Can (immune and other) gene expression help us to treat depression?

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ABSTRACT

It is becoming clearer that it might be a combination of different biological processes such as genetic, environmental, and psychological factors, together with immune system, stress response, brain neuroplasticity and the regulation of neurotransmitters, that leads to the development of major depressive disorder (MDD). A growing number of studies have tried to investigate the underlying mechanisms of MDD by analysing the expression levels of genes (mRNA) involved in such biological processes. In this review, I have highlighted a possible key role that gene expression might play in the treatment of MDD. This is critical because many patients do not respond to antidepressant treatment or can experience side effects, causing treatment to be interrupted. Unfortunately, selecting the best antidepressant for each individual is still largely a matter of making an informed guess.

1. Introduction

Major depressive disorder (MDD) is a complex psychiatric disorder and one of the main causes of disability worldwide and a major contributor to the overall global burden of disease (James et al., 2018). It is believed that the cause of MDD is a combination of genetic, environmental, and psychological factors. In fact, for instance, environmental factors and stressful adverse events experienced in childhood can affect biological systems in the brain, but also pathophysiological pathways within the entire body (Penninx et al., 2013; Belmaker and Agam, 2008). Furthermore, well-established evidence indicates that, in the pathogenesis of MDD, inflammatory response, as well as the hypothalamus-pituitary-adrenal (HPA) axis and several neuronal systems are dysregulated (Sullivan et al., 2006; Menke et al., 2012; Pitharouli et al., 2021). As such, both acute and chronic stress have been suggested as triggers of the dysregulation of these systems, leading to the development of MDD (Segman et al., 2010). While antidepressant therapy is an important treatment for MDD, a significant number of patients do not respond to it or experience serious side effects such as gastrointestinal disruptions, anxiety, agitation, and insomnia (Ferguson, 2001; https://www.inspiretheminn, 2019). Various research has been conducted to date in order to recognise and verify biomarkers involved in the response to antidepressant treatment. This could pave the way for personalised medicine, improving treatment effectiveness and reducing side effects.

Among others, gene expression is being used as an approach to understanding the molecular mechanisms underlying MDD. To date, the majority of research has primarily looked at gene expression levels in MDD patients’ post-mortem brain tissue (Mehta et al., 2010). Because of the effect of agonal and post-mortem factors on gene expression, the use of brain tissue is restricted and has many limitations (Tomita et al., 2004), while the use of peripheral blood samples appears to have numerous advantages. Indeed, peripheral blood samples allow the collection of large sample sizes, rapid RNA stabilisation, and isolation of specific cell subtypes, such as peripheral blood mononuclear cells (PBMCs) or leukocytes, as well as the monitoring of patients’ health.

Sullivan and colleagues (Sullivan et al., 2006) demonstrated the connection between the brain and the periphery several years ago, finding genes shared by whole blood and 16 brain tissues, with 60% of transcripts expressed in whole blood and at least one central nervous system tissue (CNS). In detail, genes relevant to MDD encoding neurotransmitter receptors and transporters, growth factors, hormones, and cytokines are expressed similarly in whole blood and brain tissues. In addition to these findings, transcriptional profiling of peripheral blood has led to the identification of many potential biomarkers, such as genes involved in the regulation of cell cycle, immune response and DNA repair, for patients with psychological and neurological conditions, including MDD (Menke et al., 2012; Segman et al., 2010; Spijker et al., 2010).

In our recent review (in press), we have presented several studies that looked at the expression levels of various genes in MDD patients, primarily using whole blood but also isolated mononuclear cells, isolated monocytes, and post-mortem brain tissues. Altogether, these studies have discovered a pattern of altered expression in many genes related to inflammation, neurotransmission, the HPA axis, and neuroplasticity, among other biological systems. Furthermore, our group has carried out
the largest non-interventional study so far investigating candidate mRNA gene expression in depressed patients characterised by their current depressive symptoms and by their response to antidepressant treatment (Cattaneo et al., 2020). We have found similarities in the expression of some genes (including the purinergic receptor P2RX7, interleukin (IL)-1β, beta, IL-6, TNF-α, macrophage inhibiting factor (MIF) and glucocorticoid receptor (GR)) between treatment-resistant and drug-free depressed patients, whereas responsive patients were alike controls. Hence, the use of the measurement of gene expression levels could be particularly helpful in the clinical setting for an early prediction of treatment response in MDD patients. This review aims to discuss the possible use of gene expression as a tool to improve the treatment of depression by reporting studies that looked at mRNA levels as biomarkers for predicting treatment outcomes.

2. Gene expression and treatment response

To provide evidence supporting a personalised medicine strategy for the treatment of MDD, Cattaneo et al. (2013) examined the blood mRNA expression levels of 15 candidate genes across three biological systems, including the GR complex, inflammation, and neuroplasticity that have been more consistently identified as abnormal in MDD (Chopra et al., 2011). For this purpose, they looked at a well-characterised sample of MDD patients from the GENDEP study (Uber et al., 2009, 2010) before and after 8 weeks of treatment with one of two pharmacologically distinct antidepressants: escitalopram, a selective serotonin reuptake inhibitor, and nortriptyline, a tricyclic noradrenaline reuptake inhibitor. The transcriptional levels of the following five genes were measured: FK506-binding protein (FKBP)-4 and FKBP-5, and GR for the GR complex; IL-1α, IL-1β, IL-4, IL-6, IL-7, IL-8, IL-10, MIF, and TNF-α for the inflammatory system; brain-derived neurotrophic factor (BDNF), p11, VGF for neuroplasticity.

The findings revealed a distinction between genes that predict treatment response (‘predictors’) and genes that changed over time in patients who respond to antidepressant treatment (‘targets’). Only higher levels of three inflammation-related genes, IL-1β, MIF, and TNF-α, among the 15 genes, predict a lack of antidepressant response, even if a good antidepressant response is not correlated with a reduction in these genes. A successful antidepressant response on the other hand is linked to a decrease in the inflammation-related gene IL-6, as well as the GR-associated gene FKBP-5, and an increase in the neuroplasticity-associated gene, VGF and BDNF.

Following this research, our group conducted the largest non-interventional study to date investigating candidate mRNA gene expression in depressed patients characterised by current depressive symptoms and antidepressant treatment response (Cattaneo et al., 2020). As previously mentioned, treatment-resistant and drug-free depressed patients have higher inflammasome activation (higher proinflammatory cytokines/chemokines and P2RX7 mRNA expression) and glucocorticoid resistance (lower GR and higher FKBP5 mRNA expression), while responsive patients were similar to controls except for having lower CXCL12, a chemokine involved in animal models of depression characterised by inflammation and glucocorticoid resistance (Niraula et al., 2018). These results suggest that treatment-resistant and drug-free patients come, at least in part, from phenotypically similar groups. Moreover, candidate gene studies and gene-to-environment interaction studies have related the serotonin transporter to MDD, implying that it plays a key role in MDD pathophysiology (Clarke et al., 2010; Karg et al., 2011). Many antidepressants target the serotonin transporter protein (SLC6A4), though the connection between pathophysiology and antidepressant therapeutic effects is still unclear (Sibille and Lewis, 2006; Lesch, 2001). For this reason, Belzeaux et al. (2014) investigated whether SLC6A4 mRNA may be a target biomarker of antidepressant therapy during a major depressive episode that differs between the baseline and the 30-week follow-up duration in responder patients based on previous research on SLC6A4 mRNA gene expression variation in peripheral tissues. Interestingly, decreased expression levels of SLC6A4 were observed in responder patients across a 30-week follow-up, whereas non-responder subjects showed increased mRNA levels of SLC6A4. Healthy controls, on the other hand, showed a consistent pattern of SLC6A4 mRNA expression over 30 weeks. These findings suggest that the serotonin transporter protein, which is the main target of several antidepressants, may be a useful biomarker for personalised medicine in MDD patients.

Furthermore, several studies have indicated a connection between effects on neuroplasticity and clinical reaction to antidepressant drug therapy, according to the neurotrophic hypothesis of MDD which, indeed, postulates that neuronal plasticity is a key factor in the development of depression and the clinical response to antidepressants. Breitfield et al. (2017), for example, looked for a connection between functional biomarkers linked to antidepressant neuroplasticity effects and treatment response and resistance in patient-derived lymphoblastoid cell lines (LCLs) from the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) research. The STAR*D trial enrolled outpatients with nonpsychotic major depressive disorder treated prospectively in a series of randomized controlled trials. They identified five potential biomarkers: transcription factor 7-like 2 (TCF7L2), frizzled class receptor 7 (FZD7), wingless-type MMTV integration site family member 2B (WNT2B), p-glycoprotein (ABCB1), and sulfotransferase 1 (SULTF1), which have been linked to cell proliferative effects of antidepressants (ex vivo) or LCL donors’ clinical response (SULTA41). WNT2B, FZD7, and ABCB1 were found to have the most significant variations in expression levels between responder- and treatment resistance-derived LCLs. ABCB1 is the most studied member of the ATP-binding cassette (ABC) transporter family and it is involved in cellular detoxification as well as transmembrane transport across the blood-brain barrier. Since neurotoxic agents (such as glucocorticoids, medications, and xenobiotics) are included in the solutes that are transported across lipid bilayers, ABCB1 has neuroprotective effects, potentially increasing antidepressant response. WNT2B and FZD7 are components of the WNT signalling pathway which controls neurogenesis, synaptic plasticity, and dendritic arborization (Inestrosa and Arenas, 2010). WNT2B and chronic antidepressant therapy stimulate this pathway, resulting in increased neurogenesis, while FZD7 inhibits it. Overall, these effects may be responsible for increased neuronal plasticity and most likely MDD remission.

Another intriguing MDD theory is that the inflammasome acts as a key mediator, allowing psychological and physical stressors to lead to the disorder’s development (Iwata et al., 2013). In this regard, Alcocer-Gomez et al. (2014) investigated this hypothesis to see whether the NLRP3 inflammasome could be triggered in MDD patients’ PBMC and to learn more about the function of mitochondrial oxidative stress. They also looked at how amitriptyline, a tricyclic antidepressant, affected NLRP3 inflammasome activation. The researchers discovered that MDD patients had lower levels of IL-1β and IL-18 in their blood, as well as lower levels of NLRP3 and caspase-1 activation. Furthermore, they have found a positive correlation between depressive symptoms scores and IL-1β and IL-18 serum levels, suggesting that high IL1-β and IL-18 levels may have a role in the pathophysiology of MDD. However, when controlling for antidepressant therapy, this association was reduced, implying that antidepressants can modulate inflammation levels.

Additionally, the mitochondrial translocator protein (TSPO), a 5-helical transmembrane protein found in the outer mitochondrial membrane of different cell types including microglia, is another promising candidate in the field of pharmaceutical treatment options for MDD (Stupprech et al., 2010). It has implications in the pathophysiology of immune, inflammatory, neurodegenerative, neoplastic, and psychiatric diseases because it plays a key role in neurosteroid synthesis and systemic endocrine control (Gut et al., 2015). In fact, different studies have shown that TSPO ligands are involved in the regulation of microglial activation (Choi et al., 2011; Karlstetter et al., 2014; Axrad et al., 2019; Yao et al., 2020) and its protein level is remarkably upregulated in activated glial cells, especially in microglia during neural disorders or injury (Kim and...
Yu, 2015).

Interestingly, Sarubin et al. (2016) looked at the effects of antidepressant therapy on TSPO expression levels in platelets from 37 patients with MDD, comparing TSPO levels in depressed patients before and after 6 weeks of antidepressant treatment. Within the entire group of MDD patients, there was a substantial improvement in TSPO levels after 6 weeks of treatment. Responders had a larger reduction in TSPO levels than non-responders, which was surprising. These findings contradict the authors’ hypothesis, which predicted that antidepressant treatment will result in increased TSPO levels as well as a reduction in depressive symptoms. As a result, they concluded that TSPO expression in platelets is not a suitable biomarker for assessing the progression of MDD.

Importantly, Hennings et al. have used microarray analyses performed on peripheral blood samples collected at the admission and after 2 and 5 weeks of treatment from MDD patients remitters and non-responders, in order to identify a broader range of genes that could be implicated in the response to antidepressant therapy (Hennings et al., 2015). High-throughput technologies such as microarrays allow exploring the expression levels of the whole genome and the identification of changes in gene expression by using a hypothesis-free approach. In their study, Hennings et al. have identified a total of 127 transcripts significantly associated with the treatment response. The authors also analysed these transcripts in an independent replication sample of 142 depressed inpatients confirming that lower expression of retinoid-related orphan receptor alpha (RORa), germinal centre expressed transcript 2 (GCET2) and chitinase 3-like protein 2 (CHI3L2) on admission was

### Table 1

| Citation | Sample | Antidepressant treatment | Methods | Gene | Main findings | Tissue |
|----------|--------|--------------------------|---------|------|---------------|--------|
| Cattaneo et al., 2013 | 811 adult outpatients suffering from unipolar depression: 51 responders 23 non-responders 34 healthy controls: 19 males 15 females | Escitalopram Nortriptyline | RT-qPCR | FKBP-4 FKBP-5 GR IL-1α IL-1β IL-4 IL-6 IL-7 IL-8 IL-10 TNF-α MIF BDNF p11 VGF | Higher levels of IL-1β, IL-6, MIF, TNF-α and FKBP-5, in depressed patients as compared with controls. Lower levels of IL-4, GR, BDNF, p11, and VGF in depressed patients as compared with controls. Antidepressant treatment significantly reduced FKBP5, IL-1β, MIF, TNF-α, IL-6 and VGF levels only in patients who responded to the treatment and increased GR mRNA levels and p11 levels. Antidepressant treatment increased BDNF expression more in the responders than in the non-responders. | Peripheral blood |
| Hennings et al., 2015(36) | 24 male MDD patients: 12 responders 12 non-responders 142 unipolar depressed patients: 80 responders 62 non-responders | Different antidepressants | Microarray | | | Peripheral blood |
| Belzeaux et al., 2014 | 13 patients with severe major depressive episode 13 healthy controls | Imipramine | RT-qPCR | SLC6A4 | Decrease of SLC6A4 mRNA expression in responder patients across a 30-week follow-up, while non-responder patients exhibited up-regulated SLC6A4 mRNA. | PBMC |
| Breitfeld et al., 2017 | 25 therapy-resistant patients 25 first-line therapy responders | Different antidepressants | RT-qPCR | WNT2B FZD7 ABCB1 | Significantly increased levels of genes WNT2B, FZD7 and ABCB1 in responder-derived cell lines when compared with controls, fold changes by SSRIs. | Lymphoblastoid cell lines |
| Cattaneo et al., 2020 | 130 MDD patients: 36 Treatment-responsive 36 Drug-free 36 Treatment-resistant 40 healthy controls | Different antidepressants | RT-qPCR | IL-1β IL-6 MIF TNF-α P2RX7 CCL2 CXCL12 AQP4 IQG15 STAT1 USP18 FKBP5 GR SGK1 | Evidence of increased inflammusome activation (higher proinflammatory cytokines/chemokines and P2RX7 mRNAs expression) in treatment-resistant and drug-free depressed patients compared with controls and responsive patients. Lower GR and higher FKBP5 mRNAs expression in treatment-resistant and drug-free depressed patients when compared to controls and responsive patients. Responsive patients were indistinguishable from controls, except for having lower CXCL12. | Peripheral blood |
| Alcocer-Gómez et al., 2013 | 40 MDD patients: 20 without treatments 20 treated | Amitriptyline Western blot | RT-qPCR | NLRP3 Caspase1 IL-1β IL-18 ROS LPO | Increased gene expression of NLRP3 and caspase-1 in blood cells in non-treated patients as compared with treated patients. Increased serum levels of IL-1β and IL-18 in non-treated patients as compared with treated patients. Amitriptyline treatment reduced NLRP3 and caspase-1 gene expression, and IL-1β and IL-18 serum levels. Oxidative damage was higher in MDD patients treated with amitriptyline. | PBMC |

MDD: Major depressive disorder; PCR: Polymerase chain reaction; RT-qPCR: Reverse transcription (RT) quantitative PCR
associated with beneficial treatment response. In addition, leukocyte-specific protein 1 (LSP1) significantly decreased after 5 weeks of treatment in MDD responder patients (Hennings et al., 2015).

Overall, according to the above-mentioned studies (Table 1), patients who responded to antidepressant therapy had restored levels of inflammation-related genes like IL-6 and IL-1β, stress-related genes like FKBP-5, and neuroplasticity-related genes like VGF and BDNF. Moreover, the above findings, including our findings in responder and non-responder patients (Cattaneo et al., 2020), have highlighted how the gene expression variation of selected genes, monitored over time, might be informative of clinical evolution and possible relapses or recurrences for MDD.

3. Clinical implications

As discussed extensively in this review, mRNA biomarkers can be used to predict antidepressant response when measured at baseline or to track treatment effectiveness when measured during treatment. This could lead to an increase in antidepressant response, resulting in a boost for depressed patients as well as a decrease in healthcare costs. Moreover, this evidence is consistent with our research showing transient depressive symptoms following administration of a pro-inflammatory challenge (Nettis et al., 2020) improved antidepressant response by the anti-inflammatory, minocyline, in patients with high levels of inflammation (Nettis et al., 2021). Minocyline is a tetracycline antibiotic with broad anti-inflammatory properties and, importantly, good penetration into the CNS through the blood-brain barrier which accounts for its neuroprotective ability (Soczynska et al., 2012). Indeed, this drug has inhibitory actions on mechanisms relevant to ‘inflammation-induced depression’, such as the kynurenine and the p-38 pathways (Roman and Irwin, 2020).

In this context, inflammatory mediators, particularly when measured in terms of mRNA levels, are an excellent example of how they can be used to predict treatment response in MDD patients without having to worry about the existence of similar levels in the brain. As a result, blood may be used to diagnose and prognosticate MDD by profiling peripheral gene expression levels of blood cells (Sullivan et al., 2006; Liew et al., 2006).

However, no gene expression biomarkers have yet been translated into clinical practice, since most of the available studies have relied on laboratory-specific assays that are primarily focused on relative rather than absolute quantification. The relative quantification approach compares the expression levels of a target gene in one group to those in another, such as patients and controls, with the help of internal controls (housekeeping genes) to normalise the results. While absolute quantification is based on a standard curve created from known template concentration samples. After that, every unknown sample’s concentration can be calculated by interpolating its signal into this standard curve. While it would be difficult to incorporate a relative gene expression-based approach into routine clinical practice, an approach focused on absolute gene expression quantification could be the best to use in the clinical setting since it can help clinicians predict and control antidepressant response in less time. Remarkably, absolute mRNA values allow for the establishment of defined thresholds that are more likely to be individually measured and comparable across different laboratories due to these standard parameters. For example, patients with absolute mRNA values of pro-inflammatory cytokines below the suggested cut-off could receive standard of care treatment with conventional antidepressant drugs, whereas patients with absolute mRNA values higher than the suggested cut-off could be steered into more assertive antidepressant strategies early on, with patients receiving a combination of antidepressant drugs or adjuvant therapies such as anti-inflammatory drugs to push down the inflammatory status making the antidepressant therapies more efficacious.

Hence, absolute quantification of gene expression biomarkers could prevent depressed patients from being exposed to ineffective pharmacological interventions based on trial and error.

4. Conclusions

In this review, I have presented several studies which have investigated the expression levels of different genes in MDD patients, mostly obtained from whole blood, but also from isolated mononuclear cells, isolated leukocytes. Altogether these studies have identified a pattern of altered expression in several genes belonging to different biological systems such as inflammation, neurotransmission, HPA axis and neuroplasticity associated with antidepressant treatment response. Overall, these findings suggest that measuring gene expression levels, and immune genes expression levels, may be particularly useful in the clinical setting for predicting treatment response in MDD patients.

It is important to highlight that over 35% of depressed patients fail to respond to two or more antidepressant treatments and that the prescription of antidepressant medications is currently based on clinical characteristics (e.g., possible side-effect and previous history of response) or non-clinical factors (e.g., patient or provider preference, cost and availability on insurer’s approved drug list) (Gelenberg et al., 2010), rather than biological features. Hence, the clinical practice continues to be a trial-and-error method that requires multiple treatment studies to reach adequate symptomatic control for a majority of MDD patients (Rush et al., 2006a, 2006b). Thus, there is an urgent need to personalize antidepressant treatment by maximizing the likelihood of improvement and minimizing the risk of adverse events (Trivedi, 2016). With this purpose, recent studies have started using different machine learning approaches for building predictive models of antidepressant treatment outcomes with the usage of genetic and clinical biomarkers (Lin et al., 2018). Machine learning algorithms have been created for analysing complex multivariate data with a focus on empirical predictive power and generalizability. Machine learning has demonstrated success in clinical psychiatry in terms of diagnosis, prognosis, treatment decisions, and biomarker detection (Dwyer et al., 2018), with one recent study demonstrating the effective use of this tool in identifying a serum microRNA signature for Alzheimer’s disease that could predict disease status with 85.7% accuracy (Zhao et al., 2020). To conclude with a positive and promising note, a study by Qi et al. (2020) have shown preliminary evidence that machine learning-based analysis of blood microRNA profiles could also be a reliable method to discover bio-markers of the clinical status and evolution of MDD, facilitating a more personalised approach to the treatment of patients with MDD (Trivedi et al., 2016).

Declaration of competing interest

The author declares no conflicts of interest.

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