Send Orders for Reprints to reprints@benthamscience.net

Current Neuropharmacology, **2020**, *18*, **301-318** **301**

REVIEW ARTICLE

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

Pierre Mesdom[1], Romain Colle[1,2], Elise Lebigot[3], Séverine Trabado[4,5], Eric Deflesselle[1,6], Bruno Fève[7], Laurent Becquemont[1,5], Emmanuelle Corruble[1,2] and Céline Verstuyft[1,5,*]

[1]Université Paris-Saclay, UVSQ, Inserm, CESP, Team MOODS, 94270, Le Kremlin-Bicêtre, France; [2]Service Hospitalo-Universitaire de Psychiatrie de Bicêtre, Hôpitaux Universitaires Paris-Sud, Assistance Publique-Hôpitaux de Paris, Hôpital de Bicêtre, Le Kremlin Bicêtre, F-94275, France; [3]Service de Biochimie Pharmaco-Toxicologie, APHP, Hôpitaux Universitaires Paris-Sud, Hôpital de Bicêtre, Le Kremlin Bicêtre, F-94275, France; [4]Université Paris Saclay, Faculté de Médecine Paris Saclay, Le Kremlin Bicêtre, F-94276, France; Institut National de la Santé et de la Recherche Médicale UMR-S U1185, Le Kremlin Bicêtre, F-94276, France; [5]Service de Génétique moléculaire, Pharmacogénétique et Hormonologie, Assistance Publique-Hôpitaux de Paris, Hôpitaux Universitaires Paris-Sud, Hôpital de Bicêtre, Le Kremlin Bicêtre, F-94275, France; [6]Département de Médecine Générale, Université Paris Saclay, Faculté de Médecine Paris-Sud, Le Kremlin Bicêtre, F-94276, France; [7]Sorbonne 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.

ARTICLE HISTORY

Received: July 12, 2019
Revised: October 15, 2019
Accepted: October 19, 2019

DOI: 10.2174/1570159X17666191021141057

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 mm^2 skin biopsy after 3 passages (about 35

*Address correspondence to this author at the Laboratoire de Pharmacologie, Salle 416, Bâtiment Université, Hôpital du Kremlin Bicêtre, 78 rue du Général Leclerc, 94275 Le Kremlin-Bicêtre, France; Tel: +33145213588; E-mail: celine.verstuyft@aphp.fr

1570-159X/20 $65.00+.00

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 cellular 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 pathophysiologic 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

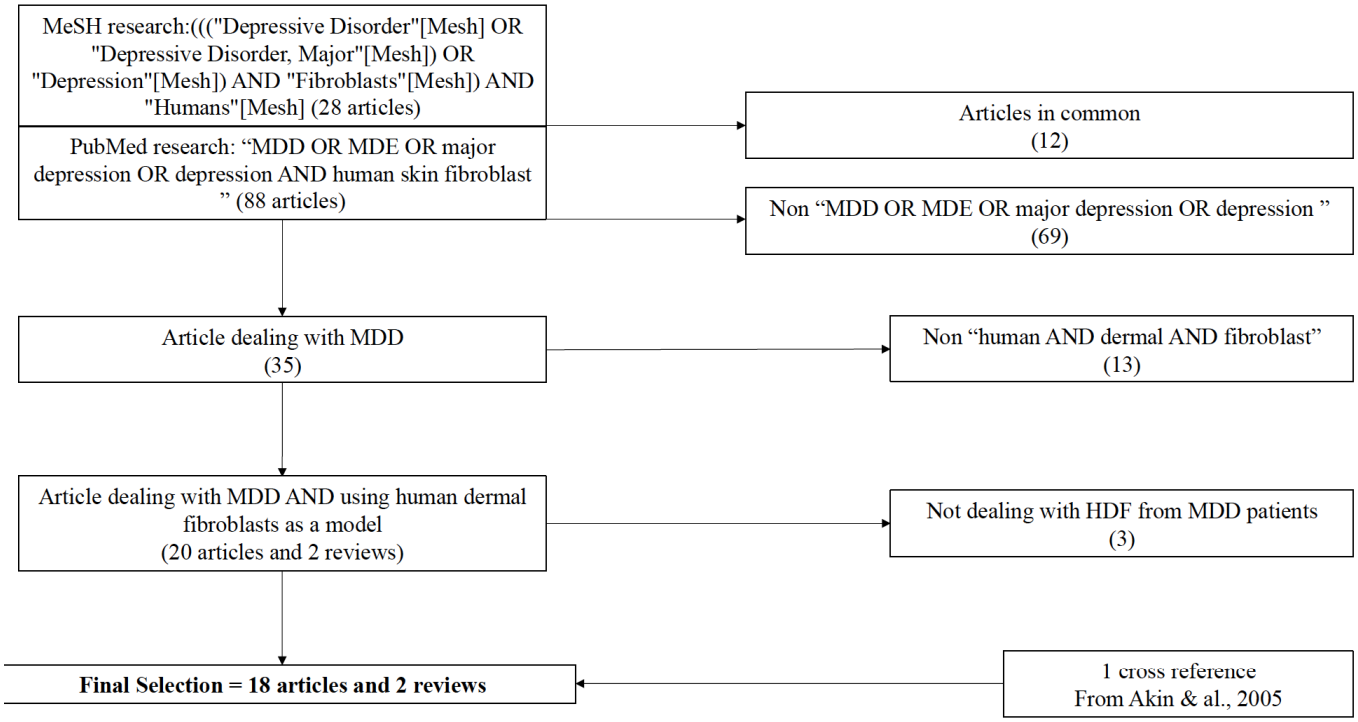

Fig. (1). Systemic research methodology for the first part. Legend: Papers published from no limit in the past until December 2018 were selected.

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 MeSH	("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 MeSH	("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 MeSH	"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) 7 reviews	(8 papers) 2 reviews (13 papers from 1970 to 1990 on glut transport and GDH deficiency in HDF)
GABA	PubMed	"Human skin fibroblast AND GABA"	18	6
Neurotrophins	PubMed	"Human dermal fibroblast AND neurotrophins"	46	5
HPA axis	PubMed MeSH	((("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	19
HPA axis	PubMed	"human skin fibroblast AND hypothalamic pituitary adrenal axis"	16	2
Circadian rhythm	PubMed	"human dermal fibroblast AND clock gene"	8	2

Abbreviations: We selected papers published from no limit in the past until December 2018.

Table 2. Articles using human dermal fibroblasts from MDE patients.

Studied Pathway		Number of Patients/Controls	Characteristics of Psychiatric Disease	Author-Year
Monoaminergic pathways	5HT2A-dependent PI hydrolysis	18/10	MDE-MDD with melancholic features	Akin 2004 [7]
	Beta-2-adrenoceptor signaling / decreased cAMP-induced PKA activity	12/10	MDE-MDD	Shelton 1996 [37]
	Beta-adrenoceptors, c-AMP, PKA	5/5	MDE-MDD	Manier 1996 [38]
	Beta-adrenoceptor linked cAMP-dependent PKA activity	35/21	MDE-MDD with melancholic features	Shelton 1999 [39]
	Involvement of CREB in the Beta-adrenoceptor, cAMP, PKA pathway	5/0	MDE-MDD	Manier 2001 [40]
	PKC/PKA pathway-dependent CREB phosphorylation	24/12	MDE-MDD with melancholic features	Akin 2005 [41]
	Muscarinic receptors	1/2	MDE-MDD	Lin 1986 [42]
Genetic mutation	MTHFR SNP / COMT mutation in MDD	27/21	MDD	Nielsen 2015 [43]
mRNA profile	mRNA profile by differential display	2/2	MDE-MDD with melancholic features	Liang 2006 [44] and Liang 2001 [45]
	mRNA profile by microarray	18/21	MDE	Cattane 2015 [46]
Micro RNA	Matched relation mRNA /microRNA	16/16	MDD	Garbett 2015b [47]
Metabolism / inflammation	HDF response to IL6 treatment between MDD and controls.	7/7	MDD	Money 2016 [24]
	Pentraxin-3 gene expression	16/8	MDE-MDD with melancholic features	Shelton 2004 [48]
	Glucocorticoid receptors	8/8	MDE-MDD	Wassef 1992 [49]
	Non-response to AD treatment and proteasome dysregulation	17/21	MDD	Minelli 2015 [50]
	Oxidative stress	16/16	MDE-MDD	Gibson 2012 [22]
Oxidative metabolism	Differential transcriptome between MDD and control HDF, in response to stress	16/16	MDD	Garbett 2015a [25]

Abbreviations: Methylenetetrahydrofolatereductase (MTHFR), Catechol-O-methyltranferase (COMT), Protein Kinase A / C (PKA/PKC), cAMP Element Binding Protein (CREB), Major Depressive Disorder (MDD), Major Depressive Episode (MDE), Cyclic Adenosine Mono-phosphate (c-AMP), Phosphatidyl-inositol (PI).

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 receptor 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-methyltranferase (*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).

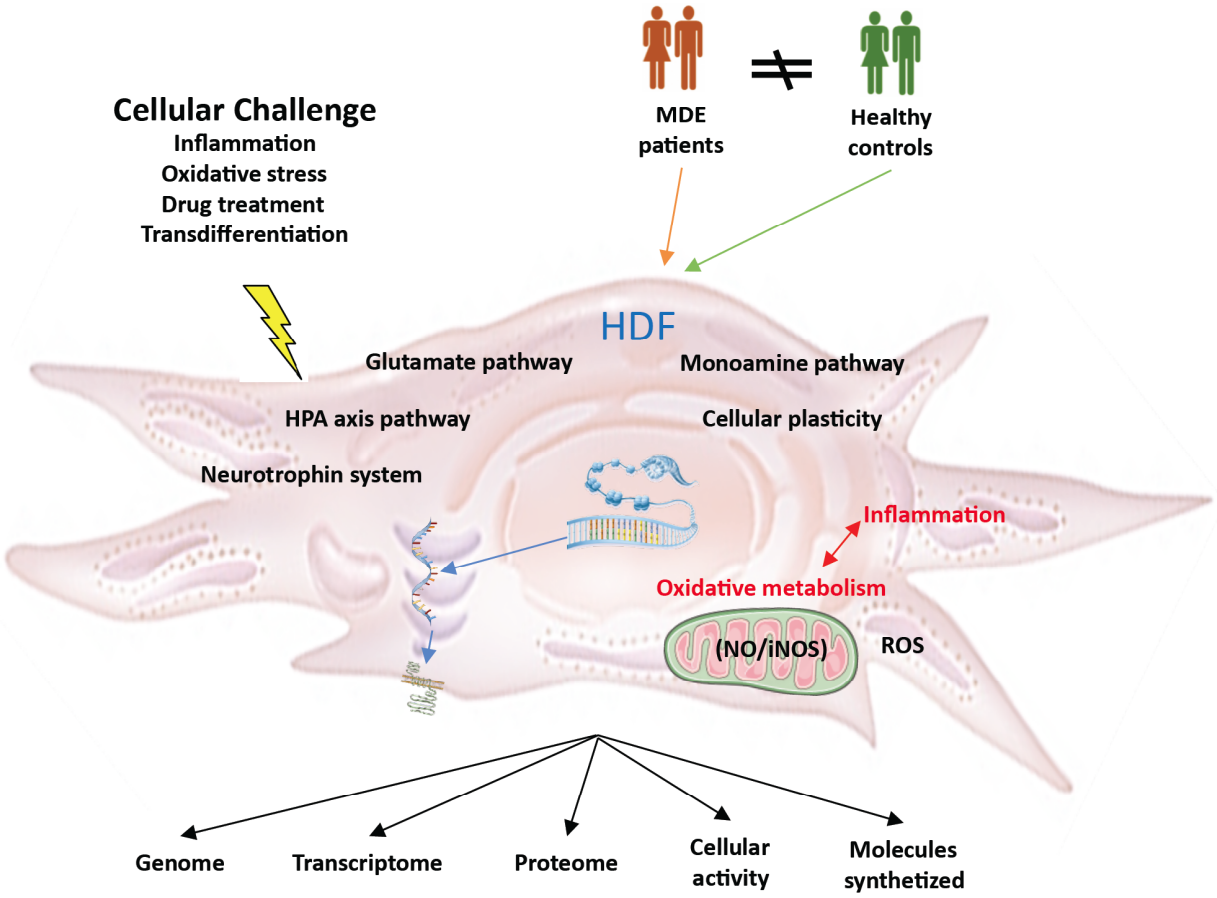

Fig. (2). HDF potential in the study of MDD related Inflammation, O&N stress and CNS molecular and cellular dysregulations. Legend: Fig. **2** illustrates the great potential of HDF as a model to study MDD related brain and peripheral impairment such as oxidative stress, inflammation, genetic related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

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 downregulated 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 *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 *in vitro* oxidative stress conditions (by *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.

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**					
Serotonin	5-HT transporter (SERT)		V	-	-	[71]
	5-HT receptor	5-HT1A	V	V	-	[72]
		5-HT1B	V	V	-	[72]
		5-HT2C	V	V	-	[72]
		5-HT2B	V	V	-	[72]
		5-HT2A	V	V	V	[7, 71]
		5-HT4	V	V	-	[73]
		5-HT7	V	V	-	[72]
	TPH1-2		-	V	-	[74]
	MAO-A		V	V	-	[10, 75-78]
Catecholamines	Adrenaline / Noradrenaline	beta-2-adrenoceptor	V	V	V	[29, 38, 79-84]
		NET	-	-	-	-
	Dopamine	Receptor D1 and D2	V	V	-	[85, 86]
		COMT	V	V	-	[43]
		Tyrosine transporter	V	V	-	[87]
Acetylcholine		Muscarinic receptor	V	V	-	[42, 88-91]
		Nicotinic receptor	V	V	-	[73]
		acetylcholinesterase	V	V	-	[92]
Glutamatergic system		AMPA	V	-	-	[93]
		NMDA	V	-	-	[94-96]
		GluR6	-	V	-	[97]
		EAAT1, EAAT2, and EAAT3	V	V	-	[94, 98, 99]
		Glutamate dehydrogenase	V	V	-	[100]
GABAergic system		GAD67	V	V	-	[101]
		GABA transporter 1	V	V	-	[102]
Neurotrophins		BDNF	V	V	-	[28]
		NGF	V	V	-	[28, 103-105]
		NT 3,4 and 5	V	V	-	[28]
		P75NTR	V	V	-	
		TrkB	V	V	-	
HPA axis		CRH / ACTH / POMC/ a-MSH and cognate receptors	V	V	-	[106-116]
		Corticotropic functionality	V	V	-	
		Cortisol	V	V	V	[117-119]
Inflammation-metabolism		CREB	V	V	V	[29, 41, 120]
		GSK3	V	V	-	[121]
		FGF2	V	V	-	[122]
		LEPTIN	V	V	-	[123]
		NLRP3	V	V	-	[124]
Oxidative stress		iNOS	V	V	-	[167]
		NO production	V	V	-	[167]
Circadian rhythm		PER2	V	V	-	[126]

Abbreviations: **V** = already published, **-** = not shown yet. *Serotonin (5-HT), serotonin receptor (5-HTR), tryptophan hydrolase 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-methylisoazol-4-propionate (AMPA), N-Methyl-(D-aspartic Acid (NMDA), glutamate receptor 6 (GluR6), Excitatory Amino Acid Transporter (EAAT), glutamate decarboxylase (GAD67), gamma-amino butyric acid (GABA), brain-derived neurotrophic factor (BDNF), nerve/neuronal growth factor (NGF), neurotrophin (NT), neurotrophic receptor P75 (P75NTR), tropomyosin kinase receptor B (TrkB), corticotropin releasing hormone (CRH), adreno-corticotropic hormone (ACTH), proopiomelanocortin (POMC), alpha-melanocyte stimulating hormone (α-MSH), cAMP 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 (PRE2).

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 GABAergic 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 inflammasome 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) represent 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 serotoninergic 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-methylisoazol-4-propionate (AMPA) receptor-PI3K-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

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-methylisoazol-4-propionate receptor
BDNF	=	Brain-Derived Neurotrophic Factor
cAMP	=	Cyclic Adenosine di-phosphate
CNS	=	Central Nervous System
COMT	=	Catechol-O-methyltransferase
CREB	=	c-AMP 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	=	Methylenetetrahydrofolate 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

STANDARD OF REPORTING

PRISMA guidelines and methodology were followed.

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

Declared none.

REFERENCES

[1] Tracy, L.E.; Minasian, R.A.; Caterson, E.J. Extracellular matrix and dermal fibroblast function in the healing wound. *Adv. Wound Care (New Rochelle),* **2016**, *5*(3), 119-136. http://dx.doi.org/10.1089/wound.2014.0561 PMID: 26989578

[2] Darby, I.A.; Laverdet, B.; Bonté, F.; Desmoulière, A. Fibroblasts and myofibroblasts in wound healing. *Clin. Cosmet. Investig. Dermatol.,* **2014**, *7*, 301-311. [PMID: 25395868

[3] Vangipuram, M.; Ting, D.; Kim, S.; Diaz, R.; Schüle, B. Skin punch biopsy explant culture for derivation of primary human fibroblasts. *J. Vis. Exp.,* **2013**, (77), e3779. http://dx.doi.org/10.3791/3779 PMID: 23852182

[4] Sherr, C.J.; DePinho, R.A. Cellular senescence: mitotic clock or culture shock? *Cell,* **2000**, *102*(4), 407-410. http://dx.doi.org/10.1016/S0092-8674(00)00046-5 PMID: 10966103

[5] Wray, S.; Self, M.; Lewis, P.A.; Taanman, J.W.; Ryan, N.S.; Mahoney, C.J.; Liang, Y.; Devine, M.J.; Sheerin, U.M.; Houlden, H.; Morris, H.R.; Healy, D.; Marti-Masso, J.F.; Preza, E.; Barker, S.; Sutherland, M.; Corriveau, R.A.; D'Andrea, M.; Schapira, A.H.; Uitti, R.J.; Guttman, M.; Opala, G.; Jasinska-Myga, B.; Puschmann, A.; Nilsson, C.; Espay, A.J.; Slawek, J.; Gutmann, L.; Boeve, B.F.; Boylan, K.; Stoessl, A.J.; Ross, O.A.; Maragakis, N.J.; Van Gerpen, J.; Gerstenhaber, M.; Gwinn, K.; Dawson, T.M.; Isacson, O.; Marder, K.S.; Clark, L.N.; Przedborski, S.E.; Finkbeiner, S.; Rothstein, J.D.; Wszolek, Z.K.; Rossor, M.N.; Hardy, J. Creation of an open-access, mutation-defined fibroblast resource for neurological disease research. *PLoS One,* **2012**, *7*(8), e43099. http://dx.doi.org/10.1371/journal.pone.0043099 PMID: 22952635

[6] Schwartz, J.C.; Podell, E.R.; Han, S.S.; Berry, J.D.; Eggan, K.C.; Cech, T.R. FUS is sequestered in nuclear aggregates in ALS patient fibroblasts. *Mol. Biol. Cell,* **2014**, *25*(17), 2571-2578. http://dx.doi.org/10.1091/mbc.e14-05-1007 PMID: 25009283

[7] Akin, D.; Manier, D.H.; Sanders-Bush, E.; Shelton, R.C. Decreased serotonin 5-HT2A receptor-stimulated phosphoinositide signaling in fibroblasts from melancholic depressed patients. *Neuropsychopharmacology,* **2004**, *29*(11), 2081-2087. http://dx.doi.org/10.1038/sj.npp.1300505 PMID: 15187984

[8] Fournier, M.; Ferrari, C.; Baumann, P.S.; Polari, A.; Monin, A.; Bellier-Teichmann, T.; Wulff, J.; Pappan, K.L.; Cuenod, M.; Conus, P.; Do, K.Q. Impaired metabolic reactivity to oxidative stress in early psychosis patients. *Schizophr. Bull.,* **2014**, *40*(5), 973-983. http://dx.doi.org/10.1093/schbul/sbu053 PMID: 24687046

[9] Kálmán, S.; Garbett, K.A.; Janka, Z.; Mirnics, K. Human dermal fibroblasts in psychiatry research. *Neuroscience,* **2016**, *320*, 105-121. [http://dx.doi.org/10.1016/j.neuroscience.2016.01.067 PMID: 26855193

[10] Denney, R.M.; Koch, H.; Craig, I.W. Association between monoamine oxidase A activity in human male skin fibroblasts and genotype of the MAOA promoter-associated variable number tandem repeat. *Hum. Genet.,* **1999**, *105*(6), 542-551. [PMID: 10647887

[11] Wagner, J.R.; Busche, S.; Ge, B.; Kwan, T.; Pastinen, T.; Blanchette, M. The relationship between DNA methylation, genetic and expression inter-individual variation in untransformed human fibroblasts. *Genome Biol.,* **2014**, *15*(2), R37. http://dx.doi.org/10.1186/gb-2014-15-2-r37 PMID: 24555846

[12] Wadman, R.I.; Stam, M.; Jansen, M.D.; van der Weegen, Y.; Wijngaarde, C.A.; Harschnitz, O.; Sodaar, P.; Braun, K.P.; Dooijes, D.; Lemmink, H.H.; van den Berg, L.H.; van der Pol, W.L. A comparative study of SMN protein and mRNA in blood and fibroblasts in patients with spinal muscular atrophy and healthy controls. *PLoS One,* **2016**, *11*(11), e0167087. http://dx.doi.org/10.1371/journal.pone.0167087 PMID: 27893852

[13] Rodriguez-Menocal, L.; Salgado, M.; Ford, D.; Van Badiavas, E. Stimulation of skin and wound fibroblast migration by mesenchymal stem cells derived from normal donors and chronic wound patients. *Stem Cells Transl. Med.,* **2012**, *1*(3), 221-229. http://dx.doi.org/10.5966/sctm.2011-0029 PMID: 23197781

[14] Nuta, O.; Somaiah, N.; Boyle, S.; Chua, M.L.; Gothard, L.; Yarnold, J.; Rothkamm, K.; Herskind, C. Correlation between the radiation responses of fibroblasts cultured from individual patients and the risk of late reaction after breast radiotherapy. *Cancer Lett.,* **2016**, *374*(2), 324-330. http://dx.doi.org/10.1016/j.canlet.2016.02.036 PMID: 26944319

[15] de Paepe, B.; Smet, J.; Leroy, J.G.; Seneca, S.; George, E.; Matthys, D.; van Maldergem, L.; Scalais, E.; Lissens, W.; de Meirleir, L.; Meulemans, A.; van Coster, R. Diagnostic value of immunostaining in cultured skin fibroblasts from patients with oxidative phosphorylation defects. *Pediatr. Res.,* **2006**, *59*(1), 2-6. http://dx.doi.org/10.1203/01.pdr.0000191294.34122.ab PMID: 16327006

[16] Bertolini, S.; Pisciotta, L.; Fasano, T.; Rabacchi, C.; Calandra, S. The study of familial hypercholesterolemia in Italy: A narrative review. *Atheroscler. Suppl.,* **2017**, *29*, 1-10. http://dx.doi.org/10.1016/j.atherosclerosissup.2017.07.003 PMID: 28965614

[17] Millioni, R.; Puricelli, L.; Iori, E.; Trevisan, R.; Tessari, P. Skin fibroblasts as a tool for identifying the risk of nephropathy in the type 1 diabetic population. *Diabetes Metab. Res. Rev.,* **2012**, *28*(1), 62-70. http://dx.doi.org/10.1002/dmrr.1287 PMID: 22218755

[18] Auburger, G.; Klinkenberg, M.; Drost, J.; Marcus, K.; Morales-Gordo, B.; Kunz, W.S.; Brandt, U.; Broccoli, V.; Reichmann, H.; Gispert, S.; Jendrach, M. Primary skin fibroblasts as a model of Parkinson's disease. *Mol. Neurobiol.,* **2012**, *46*(1), 20-27. http://dx.doi.org/10.1007/s12035-012-8245-1 PMID: 22350618

[19] Mocali, A.; Della Malva, N.; Abete, C.; Mitidieri Costanza, V.A.; Bavazzano, A.; Boddi, V.; Sanchez, L.; Dessì, S.; Pani, A.; Paoletti, F. Altered proteolysis in fibroblasts of Alzheimer patients with predictive implications for subjects at risk of disease. *Int. J. Alzheimers Dis.,* **2014**, *2014*, 520152. http://dx.doi.org/10.1155/2014/520152 PMID: 24949214

[20] Pérez, M.J.; Ponce, D.P.; Osorio-Fuentealba, C.; Behrens, M.I.; Quintanilla, R.A. Mitochondrial Bioenergetics Is Altered in Fibroblasts from Patients with Sporadic Alzheimer's Disease. *Front. Neurosci.,* **2017**, *11*, 553. http://dx.doi.org/10.3389/fnins.2017.00553 PMID: 29056898

[21] Meister, A. Glutathione biosynthesis and its inhibition. *Methods Enzymol.,* **1995**, *252*, 26-30. http://dx.doi.org/10.1016/0076-6879(95)52005-8 PMID: 7476360

[22] Gibson, S.A.; Korade, Ž.; Shelton, R.C. Oxidative stress and glutathione response in tissue cultures from persons with major depression. *J. Psychiatr. Res.,* **2012**, *46*(10), 1326-1332. http://dx.doi.org/10.1016/j.jpsychires.2012.06.008 PMID: 22841833

[23] Cataldo, A.M.; McPhie, D.L.; Lange, N.T.; Punzell, S.; Elmiligy, S.; Ye, N.Z.; Froimowitz, M.P.; Hassinger, L.C.; Menesale, E.B.; Sargent, L.W.; Logan, D.J.; Carpenter, A.E.; Cohen, B.M. Abnormalities in mitochondrial structure in cells from patients with bipolar disorder. *Am. J. Pathol.,* **2010**, *177*(2), 575-585. http://dx.doi.org/10.2353/ajpath.2010.081068 PMID: 20566748

[24] Money, K.M.; Olah, Z.; Korade, Z.; Garbett, K.A.; Shelton, R.C.; Mirnics, K. An altered peripheral IL6 response in major depressive disorder. *Neurobiol. Dis.,* **2016**, *89*, 46-54. http://dx.doi.org/10.1016/j.nbd.2016.01.015 PMID: 26804030

[25] Garbett, K.A.; Vereczkei, A.; Kálmán, S.; Wang, L.; Korade, Ž.; Shelton, R.C.; Mirnics, K. Fibroblasts from patients with major depressive disorder show distinct transcriptional response to metabolic stressors. *Transl. Psychiatry,* **2015**, *5*, e523. http://dx.doi.org/10.1038/tp.2015.14 PMID: 25756806

[26] Janmaat, C.J.; de Rooij, K.E.; Locher, H.; de Groot, S.C.; de Groot, J.C.; Frijns, J.H.; Huisman, M.A. Human Dermal Fibroblasts Demonstrate Positive Immunostaining for Neuron- and Glia- Specific Proteins. *PLoS One,* **2015**, *10*(12), e0145235. http://dx.doi.org/10.1371/journal.pone.0145235 PMID: 26678612

[27] Nordlind, K.; Azmitia, E.C.; Slominski, A. The skin as a mirror of the soul: exploring the possible roles of serotonin. *Exp. Dermatol.,* **2008**, *17*(4), 301-311. http://dx.doi.org/10.1111/j.1600-0625.2007.00670.x PMID: 18177349

[28] Palazzo, E.; Marconi, A.; Truzzi, F.; Dallaglio, K.; Petrachi, T.; Humbert, P.; Schnebert, S.; Perrier, E.; Dumas, M.; Pincelli, C. Role of neurotrophins on dermal fibroblast survival and differentiation. *J. Cell. Physiol.,* **2012**, *227*(3), 1017-1025. http://dx.doi.org/10.1002/jcp.22811 PMID: 21503896

[29] Manier, D.H.; Shelton, R.C.; Ellis, T.C.; Peterson, C.S.; Eiring, A.; Sulser, F. Human fibroblasts as a relevant model to study signal transduction in affective disorders. *J. Affect. Disord.,* **2000**, *61*(1-2), 51-58. [http://dx.doi.org/10.1016/S0165-0327(99)00190-1 PMID: 11099740

[30] Mokdad, A.H.; Forouzanfar, M.H.; Daoud, F.; Mokdad, A.A.; El Bcheraoui, C.; Moradi-Lakeh, M.; Kyu, H.H.; Barber, R.M.; Wagner, J.; Cercy, K.; Kravitz, H.; Coggeshall, M.; Chew, A.; O'Rourke, K.F.; Steiner, C.; Tuffaha, M.; Charara, R.; Al-Ghamdi, E.A.; Adi, Y.; Afifi, R.A.; Alahmadi, H.; AlBuhairan, F.; Allen, N.; AlMazroa, M.; Al-Nehmi, A.A.; AlRayess, Z.; Arora, M.; Azzopardi, P.; Barroso, C.; Basulaiman, M.; Bhutta, Z.A.; Bonell, C.; Breinbauer, C.; Degenhardt, L.; Denno, D.; Fang, J.; Fatusi, A.; Feigl, A.B.; Kakuma, R.; Karam, N.; Kennedy, E.; Khoja, T.A.; Maalouf, F.; Obermeyer, C.M.; Mattoo, A.; McGovern, T.; Memish, Z.A.; Mensah, G.A.; Patel, V.; Petroni, S.; Reavley, N.; Zertuche, D.R.; Saeedi, M.; Santelli, J.; Sawyer, S.M.; Ssewamala, F.; Taiwo, K.; Tantawy, M.; Viner, R.M.; Waldfogel, J.; Zuñiga, M.P.; Naghavi, M.; Wang, H.; Vos, T.; Lopez, A.D.; Al Rabeeah, A.A.; Patton, G.C.; Murray, C.J. Global burden of diseases, injuries, and risk factors for young people's health during 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet,* **2016**, *387*(10036), 2383-2401. http://dx.doi.org/10.1016/S0140-6736(16)00648-6 PMID: 27174305

[31] Kupfer, D.J.; Frank, E.; Phillips, M.L. Major depressive disorder: new clinical, neurobiological, and treatment perspectives. *Lancet,* **2012**, *379*(9820), 1045-1055. http://dx.doi.org/10.1016/S0140-6736(11)60602-8 PMID: 22189047

[32] Trivedi, M.H.; Rush, A.J.; Wisniewski, S.R.; Nierenberg, A.A.; Warden, D.; Ritz, L.; Norquist, G.; Howland, R.H.; Lebowitz, B.; McGrath, P.J.; Shores-Wilson, K.; Biggs, M.M.; Balasubramani, G.K.; Fava, M.; Team, S.D.S. Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice. *Am. J. Psychiatry,* **2006**, *163*(1), 28-40. http://dx.doi.org/10.1176/appi.ajp.163.1.28 PMID: 16390886

[33] Nierenberg, A.A.; Farabaugh, A.H.; Alpert, J.E.; Gordon, J.; Worthington, J.J.; Rosenbaum, J.F.; Fava, M. Timing of onset of antidepressant response with fluoxetine treatment. *Am. J. Psychiatry,* **2000**, *157*(9), 1423-1428. http://dx.doi.org/10.1176/appi.ajp.157.9.1423 PMID: 10964858

[34] Delgado, P.L. Depression: the case for a monoamine deficiency. *J. Clin. Psychiatry,* **2000**, *61*(Suppl. 6), 7-11. PMID: 10775018

[35] Albert, P.R.; Benkelfat, C.; Descarries, L. The neurobiology of depression--revisiting the serotonin hypothesis. I. Cellular and molecular mechanisms. *Philos. Trans. R. Soc. Lond. B Biol. Sci.,* **2012**, *367*(1601), 2378-2381. http://dx.doi.org/10.1098/rstb.2012.0190 PMID: 22826338

[36] Kraft, J.B.; Slager, S.L.; McGrath, P.J.; Hamilton, S.P. Sequence analysis of the serotonin transporter and associations with antidepressant response. *Biol. Psychiatry*, **2005**, 58(5), 374-81.

[37] Shelton, R.C.; Mainer, D.H.; Sulser, F. cAMP-dependent protein kinase activity in major depression. *Am. J. Psychiatry,* **1996**, *153*(8), 1037-1042. http://dx.doi.org/10.1176/ajp.153.8.1037 PMID: 8678172

[38] Manier, D.H.; Eiring, A.; Shelton, R.C.; Sulser, F. Beta-adrenoceptor-linked protein kinase A (PKA) activity in human fibroblasts from normal subjects and from patients with major depression. *Neuropsychopharmacology,* **1996**, *15*(6), 555-561. http://dx.doi.org/10.1016/S0893-133X(96)00099-1 PMID: 8946429

[39] Shelton, R.C.; Manier, D.H.; Peterson, C.S.; Ellis, T.C.; Sulser, F. Cyclic AMP-dependent protein kinase in subtypes of major depression and normal volunteers. *Int. J. Neuropsychopharmacol.,* **1999**, *2*(3), 187-192. [http://dx.doi.org/10.1017/S1461145799001509 PMID: 11281988

[40] Manier, D.H.; Shelton, R.C.; Sulser, F. Cross-talk between PKA and PKC in human fibroblasts: what are the pharmacotherapeutic implications? *J. Affect. Disord.,* **2001**, *65*(3), 275-279. http://dx.doi.org/10.1016/S0165-0327(00)00278-0 PMID: 11511407

[41] Akin, D.; Manier, D.H.; Sanders-Bush, E.; Shelton, R.C. Signal transduction abnormalities in melancholic depression. *Int. J. Neuropsychopharmacol.,* **2005**, *8*(1), 5-16. http://dx.doi.org/10.1017/S146114570400478X PMID: 15500705

[42] Lin, S.C.; Richelson, E. Low levels and lack of function of muscarinic binding sites in human skin fibroblasts from five affectively ill patients and two control subjects. *Am. J. Psychiatry,* **1986**, *143*(5), 658-660. http://dx.doi.org/10.1176/ajp.143.5.658 PMID: 3457538

[43] Gabriela Nielsen, M.; Congiu, C.; Bortolomasi, M.; Bonvicini, C.; Bignotti, S.; Abate, M.; Milanesi, E.; Conca, A.; Cattane, N.; Tessari, E.; Gennarelli, M.; Minelli, A. MTHFR: Genetic variants, expression analysis and COMT interaction in major depressive disorder. *J. Affect. Disord.,* **2015**, *183*, 179-186. http://dx.doi.org/10.1016/j.jad.2015.05.003 PMID: 26021967

[44] Liang, S.; Rossby, S.P.; Liang, P.; Shelton, R.C.; Manier, D.H.; Chakrabarti, A.; Sulser, F. Detection of an mRNA polymorphism by differential display. *Methods Mol. Biol.,* **2006**, *317*, 279-285. PMID: 16264236

[45] Liang, S.; Rossby, S.P.; Liang, P.; Shelton, R.C.; Manier, D.H.; Chakrabarti, A.; Sulser, F. Detection of an mRNA polymorphism by differential display. *Mol. Biotechnol.,* **2001**, *19*(2), 121-124. http://dx.doi.org/10.1385/MB:19:2:121 PMID: 11725481

[46] Cattane, N.; Minelli, A.; Milanesi, E.; Maj, C.; Bignotti, S.; Bortolomasi, M.; Bocchio Chiavetto, L.; Gennarelli, M. Altered gene expression in schizophrenia: findings from transcriptional signatures in fibroblasts and blood. *PLoS One,* **2015**, *10*(2), e0116686. http://dx.doi.org/10.1371/journal.pone.0116686 PMID: 25658856

[47] Garbett, K.A.; Vereczkei, A.; Kálmán, S.; Brown, J.A.; Taylor, W.D.; Faludi, G.; Korade, Ž.; Shelton, R.C.; Mirnics, K. Coordinated messenger RNA/microRNA changes in fibroblasts of patients with major depression. *Biol. Psychiatry,* **2015**, *77*(3), 256-265. http://dx.doi.org/10.1016/j.biopsych.2014.05.015 PMID: 25016317

[48] Shelton, R.C.; Liang, S.; Liang, P.; Chakrabarti, A.; Manier, D.H.; Sulser, F. Differential expression of pentraxin 3 in fibroblasts from patients with major depression. *Neuropsychopharmacology,* **2004**, *29*(1), 126-132. http://dx.doi.org/10.1038/sj.npp.1300307 PMID: 14603263

[49] Wassef, A.A.; O'Boyle, M.; Gardner, R.; Rose, R.M.; Brown, A.; Harris, A.; Nguyen, H.; Meyer, W.J., III Glucocorticoid receptor binding in three different cell types in major depressive disorder: lack of evidence of receptor binding defect. *Prog. Neuropsychopharmacol. Biol. Psychiatry,* **1992**, *16*(1), 65-78. http://dx.doi.org/10.1016/0278-5846(92)90009-4 PMID: 1557508

[50] Minelli, A.; Magri, C.; Barbon, A.; Bonvicini, C.; Segala, M.; Congiu, C.; Bignotti, S.; Milanesi, E.; Trabucchi, L.; Cattane, N.; Bortolomasi, M.; Gennarelli, M. Proteasome system dysregulation and treatment resistance mechanisms in major depressive disorder. *Transl. Psychiatry,* **2015**, *5*, e687. http://dx.doi.org/10.1038/tp.2015.180 PMID: 26624926

[51] Muiños-Gimeno, M.; Espinosa-Parrilla, Y.; Guidi, M.; Kagerbauer, B.; Sipilä, T.; Maron, E.; Pettai, K.; Kananen, L.; Navinés, R.; Martín-Santos, R.; Gratacòs, M.; Metspalu, A.; Hovatta, I.; Estivill, X. Human microRNAs miR-22, miR-138-2, miR-148a, and miR-488 are associated with panic disorder and regulate several anxiety candidate genes and related pathways. *Biol. Psychiatry,* **2011**, *69*(6), 526-533. [http://dx.doi.org/10.1016/j.biopsych.2010.10.010 PMID: 21168126

[52] Kawashima, H.; Numakawa, T.; Kumamaru, E.; Adachi, N.; Mizuno, H.; Ninomiya, M.; Kunugi, H.; Hashido, K. Glucocorticoid attenuates brain-derived neurotrophic factor-dependent upregulation of glutamate receptors via the suppression of microRNA-132 expression. *Neuroscience,* **2010**, *165*(4), 1301-1311. http://dx.doi.org/10.1016/j.neuroscience.2009.11.057 PMID: 19958814

[53] Wayman, G.A.; Davare, M.; Ando, H.; Fortin, D.; Varlamova, O.; Cheng, H.Y.; Marks, D.; Obrietan, K.; Soderling, T.R.; Goodman, R.H.; Impey, S. An activity-regulated microRNA controls dendritic plasticity by down-regulating p250GAP. *Proc. Natl. Acad. Sci. USA,* **2008**, *105*(26), 9093-9098. http://dx.doi.org/10.1073/pnas.0803072105 PMID: 18577589

[54] Marsden, W.N. Synaptic plasticity in depression: molecular, cellular and functional correlates. *Prog. Neuropsychopharmacol. Biol. Psychiatry,* **2013**, *43*, 168-184. http://dx.doi.org/10.1016/j.pnpbp.2012.12.012 PMID: 23268191

[55] Joca, S.R.L.; Sartim, A.G.; Roncalho, A.L.; Diniz, C.F.A.; Wegener, G. Nitric oxide signalling and antidepressant action revisited. *Cell Tissue Res.,* **2019**, *377*(1), 45-58. http://dx.doi.org/10.1007/s00441-018-02987-4 PMID: 30649612

[56] Kessler-Becker, D.; Krieg, T.; Eckes, B. Expression of pro-inflammatory markers by human dermal fibroblasts in a three-dimensional culture model is mediated by an autocrine interleukin-1 loop. *Biochem. J.,* **2004**, *379*(Pt 2), 351-358. http://dx.doi.org/10.1042/bj20031371 PMID: 14686880

[57] Hasler, G. Pathophysiology of depression: do we have any solid evidence of interest to clinicians? *World Psychiatry,* **2010**, *9*(3), 155-161. [http://dx.doi.org/10.1002/j.2051-5545.2010.tb00298.x PMID: 20975857

[58] Wong, D.T.; Perry, K.W.; Bymaster, F.P. Case history: the discovery of fluoxetine hydrochloride (Prozac). *Nat. Rev. Drug Discov.,* **2005**, *4*(9), 764-774. http://dx.doi.org/10.1038/nrd1821 PMID: 16121130

[59] Berton, O.; Nestler, E.J. New approaches to antidepressant drug discovery: beyond monoamines. *Nat. Rev. Neurosci.,* **2006**, *7*(2), 137-151. [http://dx.doi.org/10.1038/nrn1846 PMID: 16429123

[60] Willner, P.; Scheel-Krüger, J.; Belzung, C. The neurobiology of depression and antidepressant action. *Neurosci. Biobehav. Rev.,* **2013**, *37*(10 Pt 1), 2331-2371. http://dx.doi.org/10.1016/j.neubiorev.2012.12.007 PMID: 23261405

[61] Philip, N.S.; Carpenter, L.L.; Tyrka, A.R.; Price, L.H. Nicotinic acetylcholine receptors and depression: a review of the preclinical and clinical literature. *Psychopharmacology (Berl.),* **2010**, *212*(1), 1-12. http://dx.doi.org/10.1007/s00213-010-1932-6 PMID: 20614106

[62] Higley, M.J.; Picciotto, M.R. Neuromodulation by acetylcholine: examples from schizophrenia and depression. *Curr. Opin. Neurobiol.,* **2014**, *29*, 88-95. http://dx.doi.org/10.1016/j.conb.2014.06.004 PMID: 24983212

[63] Picciotto, M.R.; Higley, M.J.; Mineur, Y.S. Acetylcholine as a neuromodulator: cholinergic signaling shapes nervous system function and behavior. *Neuron,* **2012**, *76*(1), 116-129. http://dx.doi.org/10.1016/j.neuron.2012.08.036 PMID: 23040810

[64] Luscher, B.; Shen, Q.; Sahir, N. The GABAergic deficit hypothesis of major depressive disorder. *Mol. Psychiatry,* **2011**, *16*(4), 383-406. http://dx.doi.org/10.1038/mp.2010.120 PMID: 21079608

[65] Guidotti, G.; Calabrese, F.; Anacker, C.; Racagni, G.; Pariante, C.M.; Riva, M.A. Glucocorticoid receptor and FKBP5 expression is altered following exposure to chronic stress: modulation by antidepressant treatment. *Neuropsychopharmacology,* **2013**, *38*(4), 616-627. http://dx.doi.org/10.1038/npp.2012.225 PMID: 23169346

[66] Cowen, P.J. Not fade away: the HPA axis and depression. *Psychol. Med.,* **2010**, *40*(1), 1-4. http://dx.doi.org/10.1017/S0033291709005558 PMID: 19335939

[67] Sigalas, P.D.; Garg, H.; Watson, S.; McAllister-Williams, R.H.; Ferrier, I.N. Metyrapone in treatment-resistant depression. *Ther. Adv. Psychopharmacol.,* **2012**, *2*(4), 139-149. http://dx.doi.org/10.1177/2045125312436597 PMID: 23983967

[68] Liu, W.; Ge, T.; Leng, Y.; Pan, Z.; Fan, J.; Yang, W.; Cui, R. The Role of Neural Plasticity in Depression: From Hippocampus to Prefrontal Cortex. *Neural Plast.,* **2017**, *2017*6871089 [http://dx.doi.org/10.1155/2017/6871089 PMID: 28246558

[69] Miller, A.H.; Raison, C.L. The role of inflammation in depression: from evolutionary imperative to modern treatment target. *Nat. Rev. Immunol.,* **2016**, *16*(1), 22-34. http://dx.doi.org/10.1038/nri.2015.5 PMID: 26711676

[70] Anderson, G.; Berk, M.; Dean, O.; Moylan, S.; Maes, M. Role of immune-inflammatory and oxidative and nitrosative stress pathways in the etiology of depression: therapeutic implications. *CNS Drugs,* **2014**, *28*(1), 1-10. http://dx.doi.org/10.1007/s40263-013-0119-1 PMID: 24150993

[71] Sadiq, A.; Shah, A.; Jeschke, M. G.; Belo, C.; Qasim Hayat, M.; Murad, S.; Amini-Nik, S., The Role of Serotonin during Skin Healing in Post-Thermal Injury. *Int. J. Mol. Sci*., **2018**, *19*(4), 1034. http://dx.doi.org/10.3390/ijms19041034 PMID: 29596386

[72] Slominski, A.; Pisarchik, A.; Zbytek, B.; Tobin, D. J.; Kauser, S.; Wortsman, J., Functional activity of serotoninergic and melatoninergic systems expressed in the skin. *J. Cell Physiol*., **2003**, *196*(1), 144-153. http://dx.doi.org/10.1002/jcp.10287 PMID: 12767050

[73] Stegemann, A.; Sindrilaru, A.; Eckes, B.; del Rey, A.; Heinick, A.; Schulte, J.S.; Müller, F.U.; Grando, S.A.; Fiebich, B.L.; Scharffetter-Kochanek, K.; Luger, T.A.; Böhm, M. Tropisetron suppresses collagen synthesis in skin fibroblasts via α7 nicotinic acetylcholine receptor and attenuates fibrosis in a scleroderma mouse model. *Arthritis Rheum.,* **2013**, *65*(3), 792-804. http://dx.doi.org/10.1002/art.37809 PMID: 23440693

[74] Slominski, A.; Pisarchik, A.; Johansson, O.; Jing, C.; Semak, I.; Slugocki, G.; Wortsman, J. Tryptophan hydroxylase expression in human skin cells. *Biochim. Biophys. Acta,* **2003**, *1639*(2), 80-86. http://dx.doi.org/10.1016/S0925-4439(03)00124-8 PMID: 14559114

[75] Nordquist, N.; Oreland, L. Monoallelic expression of MAO-A in skin fibroblasts. *J. Neural Transm. (Vienna),* **2007**, *114*(6), 713-716. http://dx.doi.org/10.1007/s00702-007-0676-x PMID: 17406964

[76] Roth, J.A.; Breakefield, X.O.; Castiglione, C.M. Monoamine oxidase and catechol-O-methyltransferase activities in cultured human skin fibroblasts. *Life Sci.,* **1976**, *19*(11), 1705-1710. http://dx.doi.org/10.1016/0024-3205(76)90077-1 PMID: 1004130

[77] Groshong, R.; Gibson, D.A.; Baldessarini, R.J. Monoamine oxidase activity in cultured human skin fibroblasts. *Clin. Chim. Acta,* **1977**, *80*(1), 113-120. [http://dx.doi.org/10.1016/0009-8981(77)90270-4 PMID: 908136

[78] Pintar, J.E.; Breakefield, X.O. Monoamine oxidase (MAO) activity as a determinant in human neurophysiology. *Behav. Genet.,* **1982**, *12*(1), 53-68. http://dx.doi.org/10.1007/BF01065740 PMID: 6284115

[79] Huang, H.M.; Gibson, G.E. Altered beta-adrenergic receptor-stimulated cAMP formation in cultured skin fibroblasts from Alzheimer donors. *J. Biol. Chem.,* **1993**, *268*(20), 14616-14621. PMID: 8100816

[80] Pullar, C.E.; Isseroff, R.R. The beta 2-adrenergic receptor activates pro-migratory and pro-proliferative pathways in dermal fibroblasts via divergent mechanisms. *J. Cell Sci.,* **2006**, *119*(Pt 3), 592-602. http://dx.doi.org/10.1242/jcs.02772 PMID: 16443756

[81] Kotanko, P.; Höglinger, O.; Skrabal, F. Beta 2-adrenoceptor density in fibroblast culture correlates with human NaCl sensitivity. *Am. J. Physiol.,* **1992**, *263*(3 Pt 1), C623-C627. http://dx.doi.org/10.1152/ajpcell.1992.263.3.C623 PMID: 1329521

[82] Berrettini, W.H.; Bardakjian, J.; Barnett, A.L., Jr; Nurnberger, J.I., Jr; Gershon, E.S. Beta-adrenoceptor function in human adult skin fibroblasts: a study of manic-depressive illness. *Ciba Found. Symp.,* **1986**, *123*, 30-41. [PMID: 3028727

[83] Pullar, C.E.; Isseroff, R.R. Beta 2-adrenergic receptor activation delays dermal fibroblast-mediated contraction of collagen gels via a cAMP-dependent mechanism. *Wound Repair Regen.,* **2005**, *13*(4), 405-411. [http://dx.doi.org/10.1111/j.1067-1927.2005.130408.x PMID: 16008730

[84] Corsini, A.; Bernini, F.; Cighetti, G.; Soma, M.; Galli, G.; Fumagalli, R. Lipophilic beta-adrenoceptor antagonists stimulate cholesterol biosynthesis in human skin fibroblasts. *Biochem. Pharmacol.,* **1987**, *36*(12), 1901-1906. http://dx.doi.org/10.1016/0006-2952(87)90486-2 PMID: 2885001

[85] Chakroborty, D.; Sarkar, C.; Lu, K.; Bhat, M.; Dasgupta, P.S.; Basu, S. Activation of dopamine D1 receptors in dermal fibroblasts restores vascular endothelial growth factor-A production by these cells and subsequent angiogenesis in diabetic cutaneous wound tissues. *Am. J. Pathol.,* **2016**, *186*(9), 2262-2270. http://dx.doi.org/10.1016/j.ajpath.2016.05.008 PMID: 27422612

[86] Laengle, U.W.; Markstein, R.; Pralet, D.; Greiner, B.; Roman, D. Effects of latanoprost and GLC756, a novel dopamine D2 agonist and D1 antagonist, on cultured normal human dermal fibroblasts. *Eur. J. Ophthalmol.,* **2006**, *16*(1), 67-72. http://dx.doi.org/10.1177/112067210601600112 PMID: 16496248

[87] Vumma, R.; Johansson, J.; Venizelos, N. Proinflammatory cytokines and oxidative stress decrease the transport of dopamine precur-

sor tyrosine in human fibroblasts. *Neuropsychobiology,* **2017**, *75*(4), 178-184. http://dx.doi.org/10.1159/000485130 PMID: 29339668

[88] Nadi, N.S.; Nurnberger, J.I., Jr; Gershon, E.S. Muscarinic cholinergic receptors on skin fibroblasts in familial affective disorder. *N. Engl. J. Med.,* **1984**, *311*(4), 225-230. http://dx.doi.org/10.1056/NEJM198407263110404 PMID: 6738616

[89] Buchli, R.; Ndoye, A.; Rodriguez, J.G.; Zia, S.; Webber, R.J.; Grando, S.A. Human skin fibroblasts express m2, m4, and m5 subtypes of muscarinic acetylcholine receptors. *J. Cell. Biochem.,* **1999**, *74*(2), 264-277. http://dx.doi.org/10.1002/(SICI)1097-4644(19990801)74:2<264::AID-JCB11>3.0.CO;2-Z PMID: 10404395

[90] Vestling, M.; Cowburn, R.F.; Venizelos, N.; Lannfelt, L.; Winblad, B.; Adem, A. Characterization of muscarinic acetylcholine receptors in cultured adult skin fibroblasts: effects of the Swedish Alzheimer's disease APP 670/671 mutation on binding levels. *J. Neural Transm. Park. Dis. Dement. Sect.,* **1995**, *10*(1), 1-10. http://dx.doi.org/10.1007/BF02256625 PMID: 8619905

[91] Pancani, T.; Bolarinwa, C.; Smith, Y.; Lindsley, C.W.; Conn, P.J.; Xiang, Z. M4 mAChR-mediated modulation of glutamatergic transmission at corticostriatal synapses. *ACS Chem. Neurosci.,* **2014**, *5*(4), 318-324. http://dx.doi.org/10.1021/cn500003z PMID: 24528004

[92] Anderson, A.A.; Ushakov, D.S.; Ferenczi, M.A.; Mori, R.; Martin, P.; Saffell, J.L. Morphoregulation by acetylcholinesterase in fibroblasts and astrocytes. *J. Cell. Physiol.,* **2008**, *215*(1), 82-100. http://dx.doi.org/10.1002/jcp.21288 PMID: 17948252

[93] Tan, P.H.; Yang, L.C.; Chiang, P.T.; Jang, J.S.; Chung, H.C.; Kuo, C.H. Inflammation-induced up-regulation of ionotropic glutamate receptor expression in human skin. *Br. J. Anaesth.,* **2008**, *100*(3), 380-384. http://dx.doi.org/10.1093/bja/aem398 PMID: 18238837

[94] Tremolizzo, L.; Sala, G.; Zoia, C.P.; Ferrarese, C. Assessing glutamatergic function and dysfunction in peripheral tissues. *Curr. Med. Chem.,* **2012**, *19*(9), 1310-1315. http://dx.doi.org/10.2174/092986712799462702 PMID: 22304709

[95] Nahm, W.K.; Philpot, B.D.; Adams, M.M.; Badiavas, E.V.; Zhou, L.H.; Butmarc, J.; Bear, M.F.; Falanga, V. Significance of N-methyl-D-aspartate (NMDA) receptor-mediated signaling in human keratinocytes. *J. Cell. Physiol.,* **2004**, *200*(2), 309-317. http://dx.doi.org/10.1002/jcp.20010 PMID: 15174101

[96] Zeng, Y.; Lv, X.; Zeng, S.; Shi, J. Activity-dependent neuronal control of gap-junctional communication in fibroblasts. *Brain Res.,* **2009**, *1280*, 13-22. http://dx.doi.org/10.1016/j.brainres.2009.05.037 PMID: 19464269

[97] Zhawar, V.K.; Kaur, G.; deRiel, J.K.; Kaur, G.P.; Kandpal, R.P.; Athwal, R.S. Novel spliced variants of ionotropic glutamate receptor GluR6 in normal human fibroblast and brain cells are transcribed by tissue specific promoters. *Gene,* **2010**, *459*(1-2), 1-10. http://dx.doi.org/10.1016/j.gene.2010.03.002 PMID: 20230879

[98] Zoia, C.P.; Tagliabue, E.; Isella, V.; Begni, B.; Fumagalli, L.; Brighina, L.; Appollonio, I.; Racchi, M.; Ferrarese, C. Fibroblast glutamate transport in aging and in AD: correlations with disease severity. *Neurobiol. Aging,* **2005**, *26*(6), 825-832. http://dx.doi.org/10.1016/j.neurobiolaging.2004.07.007 PMID: 15718040

[99] Cooper, B.; Chebib, M.; Shen, J.; King, N.J.; Darvey, I.G.; Kuchel, P.W.; Rothstein, J.D.; Balcar, V.J. Structural selectivity and molecular nature of L-glutamate transport in cultured human fibroblasts. *Arch. Biochem. Biophys.,* **1998**, *353*(2), 356-364. http://dx.doi.org/10.1006/abbi.1998.0626 PMID: 9606970

[100] Tatsumi, C.; Yorifuji, S.; Kajiyama, K.; Ueno, S.; Takahashi, M.; Tarui, S. Glutamate metabolism of leukocytes and skin fibroblasts in spinocerebellar degeneration with lowered glutamate dehydrogenase activity. *Acta Neurol. Scand.,* **1989**, *79*(6), 468-475. http://dx.doi.org/10.1111/j.1600-0404.1989.tb03816.x PMID: 2782027

[101] Ito, K.; Tanaka, K.; Nishibe, Y.; Hasegawa, J.; Ueno, H. GABA-synthesizing enzyme, GAD67, from dermal fibroblasts: evidence for a new skin function. *Biochim. Biophys. Acta,* **2007**, *1770*(2), 291-296. http://dx.doi.org/10.1016/j.bbagen.2006.09.017 PMID: 17113713

[102] Sałat, K.; Podkowa, A.; Malikowska, N.; Kern, F.; Pabel, J.; Wojcieszak, E.; Kulig, K.; Wanner, K. T.; Strach, B.; Wyska, E. Novel, highly potent and *in vivo* active inhibitor of GABA transporter subtype 1 with anticonvulsant, anxiolytic, antidepressant and antinociceptive properties. *Neuropharmacology.,* **2017**, *113*(Pt A), 331-342.

[103] Reichert, O.; Fleming, T.; Neufang, G.; Schmelz, M.; Genth, H.; Kaever, V.; Wenck, H.; Stäb, F.; Terstegen, L.; Kolbe, L.; Roggenkamp, D. Impaired glyoxalase activity is associated with reduced expression of neurotrophic factors and pro-inflammatory processes in diabetic skin cells. *Exp. Dermatol.,* **2017**, *26*(1), 44-50. http://dx.doi.org/10.1111/exd.13118 PMID: 27306297

[104] Chen, J.C.; Lin, B.B.; Hu, H.W.; Lin, C.; Jin, W.Y.; Zhang, F.B.; Zhu, Y.A.; Lu, C.J.; Wei, X.J.; Chen, R.J. NGF accelerates cutaneous wound healing by promoting the migration of dermal fibroblasts via the PI3K/Akt-Rac1-JNK and ERK pathways. *BioMed. Res. Int.,* **2014**, *2014*, 547187. http://dx.doi.org/10.1155/2014/547187 PMID: 25006578

[105] Kim, M.; Shin, D.W.; Shin, H.; Noh, M.; Shin, J.H. Tensile stimuli increase nerve growth factor in human dermal fibroblasts independent of tension-induced TGFβ production. *Exp. Dermatol.,* **2013**, *22*(1), 72-74. http://dx.doi.org/10.1111/exd.12064 PMID: 23278900

[106] Luo, L.F.; Shi, Y.; Zhou, Q.; Xu, S.Z.; Lei, T.C. Insufficient expression of the melanocortin-1 receptor by human dermal fibroblasts contributes to excess collagen synthesis in keloid scars. *Exp. Dermatol.,* **2013**, *22*(11), 764-766. http://dx.doi.org/10.1111/exd.12250 PMID: 24433185

[107] Zapletal, E.; Kraus, O.; Cupić, B.; Gabrilovac, J. Differential expression of proopiomelanocortin (POMC) transcriptional variants in human skin cells. *Neuropeptides,* **2013**, *47*(2), 99-107. http://dx.doi.org/10.1016/j.npep.2012.10.010 PMID: 23218956

[108] Rassouli, O.; Liapakis, G.; Lazaridis, I.; Sakellaris, G.; Gkountelias, K.; Gravanis, A.; Margioris, A.N.; Karalis, K.P.; Venihaki, M. A novel role of peripheral corticotropin-releasing hormone (CRH) on dermal fibroblasts. *PLoS One,* **2011**, *6*(7), e21654. http://dx.doi.org/10.1371/journal.pone.0021654 PMID: 21765902

[109] Roberts, D.W.; Newton, R.A.; Beaumont, K.A.; Helen Leonard, J.; Sturm, R.A. Quantitative analysis of MC1R gene expression in human skin cell cultures. *Pigment Cell Res.,* **2006**, *19*(1), 76-89. http://dx.doi.org/10.1111/j.1600-0749.2005.00286.x PMID: 16420249

[110] Hill, R.P.; MacNeil, S.; Haycock, J.W. Melanocyte stimulating hormone peptides inhibit TNF-alpha signaling in human dermal fibroblast cells. *Peptides,* **2006**, *27*(2), 421-430. http://dx.doi.org/10.1016/j.peptides.2005.03.061 PMID: 16274855

[111] Hill, R.P.; Wheeler, P.; MacNeil, S.; Haycock, J.W. Alpha-melanocyte stimulating hormone cytoprotective biology in human dermal fibroblast cells. *Peptides,* **2005**, *26*(7), 1150-1158. http://dx.doi.org/10.1016/j.peptides.2005.01.019 PMID: 15949633

[112] Slominski, A.; Zbytek, B.; Semak, I.; Sweatman, T.; Wortsman, J. CRH stimulates POMC activity and corticosterone production in dermal fibroblasts. *J. Neuroimmunol.,* **2005**, *162*(1-2), 97-102. http://dx.doi.org/10.1016/j.jneuroim.2005.01.014 PMID: 15833364

[113] Böhm, M.; Luger, T.A. Melanocortins in fibroblast biology--current update and future perspective for dermatology. *Exp. Dermatol.,* **2004**, *13*(Suppl. 4), 16-21. http://dx.doi.org/10.1111/j.1600-0625.2004.00256.x PMID: 15507107

[114] Slominski, A.; Pisarchik, A.; Tobin, D.J.; Mazurkiewicz, J.E.; Wortsman, J. Differential expression of a cutaneous corticotropin-releasing hormone system. *Endocrinology,* **2004**, *145*(2), 941-950. http://dx.doi.org/10.1210/en.2003-0851 PMID: 14605004

[115] Schiller, M.; Raghunath, M.; Kubitscheck, U.; Scholzen, T.E.; Fisbeck, T.; Metze, D.; Luger, T.A.; Böhm, M. Human dermal fibroblasts express prohormone convertases 1 and 2 and produce proopiomelanocortin-derived peptides. *J. Invest. Dermatol.,* **2001**, *117*(2), 227-235. http://dx.doi.org/10.1046/j.0022-202x.2001.01412.x PMID: 11511298

[116] Slominski, A.; Wortsman, J.; Tuckey, R.C.; Paus, R. Differential expression of HPA axis homolog in the skin. *Mol. Cell. Endocrinol.,* **2007**, *265-266*, 143-149.

http://dx.doi.org/10.1016/j.mce.2006.12.012 PMID: 17197073

[117] Slominski, A.; Zbytek, B.; Szczesniewski, A.; Wortsman, J. Cultured human dermal fibroblasts do produce cortisol. *J. Invest. Dermatol.,* **2006**, *126*(5), 1177-1178. http://dx.doi.org/10.1038/sj.jid.5700204 PMID: 16484985

[118] Harvey, W.; Grahame, R.; Panayi, G.S. Effects of steriod hormones on human fibroblasts in vitro. II. Antagonism by androgens of cortisol-induced inhibition. *Ann. Rheum. Dis.,* **1976**, *35*(2), 148-151. http://dx.doi.org/10.1136/ard.35.2.148 PMID: 182091

[119] Harvey, W.; Grahame, R. Effect of some adrenal steroid hormones on skin fibroblast replication in vitro. *Ann. Rheum. Dis.,* **1973**, *32*(3), 272. http://dx.doi.org/10.1136/ard.32.3.272-a PMID: 4351823

[120] Gaspar, L.; van de Werken, M.; Johansson, A.S.; Moriggi, E.; Owe-Larsson, B.; Kocks, J.W.; Lundkvist, G.B.; Gordijn, M.C.; Brown, S.A. Human cellular differences in cAMP--CREB signaling correlate with light-dependent melatonin suppression and bipolar disorder. *Eur. J. Neurosci.,* **2014**, *40*(1), 2206-2215. http://dx.doi.org/10.1111/ejn.12602 PMID: 24898566

[121] Bergmann, C.; Akhmetshina, A.; Dees, C.; Palumbo, K.; Zerr, P.; Beyer, C.; Zwerina, J.; Distler, O.; Schett, G.; Distler, J.H. Inhibition of glycogen synthase kinase 3β induces dermal fibrosis by activation of the canonical Wnt pathway. *Ann. Rheum. Dis.,* **2011**, *70*(12), 2191-2198. http://dx.doi.org/10.1136/ard.2010.147140 PMID: 21873331

[122] Makino, T.; Jinnin, M.; Muchemwa, F.C.; Fukushima, S.; Kogushi-Nishi, H.; Moriya, C.; Igata, T.; Fujisawa, A.; Johno, T.; Ihn, H. Basic fibroblast growth factor stimulates the proliferation of human dermal fibroblasts via the ERK1/2 and JNK pathways. *Br. J. Dermatol.,* **2010**, *162*(4), 717-723. http://dx.doi.org/10.1111/j.1365-2133.2009.09581.x PMID: 19995368

[123] Glasow, A.; Kiess, W.; Anderegg, U.; Berthold, A.; Bottner, A.; Kratzsch, J. Expression of leptin (Ob) and leptin receptor (Ob-R) in human fibroblasts: regulation of leptin secretion by insulin. *J. Clin. Endocrinol. Metab.,* **2001**, *86*(9), 4472-4479. http://dx.doi.org/10.1210/jcem.86.9.7792 PMID: 11549696

[124] Artlett, C.M.; Sassi-Gaha, S.; Rieger, J.L.; Boesteanu, A.C.; Feghali-Bostwick, C.A.; Katsikis, P.D. The inflammasome activating caspase 1 mediates fibrosis and myofibroblast differentiation in systemic sclerosis. *Arthritis Rheum.,* **2011**, *63*(11), 3563-3574. http://dx.doi.org/10.1002/art.30568 PMID: 21792841

[125] Masetti, R.; Togni, M.; Astolfi, A.; Pigazzi, M.; Indio, V.; Rivalta, B.; Manara, E.; Rutella, S.; Basso, G.; Pession, A.; Locatelli, F. Whole transcriptome sequencing of a paediatric case of de novo acute myeloid leukaemia with del(5q) reveals RUNX1-USP42 and PRDM16-SKI fusion transcripts. *Br. J. Haematol.,* **2014**, *166*(3), 449-452. http://dx.doi.org/10.1111/bjh.12855 PMID: 24673627

[126] Lippert, J.; Halfter, H.; Heidbreder, A.; Röhr, D.; Gess, B.; Boentert, M.; Osada, N.; Young, P. Altered dynamics in the circadian oscillation of clock genes in dermal fibroblasts of patients suffering from idiopathic hypersomnia. *PLoS One,* **2014**, *9*(1)e85255 [http://dx.doi.org/10.1371/journal.pone.0085255 PMID: 24454829

[127] Meyer, J.H.; Ginovart, N.; Boovariwala, A.; Sagrati, S.; Hussey, D.; Garcia, A.; Young, T.; Praschak-Rieder, N.; Wilson, A.A.; Houle, S. Elevated monoamine oxidase a levels in the brain: an explanation for the monoamine imbalance of major depression. *Arch. Gen. Psychiatry,* **2006**, *63*(11), 1209-1216. http://dx.doi.org/10.1001/archpsyc.63.11.1209 PMID: 17088501

[128] Krishnan, V.; Nestler, E.J. The molecular neurobiology of depression. *Nature,* **2008**, *455*(7215), 894-902. http://dx.doi.org/10.1038/nature07455 PMID: 18923511

[129] Slominski, A.T.; Kleszczyński, K.; Semak, I.; Janjetovic, Z.; Zmijewski, M.A.; Kim, T.K.; Slominski, R.M.; Reiter, R.J.; Fischer, T.W. Local melatoninergic system as the protector of skin integrity. *Int. J. Mol. Sci.,* **2014**, *15*(10), 17705-17732. http://dx.doi.org/10.3390/ijms151017705 PMID: 25272227

[130] Brunner, H.G.; Nelen, M.; Breakefield, X.O.; Ropers, H.H.; van Oost, B.A. Abnormal behavior associated with a point mutation in the structural gene for monoamine oxidase A. *Science,* **1993**, *262*(5133), 578-580. http://dx.doi.org/10.1126/science.8211186 PMID: 8211186

[131] Vumma, R.; Johansson, J.; Lewander, T.; Venizelos, N. Tryptophan transport in human fibroblast cells-a functional characterization. *Int. J. Tryptophan Res.,* **2011**, *4*, 19-27. http://dx.doi.org/10.4137/IJTR.S6913 PMID: 22084600

[132] Johansson, J.; Landgren, M.; Fernell, E.; Vumma, R.; Åhlin, A.; Bjerkenstedt, L.; Venizelos, N. Altered tryptophan and alanine transport in fibroblasts from boys with attention-deficit/hyperactivity disorder (ADHD): an in vitro study. *Behav. Brain Funct.,* **2011**, *7*, 40. http://dx.doi.org/10.1186/1744-9081-7-40 PMID: 21942982

[133] Olsson, E.; Wiesel, F.A.; Bjerkenstedt, L.; Venizelos, N. Tyrosine transport in fibroblasts from healthy volunteers and patients with schizophrenia. *Neurosci. Lett.,* **2006**, *393*(2-3), 211-215. http://dx.doi.org/10.1016/j.neulet.2005.09.070 PMID: 16274928

[134] Persson, M.L.; Johansson, J.; Vumma, R.; Raita, J.; Bjerkenstedt, L.; Wiesel, F.A.; Venizelos, N. Aberrant amino acid transport in fibroblasts from patients with bipolar disorder. *Neurosci. Lett.,* **2009**, *457*(1), 49-52. http://dx.doi.org/10.1016/j.neulet.2009.03.095 PMID: 19429160

[135] Fernell, E.; Karagiannakis, A.; Edman, G.; Bjerkenstedt, L.; Wiesel, F.A.; Venizelos, N. Aberrant amino acid transport in fibroblasts from children with autism. *Neurosci. Lett.,* **2007**, *418*(1), 82-86. http://dx.doi.org/10.1016/j.neulet.2007.03.004 PMID: 17412511

[136] Antypa, N.; Drago, A.; Serretti, A. The role of COMT gene variants in depression: Bridging neuropsychological, behavioral and clinical phenotypes. *Neurosci. Biobehav. Rev.,* **2013**, *37*(8), 1597-1610. [http://dx.doi.org/10.1016/j.neubiorev.2013.06.006 PMID: 23792050

[137] Arredondo, J.; Hall, L.L.; Ndoye, A.; Nguyen, V.T.; Chernyavsky, A.I.; Bercovich, D.; Orr-Urtreger, A.; Beaudet, A.L.; Grando, S.A. Central role of fibroblast alpha3 nicotinic acetylcholine receptor in mediating cutaneous effects of nicotine. *Lab. Invest.,* **2003**, *83*(2), 207-225. [http://dx.doi.org/10.1097/01.LAB.0000053917.46614.12 PMID: 12594236

[138] Reina, S.; Sterin-Borda, L.; Passafaro, D.; Borda, E. Muscarinic cholinoceptor activation by pilocarpine triggers apoptosis in human skin fibroblast cells. *J. Cell. Physiol.,* **2010**, *222*(3), 640-647. PMID: 19927300

[139] Malpass, G.E.; Arimilli, S.; Prasad, G.L.; Howlett, A.C. Regulation of gene expression by tobacco product preparations in cultured human dermal fibroblasts. *Toxicol. Appl. Pharmacol.,* **2014**, *279*(2), 211-219. http://dx.doi.org/10.1016/j.taap.2014.06.001 PMID: 24927667

[140] Uehara, E.; Hokazono, H.; Sasaki, T.; Yoshioka, H.; Matsuo, N. Effects of GABA on the expression of type I collagen gene in normal human dermal fibroblasts. *Biosci. Biotechnol. Biochem.,* **2017**, *81*(2), 376-379. http://dx.doi.org/10.1080/09168451.2016.1238296 PMID: 27691923

[141] Uehara, E.; Hokazono, H.; Hida, M.; Sasaki, T.; Yoshioka, H.; Matsuo, N. GABA promotes elastin synthesis and elastin fiber formation in normal human dermal fibroblasts (HDFs). *Biosci. Biotechnol. Biochem.,* **2017**, *81*(6), 1198-1205. http://dx.doi.org/10.1080/09168451.2017.1290518 PMID: 28485217

[142] Berry, C.C.; Charles, S.; Wells, S.; Dalby, M.J.; Curtis, A.S. The influence of transferrin stabilised magnetic nanoparticles on human dermal fibroblasts in culture. *Int. J. Pharm.,* **2004**, *269*(1), 211-225. http://dx.doi.org/10.1016/j.ijpharm.2003.09.042 PMID: 14698593

[143] Karolewicz, B.; Maciag, D.; O'Dwyer, G.; Stockmeier, C.A.; Feyissa, A.M.; Rajkowska, G. Reduced level of glutamic acid decarboxylase-67 kDa in the prefrontal cortex in major depression. *Int. J. Neuropsychopharmacol.,* **2010**, *13*(4), 411-420. http://dx.doi.org/10.1017/S1461145709990587 PMID: 20236554

[144] Göhlich, G.; Kuhn, W.; Höhn, H.; Przuntek, H. Huntington's disease: biochemical prediction by determination of GABA synthesis of cultured fibroblasts. *J. Neurol.,* **1984**, *231*(1), 50-51. http://dx.doi.org/10.1007/BF00313653 PMID: 6232351

[145] Cepeda, C.; Starling, A.J.; Wu, N.; Nguyen, O.K.; Uzgil, B.; Soda, T.; André, V.M.; Ariano, M.A.; Levine, M.S. Increased GABAergic function in mouse models of Huntington's disease: reversal by BDNF. *J. Neurosci. Res.,* **2004**, *78*(6), 855-867.

http://dx.doi.org/10.1002/jnr.20344 PMID: 15505789

[146] Zoia, C.P.; Riva, C.; Isella, V.; Proserpio, P.; Terruzzi, A.; Arban, S.; Salerno, D.; Cassina, V.; Mantegazza, F.; Tremolizzo, L.; Ferrarese, C. Nonfibrillar Abeta 1-42 inhibits glutamate uptake and phosphorylates p38 in human fibroblasts. *Alzheimer Dis. Assoc. Disord.,* **2011**, *25*(2), 164-172. http://dx.doi.org/10.1097/WAD.0b013e3181f9860f PMID: 20921877

[147] Balcar, V.J.; Shen, J.; Bao, S.; King, N.J. Na(+)-dependent high affinity uptake of L-glutamate in primary cultures of human fibroblasts isolated from three different types of tissue. *FEBS Lett.,* **1994**, *339*(1-2), 50-54. http://dx.doi.org/10.1016/0014-5793(94)80382-X PMID: 7906230

[148] Begni, B.; Brighina, L.; Sirtori, E.; Fumagalli, L.; Andreoni, S.; Beretta, S.; Oster, T.; Malaplate-Armand, C.; Isella, V.; Appollonio, I.; Ferrarese, C. Oxidative stress impairs glutamate uptake in fibroblasts from patients with Alzheimer's disease. *Free Radic. Biol. Med.,* **2004**, *37*(6), 892-901. http://dx.doi.org/10.1016/j.freeradbiomed.2004.05.028 PMID: 15304259

[149] Batalla, A.; Bargalló, N.; Gassó, P.; Molina, O.; Pareto, D.; Mas, S.; Roca, J.M.; Bernardo, M.; Lafuente, A.; Parellada, E. Apoptotic markers in cultured fibroblasts correlate with brain metabolites and regional brain volume in antipsychotic-naive first-episode schizophrenia and healthy controls. *Transl. Psychiatry,* **2015**, *5*, e626. http://dx.doi.org/10.1038/tp.2015.122 PMID: 26305477

[150] Huang, E.J.; Reichardt, L.F. Neurotrophins: roles in neuronal development and function. *Annu. Rev. Neurosci.,* **2001**, *24*, 677-736. http://dx.doi.org/10.1146/annurev.neuro.24.1.677 PMID: 11520916

[151] Kim, S.; Lee, Y.; Seo, J.E.; Cho, K.H.; Chung, J.H. Caveolin-1 increases basal and TGF-beta1-induced expression of type I procollagen through PI-3 kinase/Akt/mTOR pathway in human dermal fibroblasts. *Cell. Signal.,* **2008**, *20*(7), 1313-1319. http://dx.doi.org/10.1016/j.cellsig.2008.02.020 PMID: 18434090

[152] Teofoli, P.; Frezzolini, A.; Puddu, P.; De Pità, O.; Mauviel, A.; Lotti, T. The role of proopiomelanocortin-derived peptides in skin fibroblast and mast cell functions. *Ann. N. Y. Acad. Sci.,* **1999**, *885*, 268-276. [http://dx.doi.org/10.1111/j.1749-6632.1999.tb08684.x PMID: 10816660

[153] Vitellius, G.; Trabado, S.; Hoeffel, C.; Bouligand, J.; Bennet, A.; Castinetti, F.; Decoudier, B.; Guiochon-Mantel, A.; Lombes, M.; Delemer, B. Study, i. o. t. M.-G., Significant prevalence of. *Eur. J. Endocrinol.,* **2018**, *178*(4), 411-423. http://dx.doi.org/10.1530/EJE-17-1071 PMID: 29444898

[154] Milaneschi, Y.; Simmons, W.K.; van Rossum, E.F.C.; Penninx, B.W. Depression and obesity: evidence of shared biological mechanisms. *Mol. Psychiatry,* **2018**. [PMID: 29453413

[155] Ng, F.; Berk, M.; Dean, O.; Bush, A.I. Oxidative stress in psychiatric disorders: evidence base and therapeutic implications. *Int. J. Neuropsychopharmacol.,* **2008**, *11*(6), 851-876. http://dx.doi.org/10.1017/S1461145707008401 PMID: 18205981

[156] Cobley, J.N.; Fiorello, M.L.; Bailey, D.M. 13 reasons why the brain is susceptible to oxidative stress. *Redox Biol.,* **2018**, *15*, 490-503. http://dx.doi.org/10.1016/j.redox.2018.01.008 PMID: 29413961

[157] Morris, G.; Puri, B.K.; Walker, A.J.; Berk, M.; Walder, K.; Bortolasci, C.C.; Marx, W.; Carvalho, A.F.; Maes, M. The compensatory antioxidant response system with a focus on neuroprogressive disorders. *Prog. Neuropsychopharmacol. Biol. Psychiatry,* **2019**, *95*, 109708. http://dx.doi.org/10.1016/j.pnpbp.2019.109708 PMID: 31351160

[158] Migliore, L.; Fontana, I.; Colognato, R.; Coppede, F.; Siciliano, G.; Murri, L. Searching for the role and the most suitable biomarkers of oxidative stress in Alzheimer's disease and in other neurodegenerative diseases. *Neurobiol. Aging,* **2005**, *26*(5), 587-595. http://dx.doi.org/10.1016/j.neurobiolaging.2004.10.002 PMID: 15708433

[159] Maes, M.; Galecki, P.; Chang, Y.S.; Berk, M. A review on the oxidative and nitrosative stress (O&NS) pathways in major depression and their possible contribution to the (neuro)degenerative processes in that illness. *Prog. Neuropsychopharmacol. Biol. Psychiatry,* **2011**, *35*(3), 676-692. http://dx.doi.org/10.1016/j.pnpbp.2010.05.004 PMID: 20471444

[160] Black, C.N.; Bot, M.; Scheffer, P.G.; Cuijpers, P.; Penninx, B.W. Is depression associated with increased oxidative stress? A systematic review and meta-analysis. *Psychoneuroendocrinology,* **2015**, *51*, 164-175. [http://dx.doi.org/10.1016/j.psyneuen.2014.09.025 PMID: 25462890

[161] Gibbs, S.M. Regulation of neuronal proliferation and differentiation by nitric oxide. *Mol. Neurobiol.,* **2003**, *27*(2), 107-120. http://dx.doi.org/10.1385/MN:27:2:107 PMID: 12777682

[162] Banoujaafar, H.; Monnier, A.; Pernet, N.; Quirié, A.; Garnier, P.; Prigent-Tessier, A.; Marie, C. Brain BDNF levels are dependent on cerebrovascular endothelium-derived nitric oxide. *Eur. J. Neurosci.,* **2016**, *44*(5), 2226-2235. http://dx.doi.org/10.1111/ejn.13301 PMID: 27306299

[163] Canossa, M.; Giordano, E.; Cappello, S.; Guarnieri, C.; Ferri, S. Nitric oxide down-regulates brain-derived neurotrophic factor secretion in cultured hippocampal neurons. *Proc. Natl. Acad. Sci. USA,* **2002**, *99*(5), 3282-3287. http://dx.doi.org/10.1073/pnas.042504299 PMID: 11867712

[164] Yuste, J.E.; Tarragon, E.; Campuzano, C.M.; Ros-Bernal, F. Implications of glial nitric oxide in neurodegenerative diseases. *Front. Cell. Neurosci.,* **2015**, *9*, 322. http://dx.doi.org/10.3389/fncel.2015.00322 PMID: 26347610

[165] Gałecki, P.; Maes, M.; Florkowski, A.; Lewiński, A.; Gałecka, E.; Bieńkiewicz, M.; Szemraj, J. Association between inducible and neuronal nitric oxide synthase polymorphisms and recurrent depressive disorder. *J. Affect. Disord.,* **2011**, *129*(1-3), 175-182. http://dx.doi.org/10.1016/j.jad.2010.09.005 PMID: 20888049

[166] Talarowska, M.; Gałecki, P.; Maes, M.; Orzechowska, A.; Chamielec, M.; Bartosz, G.; Kowalczyk, E. Nitric oxide plasma concentration associated with cognitive impairment in patients with recurrent depressive disorder. *Neurosci. Lett.,* **2012**, *510*(2), 127-131. http://dx.doi.org/10.1016/j.neulet.2012.01.018 PMID: 22273980

[167] Frank, S.; Kämpfer, H.; Wetzler, C.; Pfeilschifter, J. Nitric oxide drives skin repair: novel functions of an established mediator. *Kidney Int.,* **2002**, *61*(3), 882-888. http://dx.doi.org/10.1046/j.1523-1755.2002.00237.x PMID: 11849442

[168] Kasahara, T.; Kato, T. What can mitochondrial DNA analysis tell us about mood disorders? *Biol. Psychiatry,* **2018**, *83*(9), 731-738. [http://dx.doi.org/10.1016/j.biopsych.2017.09.010 PMID: 29102411

[169] Naderi, J.; Lopez, C.; Pandey, S. Chronically increased oxidative stress in fibroblasts from Alzheimer's disease patients causes early senescence and renders resistance to apoptosis by oxidative stress. *Mech. Ageing Dev.,* **2006**, *127*(1), 25-35. http://dx.doi.org/10.1016/j.mad.2005.08.006 PMID: 16188294

[170] Cecchi, C.; Fiorillo, C.; Sorbi, S.; Latorraca, S.; Nacmias, B.; Bagnoli, S.; Nassi, P.; Liguri, G. Oxidative stress and reduced antioxidant defenses in peripheral cells from familial Alzheimer's patients. *Free Radic. Biol. Med.,* **2002**, *33*(10), 1372-1379. http://dx.doi.org/10.1016/S0891-5849(02)01049-3 PMID: 12419469

[171] Moreira, P.I.; Harris, P.L.; Zhu, X.; Santos, M.S.; Oliveira, C.R.; Smith, M.A.; Perry, G. Lipoic acid and N-acetyl cysteine decrease mitochondrial-related oxidative stress in Alzheimer disease patient fibroblasts. *J. Alzheimers Dis.,* **2007**, *12*(2), 195-206. http://dx.doi.org/10.3233/JAD-2007-12210 PMID: 17917164

[172] Curti, D.; Rognoni, F.; Gasparini, L.; Cattaneo, A.; Paolillo, M.; Racchi, M.; Zani, L.; Bianchetti, A.; Trabucchi, M.; Bergamaschi, S.; Govoni, S. Oxidative metabolism in cultured fibroblasts derived from sporadic Alzheimer's disease (AD) patients. *Neurosci. Lett.,* **1997**, *236*(1), 13-16. http://dx.doi.org/10.1016/S0304-3940(97)00741-6 PMID: 9404940

[173] Ramamoorthy, M.; Sykora, P.; Scheibye-Knudsen, M.; Dunn, C.; Kasmer, C.; Zhang, Y.; Becker, K.G.; Croteau, D.L.; Bohr, V.A. Sporadic Alzheimer disease fibroblasts display an oxidative stress phenotype. *Free Radic. Biol. Med.,* **2012**, *53*(6), 1371-1380. http://dx.doi.org/10.1016/j.freeradbiomed.2012.07.018 PMID: 22885031

[174] Martín-Maestro, P.; Gargini, R.; García, E.; Perry, G.; Avila, J.; García-Escudero, V. Slower dynamics and aged mitochondria in sporadic alzheimer's disease. *Oxid. Med. Cell. Longev.,* **2017**, *2017*, 9302761. http://dx.doi.org/10.1155/2017/9302761 PMID: 29201274

[175] Gibson, G.E.; Huang, H.M. Oxidative processes in the brain and non-neuronal tissues as biomarkers of Alzheimer's disease. *Front. Biosci.,* **2002**, *7*, d1007-d1015. http://dx.doi.org/10.2741/gibson PMID: 11897553

[176] Xu, Z.; Jiang, H.; Zhong, P.; Yan, Z.; Chen, S.; Feng, J. Direct conversion of human fibroblasts to induced serotonergic neurons. *Mol. Psychiatry,* **2016**, *21*(1), 62-70. http://dx.doi.org/10.1038/mp.2015.101 PMID: 26216300

[177] Vadodaria, K.C.; Mertens, J.; Paquola, A.; Bardy, C.; Li, X.; Jappelli, R.; Fung, L.; Marchetto, M.C.; Hamm, M.; Gorris, M.; Koch, P.; Gage, F.H. Generation of functional human serotonergic neurons from fibroblasts. *Mol. Psychiatry,* **2016**, *21*(1), 49-61. http://dx.doi.org/10.1038/mp.2015.161 PMID: 26503761

[178] Vierbuchen, T.; Ostermeier, A.; Pang, Z.P.; Kokubu, Y.; Südhof, T.C.; Wernig, M. Direct conversion of fibroblasts to functional neurons by defined factors. *Nature,* **2010**, *463*(7284), 1035-1041. http://dx.doi.org/10.1038/nature08797 PMID: 20107439

[179] Hu, W.; Qiu, B.; Guan, W.; Wang, Q.; Wang, M.; Li, W.; Gao, L.; Shen, L.; Huang, Y.; Xie, G.; Zhao, H.; Jin, Y.; Tang, B.; Yu, Y.; Zhao, J.; Pei, G. Direct conversion of normal and alzheimer's disease human fibroblasts into neuronal cells by small molecules. *Cell Stem Cell,* **2015**, *17*(2), 204-212. http://dx.doi.org/10.1016/j.stem.2015.07.006 PMID: 26253202

[180] Pfisterer, U.; Kirkeby, A.; Torper, O.; Wood, J.; Nelander, J.; Dufour, A.; Björklund, A.; Lindvall, O.; Jakobsson, J.; Parmar, M. Direct conversion of human fibroblasts to dopaminergic neurons. *Proc. Natl. Acad. Sci. USA,* **2011**, *108*(25), 10343-10348. http://dx.doi.org/10.1073/pnas.1105135108 PMID: 21646515

[181] Xiao, D.; Liu, X.; Zhang, M.; Zou, M.; Deng, Q.; Sun, D.; Bian, X.; Cai, Y.; Guo, Y.; Liu, S.; Li, S.; Shiang, E.; Zhong, H.; Cheng, L.; Xu, H.; Jin, K.; Xiang, M. Direct reprogramming of fibroblasts into neural stem cells by single non-neural progenitor transcription factor Ptf1a. *Nat. Commun.,* **2018**, *9*(1), 2865. http://dx.doi.org/10.1038/s41467-018-05209-1 PMID: 30030434

[182] Gysin, R.; Riederer, I.M.; Cuénod, M.; Do, K.Q.; Riederer, B.M. Skin fibroblast model to study an impaired glutathione synthesis: consequences of a genetic polymorphism on the proteome. *Brain Res. Bull.,* **2009**, *79*(1), 46-52. http://dx.doi.org/10.1016/j.brainresbull.2008.10.015 PMID: 19041695

[183] Slominski, A.; Wortsman, J.; Tobin, D.J. The cutaneous serotoninergic/melatoninergic system: securing a place under the sun. *FASEB J.,* **2005**, *19*(2), 176-194. http://dx.doi.org/10.1096/fj.04-2079rev PMID: 15677341

[184] Welsh, D.J.; Harnett, M.; MacLean, M.; Peacock, A.J. Proliferation and signaling in fibroblasts: role of 5-hydroxytryptamine2A receptor and transporter. *Am. J. Respir. Crit. Care Med.,* **2004**, *170*(3), 252-259. [http://dx.doi.org/10.1164/rccm.200302-264OC PMID: 15087293

[185] Honegger, U.E.; Disler, B.; Wiesmann, U.N. Chronic exposure of human cells in culture to the tricyclic antidepressant desipramine reduces the number of beta-adrenoceptors. *Biochem. Pharmacol.,* **1986**, *35*(11), 1899-1902. http://dx.doi.org/10.1016/0006-2952(86)90309-6 PMID: 3013202

[186] Romeo, B.; Choucha, W.; Fossati, P.; Rotge, J.Y. Meta-analysis of short- and mid-term efficacy of ketamine in unipolar and bipolar depression. *Psychiatry Res.,* **2015**, *230*(2), 682-688. http://dx.doi.org/10.1016/j.psychres.2015.10.032 PMID: 26548981

[187] Kim, Y.K.; Na, K.S. Role of glutamate receptors and glial cells in the pathophysiology of treatment-resistant depression. *Prog. Neuropsychopharmacol. Biol. Psychiatry,* **2016**, *70*, 117-126. http://dx.doi.org/10.1016/j.pnpbp.2016.03.009 PMID: 27046518

[188] Deutschenbaur, L.; Beck, J.; Kiyhankhadiv, A.; Mühlhauser, M.; Borgwardt, S.; Walter, M.; Hasler, G.; Sollberger, D.; Lang, U.E. Role of calcium, glutamate and NMDA in major depression and therapeutic application. *Prog. Neuropsychopharmacol. Biol. Psychiatry,* **2016**, *64*, 325-333. http://dx.doi.org/10.1016/j.pnpbp.2015.02.015 PMID: 25747801

[189] Ortega, F.; Pérez-Sen, R.; Morente, V.; Delicado, E.G.; Miras-Portugal, M.T. P2X7, NMDA and BDNF receptors converge on GSK3 phosphorylation and cooperate to promote survival in cerebellar granule neurons. *Cell. Mol. Life Sci.,* **2010**, *67*(10), 1723-1733. http://dx.doi.org/10.1007/s00018-010-0278-x PMID: 20146080

[190] Castrén, E.; Antila, H. Neuronal plasticity and neurotrophic factors in drug responses. *Mol. Psychiatry,* **2017**, *22*(8), 1085-1095. http://dx.doi.org/10.1038/mp.2017.61 PMID: 28397840

[191] Breitfeld, J.; Scholl, C.; Steffens, M.; Laje, G.; Stingl, J.C. Gene expression and proliferation biomarkers for antidepressant treatment resistance. *Transl. Psychiatry,* **2017**, *7*(3), e1061. http://dx.doi.org/10.1038/tp.2017.16 PMID: 28291260

[192] Breitfeld, J.; Scholl, C.; Steffens, M.; Brandenburg, K.; Probst-Schendzielorz, K.; Efimkina, O.; Gurwitz, D.; Ising, M.; Holsboer, F.; Lucae, S.; Stingl, J.C. Proliferation rates and gene expression profiles in human lymphoblastoid cell lines from patients with depression characterized in response to antidepressant drug therapy. *Transl. Psychiatry,* **2016**, *6*(11), e950. http://dx.doi.org/10.1038/tp.2016.185 PMID: 27845776

[193] Evans, S.J.; Choudary, P.V.; Neal, C.R.; Li, J.Z.; Vawter, M.P.; Tomita, H.; Lopez, J.F.; Thompson, R.C.; Meng, F.; Stead, J.D.; Walsh, D.M.; Myers, R.M.; Bunney, W.E.; Watson, S.J.; Jones, E.G.; Akil, H. Dysregulation of the fibroblast growth factor system in major depression. *Proc. Natl. Acad. Sci. USA,* **2004**, *101*(43), 15506-15511. http://dx.doi.org/10.1073/pnas.0406788101 PMID: 15483108

[194] Rodriguez-Lafrasse, C.; Rousson, R.; Bonnet, J.; Pentchev, P.G.; Louisot, P.; Vanier, M.T. Abnormal cholesterol metabolism in imipramine-treated fibroblast cultures. Similarities with Niemann-Pick type C disease. *Biochim. Biophys. Acta,* **1990**, *1043*(2), 123-128. http://dx.doi.org/10.1016/0005-2760(90)90284-5 PMID: 2317521

[195] Hurwitz, R.; Ferlinz, K.; Sandhoff, K. The tricyclic antidepressant desipramine causes proteolytic degradation of lysosomal sphingomyelinase in human fibroblasts. *Biol. Chem. Hoppe Seyler,* **1994**, *375*(7), 447-450. [http://dx.doi.org/10.1515/bchm3.1994.375.7.447 PMID: 7945993