Gene expression profile associated with major depression and with antidepressant response

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METHODS

We have analysed the expression levels of genes involved in HPA axis functionality (GR, FKBP-5 and FKBP-6), inflammation (IL-1, IL-6, IL-10, 4, IL-6, IL-7, IL-8, IL-10, MF and TNF-α) and neuroplasticity (BDNF, VGF and p11) in 74 depressed patients and 49 controls. Depressive symptoms were assessed by weekly administration of three established measures of depression severity: the clinician-rated 10-item Montgomery-Asberg Depression Rating Scale (MADRS), the 17-item Hamilton Rating Scale for Depression (HRS-D-17) and the Beck Depression Inventory (BDI). The response to antidepressant medication was quantified as percentage reduction in MADRS score from baseline to week 12, and responder patients were identified as patients. Controls were screened using the Psychosis Screening Questionnaire (PSQ), and excluded if they met criteria for a present or past psychotic disorder. Controls were also excluded if they had any kind of hormonal treatment.

CONCLUSIONS

Our main finding is that the expression levels of three pro-inflammatory cytokines, namely IL-1 α and TNF-α and MF predict the treatment outcome. In particular we found that the best predictive model was when considering all the three cytokines in the linear expression, suggesting that they tap in both similar and different molecular mechanisms. Moreover, we find that some genes are both abnormal in depressed patients (vs. controls) and are normalized by antidepressant treatment, but not in combination with antidepressant response (at least within the 8 weeks time-frame), suggesting that some biological abnormalities in depression are targeted by antidepressants pharmacological action but not in patients who are not improving.

Finally, a normalization of FKBP5 levels in depressed patients only suggest that depression is characterized by the coexistence of higher FKBP5 and lower GR, leading to GR resistance, and that antidepressant treatment requires normalization of GR function via normalization of both genes.

References


Non-responders had higher mRNA levels of the three pro-inflammatory cytokines, IL-1α (+58%, F=87.7, p<0.0001), IL-6 (+27%, F=69.4, p<0.0001) and TNF-α (+33%, F=55.9, p<0.0001), and lower levels of MIF (+48%, F=14.6, p<0.0001) and TNF-α (+58%, F=58.7, p<0.0001), and lower levels of IL-4 (-9%, F=5.6, p=0.02). Finally, depressed patients had lower mRNA levels of the neuroplastic molecules, BDNF (-24%, F=46.5, p<0.0001), p11 (-16%, F=12.1, p=0.001) and VGF (-36%, F=37.3, p<0.0001).

Baseline differences in biomarkers between responders and non-responders (‘predictors’).

Based on the percentage change in MADRS score, in our cohort of depressed patients we had 51 responders and 23 non-responders.

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