Identifying Molecular Patterns in Response to Antidepressants and Antipsychotics

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Treatment for psychiatric disorders such as Major Depressive Disorder (MDD) and Schizophrenia (SCZ) relies on trial and error to identify the most effective medication for a given patient, sometimes even resulting in a worsening of their clinical profile. Though MDD and SCZ have been extensively studied, a predictive model for medication response has yet to be established. Blood plasma shows potential, permitting minimally invasive collection while paving the way for more personalized treatment. Initial proteomic investigations have been carried out and which will be integrated with future metabolomic and lipidomic data.

We conducted a longitudinal proteomic analysis of plasma samples from MDD (n=30) and SCZ (n=50) patients upon hospital admission and after six weeks of treatment with different medications, and stratified into poor and good responders. We performed a quantitative, label-free, shotgun proteomic analysis with data-independent acquisition (LC-MS/MS-DIA). Data were processed for both differential expression and ontological overrepresentation to understand the biological pathways associated with a positive or negative response to medication.

Preliminary results from the SCZ cohort analysis showed that responders to antipsychotics share pathway alterations such as cholesterol metabolism and regulation of IGF transport and uptake by IGFBPs. Benzepine responders present longitudinal alterations in non-responders: IL1 and megakaryocytes in obesity and selenium metabolism, which may be related to metabolic syndrome in patients.

In the next steps, global lipid and metabolic profiles will be collected, whereupon machine learning strategies will be employed to establish a predictive model using combined protein, lipid, and metabolite data to generate a model capable of predicting the type of response a patient
may exhibit to a given treatment option, allowing psychiatrists to make more informed and precise medication selections. While these data will be applicable only to the currently studied psychiatric diseases, this pipeline may show potential for extension to other diseases.

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