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LETTER TO THE EDITOR

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Psychological status in depressive patients correlates with metabolic gene expression

Major depressive disorder (MDD) is a psychiatric disease characterized by important mood changes accompanied by other symptoms such as low self-esteem, anhedonia, sleep disorder, cognition, and eating and which is estimated to be the second major illness measured by social and economic burden by 2020.[1] MDD has prevalence about 10% of the general population worldwide, and however, its pathogenic mechanism is still unknown.[1] According to this, the molecular and cellular pathophysiology of MDD is being deeply studied. Several hypotheses suggest an important role of inflammation and the inflammasome complex and impaired bioenergetics pathways in peripheral and central tissues. In this sense, it has been shown significant activation of inflammatory pathways showing increased level of pro-inflammatory cytokines in MDD,[2] and important implications of oxidative stress and mitochondria in MDD where mitochondrial dysfunction biomarkers such as reduced mitochondrial respiratory chain activity, decreased bioenergetic levels and reduced antioxidative defenses have been described in patient with MDD and animal models of depression.[3] However, it is not clear how dysfunctional metabolic pathways can be involved in the psychological status of patients with MDD. Recently, our group has shown a reduced gene expression of mitochondrial biogenesis and antioxidant biosynthesis which showed an implication of mitochondrial metabolism in MDD.[4] Working in the same research line, in this study, we propose to examine whether metabolic changes observed in gene expression are involved in the psychological status of the patients. According to this, we will determine the correlation of gene expression from mitochondrial, antioxidant, and inflammatory pathways with the psychological status of MDD determined by Symptom Distress Checklist (SCL-90-R).

We selected forty patient with MDD diagnosed with melancholic depression according to DSM-IV F33 ICD-10 CODE criteria, by an experimented psychiatrist from the Psychiatry Unit of Hospital Virgen Macarena in Seville, Spain. Diagnosis was established by personal interview by the experimented psychiatrist, and the samples were selected according to the diagnosis of melancholic depression, before antidepressant medication regimen and heparinized blood samples were collected after 12-h fasting from patients by an experimented nurse. Blood mononuclear cells (BMCs) were purified from heparinized blood by isopycnic centrifugation using Histopaque-1119 and Histopaque-1077 (Sigma Chemical Co., St. Louis, MO, USA). All patients were at least 18 years of age (Table 1 in reference 4), and either they gave informed consent to participate in this study. Healthy volunteers were included in the study matching the age range, gender, ethnicity, and demographics of the recruited patients. The healthy volunteers were recruited from among the staff at the Hospital Virgen Macarena in Seville, Spain. Psychological distress was assessed using the SCL-90-R,[5] a 90-item self-report symptom inventory designed to measure a wide range of psychopathological dimensions. Previously, this study was approved by the ethical committee of our institution and protocol has been carried out according to the Declaration of Helsinki and. Data in Figure 1 are shown as mean ± SD. Data between different groups were analyzed statistically using ANOVA on Ranks with Sigma Plot and Sigma Stat statistical software (SPSS for Windows, 19, 2010, SPSS, Inc.) using an all pairwise multiple comparison procedure (Tukey's test) for correction. A value of $P < .05$ was considered significant. Statistical analyses included Pearson's correlation coefficients between gene expression levels and SCL-90 subscales.

Forty female controls and 20 female patients with MDD were selected for this study. There were no statistical differences between groups by age (49.5 ± 6.1 in control groups vs. 46.1 ± 8 in MDD group) and body mass index (BMI) (23.9 ± 1.5 kg/m^2 in control groups vs. 24.2 ± 1.5 kg/m^2); however, we observed increased levels of the BDI score (41.2 ± 5.9) in patient with MDD compared to the control group (4.9 ± 3.2) ($P < .001$) (all this data were showed in our previous study[4]). Previously, the patients showed interesting impairment in the mitochondrial metabolism related to inflammation (IL-6 and TNF-α) and inflammasome (NLRP3 and IL-1β) response, mitochondrial biogenesis (PGC-1α, TFAM, NRF1), and antioxidant defenses (CuZnSOD and MnSOD) in blood monocyte cells (BMCs).[4] We include a study about the autophagy gene expression of microtubule-associated protein 1 light chain 3 (LC3), ATG12, and Beclin 1. BMCs from patient with MDD showed upregulation of autophagy gene expression ($P < .001$) (Figure 1). Interestingly after analyzing statistical correlations between gene expressions and SCL-90-R subscales, we observed an important association of the AMP-activated protein kinase (AMPK) and autophagy gene expressions and the nine subscales (Table 1). In this sense, reduced expression of AMPK is associated by a negative statistical correlation with somatization, obsessive-compulsive, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, and psychoticism, and the increased LC3 gene expression is associated by a positive statistical correlation with the nine subscales (Table 1). Indeed, other metabolic and autophagy gene expressions were related with the different subscales. According to this, MnSOD showed negative correlations with somatization, interpersonal sensitivity and phobic anxiety, paranoid ideation, psychoticism, PGC-1α with interpersonal sensitivity, and paranoid ideation, and other correlations were observed with inflammatory and inflammasome gene expressions (Table 1).

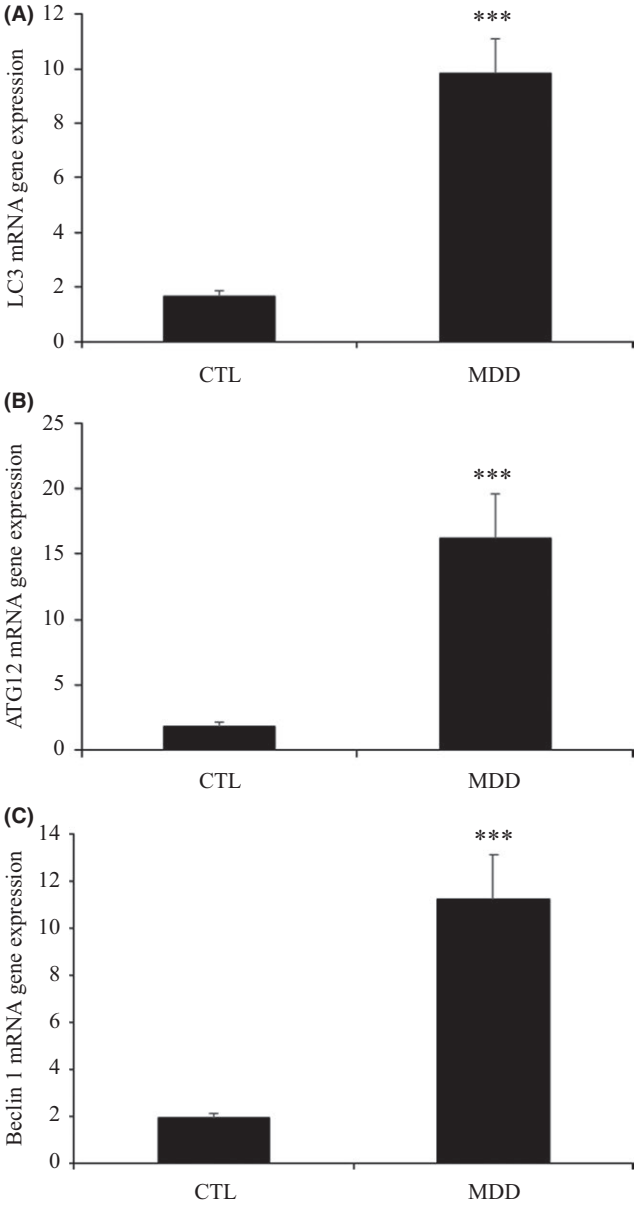

FIGURE 1 Autophagy gene expression profile in patients compared to healthy controls. n = 40 and 20 for MDD and control groups, respectively. Relative gene expressions of LC3 (A), ATG12 (B), and Beclin 1 (C), (means ± SD) determined by quantitative PCR in BMCs. ***P < .001 between patients and controls. BMCs, blood mononuclear cells; MDD, major depressive disorder

AMPK and autophagy (LC3, ATG12) were the most correlated genes. It is very interesting because both are involved in many different processes about the homeostasis. In this sense, autophagy has been implicated in the pathophysiology of MDD[6] and involved in the antidepressant treatment responses and the inflammasome inhibition in depressive patients.[7,8] Dysregulation of the autophagic pathways has several consequences such as reduced control of oxidative stress and inflammation[6] which are involved in the pathophysiology of MDD. According to this, our study shows data in the same line because dysregulated autophagy was associated with the altered antioxidant gene expressions and increased inflammation

TABLE 1 Correlation between gene expression and SCL-90-R findings in patients

	SOD 1	SOD 2	IL-6	IL-8	TNF-alpha	PGC1alpha	NRF1	AMPK	LKB1	NLRP3	IL-1beta	LC3	ATG12	Beclin 1
PDSOM	−0.105	−0.332*	0.076	−0.007	−0.115	−0.175	0.127	−0.579***	0.228	0.233	0.346*	0.697***	0.519***	0.499**
PDOBS	−0.321*	−0.259	0.272	−0.312	−0.209	−0.170	0.248	−0.656***	0.029	0.409**	0.212	0.581***	0.441**	0.384*
PDINT	−0.217	−0.517***	0.180	−0.462	−0.184	−0.380*	0.223	−0.888***	0.237	0.281	0.270	0.553***	0.451**	0.398*
PDDEP	−0.250	−0.223	0.303	−0.372	−0.001	0.082	0.227	−0.685***	0.172	0.546***	0.350*	0.551***	0.390*	0.135
PDANS	−0.116	−0.193	0.038	−0.345	−0.234	−0.009	−0.017	−0.697***	0.245	0.264	−0.021	0.862***	0.598***	0.250
PDHOS	0.017	−0.273	−0.071	−0.619	−0.100	−0.314	0.277	−0.886***	0.302	0.249	0.071	0.564***	0.656***	0.418**
PDFOB	−0.280	−0.590***	0.261	−0.454	−0.088	−0.204	0.060	−0.792***	0.260	0.321*	0.273	0.522***	0.219	0.034
PDPAR	−0.122	−0.607***	0.059	−0.191	−0.251	−0.437**	0.159	−0.758***	0.272	0.029	0.266	0.660***	0.449**	0.494**
PDPSI	−0.121	−0.393*	0.103	−0.593	−0.135	−0.252	0.212	−0.910***	0.249	0.297	0.152	0.624***	0.548***	0.289

PDSOM, somatization; PDOBS, obsessive-compulsive; PDINT, interpersonal sensitivity; PDDEP, depression; PDANS, anxiety; PDHOS, hostility; PDFOB, phobic anxiety; PDPAR, paranoid ideation; PDPSI, psychoticism; Pearson's correlation coefficient.
*P < .05; **P < .01; ***P < .001.

and inflammasome pathways. So, the correlation observed with psychological status proposes an interesting molecular targets in which a pharmacological correction could improve the psychological status of the patients.[6,7] Furthermore, AMPK has been demonstrated to play roles in regulating autophagy,[9] so the AMPK impairment would induce a deleterious control of autophagy. Autophagy is very important for most cells in various tissues including the central nervous system. It is sensitive to the accumulation of toxic proteins and damaged organelles, so neuronal autophagy signaling pathways play an important role in MDD.[6] In this study, we aimed to investigate whether molecular changes in depression are associated with the development of psychopathological symptoms. Many changes in molecular gene expressions are associated with MDD patients. Our study shows a very high correlation of these molecular changes with SCL-90-R subscales proposing a biological connection between molecular pathophysiology and clinical profile of MDD. As discussed above, pharmacological approach to autophagy could be an interesting target, but also, antioxidant therapy could propose another molecular target to improve psychological status in patient with MDD, which has been proposed.[10] In this sense, molecular modification of the gene expression showed in this study could be the basis for a valuable new therapeutic target/strategy and the association between the biological changes with psychological status of the patients. However, we are aware of the limitation of our work, taking into account the reduced number of patients and control included in the study, the only inclusion of women, and dietary intake according to several diet habits that could induce inflammatory events. Furthermore, our results suggest a potential for a composite gene expression measure as a diagnostic biomarker. Given the complexity of the disease, the findings need replication in larger samples.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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