.1.5. Hypothalamic-pituitary-adrenal Axis (HPA)

Several studies [112, 116, 117] investigated the HPA axis in HDF. They showed that HDF can synthesize cortisol [117] and express other important HPA axis factors such as proopiomelanocortin (POMC), adrenocorticotropic hormone (ACTH) [107, 115, 152], and corticotropin releasing hormone (CRH). It has been shown that HDF treatment by cortisol reduces cell proliferation [118, 119]. Moreover, HDF express melanocortin receptor 1 (MCR1) [109-111, 113] as well as CRH receptors [108, 114]. HDF were also used to study the functional consequences of a glucocorticoid receptor gene mutation [153]. Therefore, HDF could be used as a model to study HPA axis dysregulation in MDD pathophysiology.

4.2.1.6. Metabolism-inflammation Pathways

MDD is a multifactorial disease characterized by central as well as peripheral dysfunctions. HDF represent both a potential model of central cells and a sensor of peripheral dysregulation. Noteworthy, depression and obesity are associated and share biological pathway dysregulations such as leptin increased expression, reduced insulin sensitivity and chronic inflammation [123, 154]. Interestingly, HDF expressed the leptin receptor and are sensitive to inflammatory cytokines [24]. Moreover, HDF express nucleotide-binding oligomerization domain (NOD)-like receptor 3 (NLRP3), a protein involved in inflammesome regulation [124]. NLRP3 has already been studied in peripheral blood mononuclear cells (PBMC) of MDE patients [69], but NLRP3 study in HDF, a more stable model, would provide interesting supplemental information.

4.2.1.7. Oxidative Metabolism

Oxidative homeostasis is a precarious balance between reactive oxygen species (ROS) production and antioxidant mechanisms [155]. CNS cells require a lot of energy to ensure their function and are therefore high O2 consumers and exposed to oxidative stress for many reasons already reviewed [156]. Oxidative homeostasis dysregulation results in an excess of ROS leading to an increase in lipid peroxidation, protein misfolding and DNA damage [157]. Psychiatric disorders, as well as neurodegenerative diseases, have been associated with central oxidative stress [155, 158]. MDD pathophysiology has also been associated with oxidative stress as already reviewed [159] and meta-analyzed [160]. Among the oxidative mechanism associated with MDD, the increased nitric oxide and nitric oxide synthase (NOS) represents a hinge mechanism between inflammation, oxidative stress, cerebral plasticity and synaptic functionality [55]. Under physiological condition, NOS mechanism participates in brain homeostasis, regulating neuron proliferation, differentiation and survival [161], and modulating BDNF expression via nitric oxide (NO) production [162, 163]. However, under pathological conditions, it can be deleterious and involved in the neurodegeneration processes [164]. Pre-clinical studies have evidenced NOS mechanism involvement in depression physiopathology and in antidepressant mechanism of action [55] (Fig. 2). Moreover, inducible NOS (iNOS) gene polymorphisms have already been associated with major depression [165] and NO plasma concentration has been associated with cognitive impairment in recurrent MDD patient [166]. Three different isoforms of the protein have been identified and are expressed in the central CNS cells: iNOS is activated in response to pro-inflammatory signal under pathological conditions, whereas the neuronal NOS (nNOS) and the endothelial NOS (eNOS) are constitutively expressed. Interestingly, both CNS cells and HDF express iNOS [159, 167], which would allow the study of iNOS induction in response to inflammation in HDF from MDE patient as...
compared to healthy controls. Also, the mitochondria is the central organelle in oxidative stress regulation and is present in HDF. Therefore, HDF can be used to study mitochondrial DNA (polymorphism, deletion) association with MDD [168], and especially, to study the peripheral mitochondrial impairments, as already done in the context of bipolar disorder [23]. Moreover, in the context of Alzheimer disease study, HDF already served as a peripheral sensor of CNS oxidative stress [169-173] and of mitochondrial bioenergetic impairment [20, 174]. HDF is presented as a unique in vitro model to determine if the observed Alzheimer related mechanism dysfunctions are inherent to Alzheimer patient cells or are secondary to pathology [175]. Therefore, HDF is a promising model to study oxidative metabolism impairments in the context of MDD.

4.2.1.8. HDF Transdifferentiation to Neurons

Whereas HDF mimic some phenotypic features of neurons, they are not neurons and one of the main limits is the impossibility to transcribe neuronal functionality. Therefore, results drawn from HDF should be interpreted cautiously. However, although HDF cannot reflect neuronal functionality, they could be considered as neuron precursors. Indeed, recent studies found a way to transdifferentiate HDF into functional neurons [176-178]. This transdifferentiation can be done from patients’ HDF [179], and can lead to different neuron types such as serotonergic and dopaminergic neurons [176, 180]. Therefore, HDF have already been used in the context of Alzheimer disease for clinical and pre-clinical research. HDF were used as precursor cells for in vitro reconstitution of neuron from Alzheimer disease patients [179] and were used as progenitor of induced neural stem cells (iNSC) in pre-clinical model of Alzheimer disease [181]. This characteristic strongly increases the HDF potential in research on depression and psychiatric disorders, even if neurons transdifferentiated from fibroblasts require more skills, cost and time than simple HDF [9]. However, since many biological disturbances observed in MDD are not only brain-specific, a cellular peripheral model of the disorder may be of interest.

4.2.1.9. Potential as a Tool to Assess the Functionality of Genetic Trait

HDF is a human cellular model that does not require genetic modification prior to in vitro culture and nitrogen congelation survival. It conserves an intact genetic background of the donor, and is not exposed to environmental variations since they grow in the same controlled culture conditions. Therefore, HDF is a more suitable tool compared to other immortalized human cells, to explore the functional consequences of rare variants discovered by NGS. For instance, leukocytes and fibroblasts were used to study the effect of the COMT genetic polymorphism val158met (rs4680) and methylenetetrahydrofolate reductase (MTHFR) genetic polymorphisms on mRNA expression [43]. Results show that MTHFR mRNA expression is slightly but significantly reduced in leukocytes from MDD patients but not in HDF. These differential results were explained by the difference in gene expression stability between these two models. HDF are considered more stable in comparison to leukocytes, in which gene expression is modulated by donor environmental factors (hormonal state, treatment...). Results from leukocytes study were hypothesized as a probable false positive [43]. Interestingly, two studies [9, 43] share the same idea that HDF is a genetic and environmental stable model, which represents a great advantage to study genetic and gene expression impairments in MDD, compared to peripheral blood cells. Another study assessed a transcriptomic microarray on HDF and peripheral blood cells (PBC) from patients with schizophrenia, bipolar disorder and MDD as compared to healthy controls [46]. In HDF from patients with schizophrenia, they identified several mRNAs differentially expressed compared to healthy controls. However, only one mRNA species was found differentially expressed in PBC between the same patients and controls. This also illustrates the stability of HDF transcriptome as compared to blood cells which are more exposed to environmental- associated transcriptome variations [46]. Moreover, HDF have been widely used in other contexts to assess genetic mutation functionality [153, 182].

4.2.2. HDF as an Underused Model Regarding its Potential for the Research on AD Mechanism of Action

Most of the AD treatments modulate monoamine central concentration by targeting reuptake and degradation [58-60]. The presence of serotonin transporter (SERT) in HDF has not been reported yet. However, SERT expression has been shown in HDF neighboring cells (keratinocytes) [183], and in rat pulmonary artery fibroblasts [184]. Moreover, MAO-A has already been identified in HDF. Indeed, HDF have been used to study the effect of MAO-A genetic polymorphism on protein expression and enzyme activity [10, 76]. Therefore, HDF can be useful to study both reuptake and degradation of monoamines after treatment. Because HDF express many components of several central pathways such as serotoninergic, dopaminergic, adrenergic, GABAergic, glutamatergic and cholinergic signaling molecules, they can be considered as a tool to study the interactions between these pathways, in response to AD treatment or in MDE patients.

For instance, selective serotonin reuptake inhibitors are among the most prescribed AD. Their main effect is mediated by SERT inhibition, but it is known that they have other potential effects such as agonist properties of alpha- and beta-adrenoceptors, dopamine and muscarinic receptors, many of which are expressed in HDF (Table 3). Moreover, HDF respond to serotonin receptor 5HT2A agonists [7] by an increase in phosphatidylinositol hydrolysis, and also respond to 5-HT2A antagonists (ketanserin) [71], to serotonin and to the serotonin reuptake inhibitor fluoxetine by growth and proliferation modifications. A low dose of fluoxetine (10 nM) has been shown to increase both HDF survival and proliferation [71]. This response could reflect the fluoxetine effect on SERT in HDF. HDF also respond to the tricyclic antidepressant desipramine in vitro treatment by a decrease in beta-2-adrenoceptor protein expression, revealing a potential method to study the treatment of AD through catecholamine signaling [185].

Even if GABA receptor A has not been identified yet in HDF, this model presents several GABA pathway components as mentioned above. Noteworthy, the brain GABAergic system is ubiquitous and most AD mechanisms of ac-
tions are partly mediated by GABAergic system regulation [64]. For instance, it has been shown that GAD67, a protein expressed in HDF, is decreased in the brains of untreated MDD patients who committed suicide as compared to controls (death by cardiovascular disease), but this difference in GAD67 brain expression is no longer observed in AD-treated MDD patients as compared to controls [143]. Therefore, it would be of interest to follow the evolution of GAD67 in HDF from MDD patients after in vitro HDF AD treatment.

The glutamatergic system has reached great interest in MDD since it has been shown that low doses of ketamine (a NMDA-R glutamatergic antagonist) had AD effects in depressed patients [186]. The effect of ketamine on depression seems to be dependent on α-amino-3-hydroxy-5-methylisoxazole-4-propionate (AMPA) receptor-P13K-ERK-AKT-mTOR pathway [187]. The mTOR-ERK-AKT pathway has been identified in HDF [151] and AMPA receptors are present in the human skin [93], but has not been reported in HDF yet [94]. At last, glutamatergic AD effects require BDNF upregulation, a key protein in neuroplasticity homeostasis [188], and a PI3K-Akt-dependent phosphorylation of GSK3 [189], components that are also present in HDF but have never been studied in MDE patients’ HDF.

It is now accepted that AD effects are partly mediated by increased expression of neurotrophins, neurogenesis and synaptic plasticity [190]. Two studies from the same laboratory [191, 192] aimed at comparing the proliferation rate in lymphoblastoid cell lines (LCL) from MDE patients who were responders or non-responders to AD. They demonstrate that proliferation rate in response to AD in vitro is higher in LCL from responder patients as compared to non-responder patients. In vitro proliferation in response to AD treatment can therefore serve as a biomarker of individual AD-related neuroplasticity. Interestingly, HDF are characterized by a high proliferation rate which can be modulated by AD [71]. Thus, HDF proliferation rate can be used as a sensor of AD response in depressed patients. Moreover, fibroblast growth factor 2 (FGF2), which is highly expressed in HDF, is one of the main growth factors involved in proliferation [122]. Noteworthy, FGF2 expression downregulated in frontal cortex and hypothalamus from MDD patients and this dysregulation is partly corrected by treatment with selective serotonin reuptake inhibitors (SSRI) [193]. O&N stress can also modulate cellular plasticity and neurotransmission. Interestingly, it has been shown that antidepressant effect and oxidative metabolism are closely linked [55]. Therefore, the drug effect on oxidative stress can be studied in HDF and the results can be related to the MDE patient response to AD treatment (Fig. 2).

HDF also represent an interesting non-invasive human cellular model with several features of brain cells. Therefore, some groups used HDF to assess AD mechanisms of action. HDF were used to study the role of serotonin in post-thermal skin healing. In this context, they were treated with fluoxetine and ketanserin to interfere with HDF serotonin pathway and to demonstrate that serotonin pathway impairment alters skin healing in post-thermal injury [71]. HDF were also treated with desipramine to understand the mechanism of action of this AD [185]. HDF treatment with desipramine reduces beta-adrenoceptor expression in HDF membranes, illustrated by a reduction in beta-adrenoceptor binding sites. It demonstrates that desipramine central action on adrenoceptors does not only involve changes from presynaptic events but also implicates the intrinsic AD mechanism of action [185]. Other works also treated HDF with tricyclic antidepressants and studied the consequences on lipid metabolism, including that of cholesterol [194] and ceramides [195].

CONCLUSION

The 18 studies retained in our first part demonstrate that several mechanisms and protagonists from monoamine metabolism, inflammation, oxidative stress and cellular plasticity pathways are altered in HDF from MDE patients as compared to healthy controls. Moreover, one study describes AD response in HDF from responder MDE patients as compared to resistant patients. HDF are not only used as peripheral sensors of central dysregulation but also allowed the study of genetic functionality and peripheral impairment related to MDD. According to the previous reviews on HDF use in psychiatry research, HDF model is a good compromise as compared to other cellular human models. Their main advantages have been described as their genetic stability, their potential to be cultured without genetic modification, their relatively easy implementation and their numerous mechanisms shared with CNS cells. The second part of our review identified and listed many mechanisms present both in HDF and relevant regarding MDD pathophysiology and AD mechanisms of action. However, despite the presence of this set of interesting features, few works were performed in HDF from MDE patients or in HDF treated with AD as illustrated by the important difference between the number of listed references in part 1 (18 papers from the flow chart illustrated in Fig. 1) and in part 2 (110 papers listed in Table 1). However, as previously reviewed, HDF have been widely used as a model for studying other psychiatric and neurodegenerative diseases. One of the hinge mechanisms in psychiatric and neurodegenerative diseases pathophysiology is the O&N stress. It is at the crossroad between inflammation, environmental factors and brain dysfunction. Interestingly, oxidative metabolism related to neurodegenerative diseases has already been studied in HDF from patients as compared to healthy controls and highlights HDF as a potential tool to study mechanisms of CNS cell oxidative stress [9]. Therefore, our work demonstrates that the HDF is an underused, but promising model for research on MDD, on AD mechanisms of action and on AD treatment response markers.

The main limits are: first, the number of studies available regarding HDF in MDD patients is low. Indeed, this model requires cell culture skills and facilities. Secondly, skin biopsies are more invasive than a blood test and cell culture is time- and cost-consuming. Therefore, studies using MDE patient fibroblasts included relatively small numbers of patients. Thus, further works on MDE patients’ HDF would allow to replicate previous studies and help standardize HDF as a tool in MDD research.

PERSPECTIVES

Further studies can be established based on depressed patient cohorts in which it could be possible to compare
pathways listed in Table 3 in HDF from MDD patients as compared to controls. Such studies would help identify altered metabolism mechanisms particularly those available only in cellular model (i.e. oxidative stress). Furthermore, studies assessing these pathways in HDF from AD responder as compared to non-responder patients will be useful to find new potential biomarkers of AD response and to develop biomarkers for individual response prognosis.

Finally, HDF can be dedifferentiated in induced pluripotent stem cells and can also be transdifferentiated into functional neurons. This opens many perspectives in the comparison of neuronal functionality between MDE patients and healthy controls, to study MDD and AD mechanisms in cellular models that share a large panel of features with CNS cells.

**LIST OF ABBREVIATIONS**

| Abbreviation | Description |
|--------------|-------------|
| 5-HT2A       | Serotonin receptor 2A |
| ACTH         | Adrenocorticotropic Hormone |
| AD           | Antidepressant Drug |
| ADHD         | Attention-Deficit Hyperactivity Disorders |
| AKT          | Protein Kinase B |
| AMPA receptor | α-amino-3-hydroxy-5-methylisoxazole-4-propionate receptor |
| BDNF         | Brain-Derived Neurotrophic Factor |
| cAMP         | Cyclic Adenosine di-phosphate |
| CNS          | Central Nervous System |
| COMT         | Catechol-O-methyltransferase |
| CREB         | c-Amy Response Element Binding protein |
| CRH          | Corticotropin Releasing Hormone |
| D1 receptor  | Dopamine receptor 1 |
| EAAT1, 2 and 3 | Excitatory Amino Acid Transporter 1, 2 and 3 |
| ECM          | Extracellular Matrix |
| ERK          | Extracellular Signal-Regulated Kinase |
| FGF2         | Fibroblast Growth Factor 2 |
| GABA         | Gamma Aminobutyric Acid |
| GAD67        | Glutamic Acid Decarboxylase |
| GAT1         | GABA Transporter 1 |
| GSK3         | Glycogen Synthase Kinase 3 |
| HDF          | Human Dermal Fibroblast |
| HPA          | Hypothalamic-Pituitary-Adrenal Axis |
| IL-6 or -1β  | Interleukine-6 or -1β |
| iNOS         | Inducible Nitric Oxide Synthase |
| iNSC         | Induced Neural Stem Cells |
| LAT1         | Tryptophan Transporter L-type Amino acid Transporter 1 |
| LCL          | Lymphoblastoid Cell Lines |
| MAO          | Monoamine Oxidase |
| MCR1         | Melanocortin Receptor 1 |
| MDD          | Major Depressive Disorder |
| MDE          | Major Depressive Episode |
| miRNA        | Micro RNA |
| mRNA         | Messenger Ribonucleic Acid |
| MTHFR        | Methylene tetrahydrofolate Reductase |
| mTOR         | Mechanistic Target of Rapamycin |
| NGF          | Neuronal Growth Factor |
| NLRP3        | Nucleotide-binding oligomerization domain (NOD)-like Receptor 3 |
| NO           | Nitric Oxide |
| NT           | Neurotrophin |
| O&N stress   | Oxidative and Nitrostative Stress |
| PBMC         | Peripheral Blood Mononuclear Cells |
| PI3K         | Phosphatidylinositol 3-Kinase |
| PKA          | Protein Kinase A |
| POMC         | Proopiomelanocortin |
| PSMD13       | Proteasome 26S subunit, non-ATPase 13 |
| ROS          | Reactive Oxygen Species |
| SERT         | Serotonin Transporter |
| SNP          | Single Nucleotide Polymorphism |
| SSRI         | Selective Serotonin Reuptake Inhibitor |
| TNF-α        | Tumor Necrosis Factor alpha |
| TPH          | Tryptophan Hydroxylase |
| Trk          | Tropomyosin Receptor Kinase |

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PRISMA guidelines and methodology were followed.

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