M54. PHARMACO-EPIGENOMIC RESPONSE OF ANTIPSYCHOTIC DRUGS IN THERANOSTICS OF SCHIZOPHRENIA
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Background Antipsychotic drugs are considered as the first line treatment for psychotic disorders including Schizophrenia. The patients receiving antipsychotic medications show a wide variability in drug response and drug induced side effects which could be attributed to genetic or non-genetic components influencing drug response. Epigenetic mechanisms can offer an alternate mechanism for interindividual drug variability which cannot be explained by genetic polymorphisms. The present study involves evaluating the epigenetic modifications induced by antipsychotic drugs, first in an in-vitro system and then follows it up, to understand its implication in therapeutic response in schizophrenia patients.

Methods In the in-vitro study, HepG2, a liver cell line was treated with various antipsychotic drugs including haloperidol, clozapine and olanzapine in varying concentrations for different time interval, either individually or in combination. Various epigenetic parameters were measured at global as well as gene specific level post antipsychotic treatment. Assessment of global DNA methylation and global histone modifications were carried out. The gene expression status of various epigenetic genes and pharmacologically relevant genes and their target miRNA profiles were also evaluated. The conclusions from in-vitro data were extrapolated to a clinical setting by validating the observations between schizophrenia and healthy subjects and between drug responsive and non-responsive schizophrenia patients.

Results Our in-vitro data showed that antipsychotic drugs induced increase in global DNA methylation at 5-methylcytosine and 5-hydroxymethylcytosine level in a dosage and time dependent manner. These alterations in methylation were attributed to the increase in gene expression of various epigenetic genes including DNA methyltransferases, methyl CpG binding proteins and DNA demethylases which in turn was regulated by their target microRNAs. The gene expression of various pharmacologically relevant genes including multi drug transporter and drug metabolizing enzymes were upregulated by antipsychotic drugs and this was mediated by altered expression of miRNAs that regulate these genes. Validation of in-vitro observations in a clinical setting have shown that global DNA methylation, epigenetic as well as pharmacologically relevant gene expression and their target microRNA expression was significantly different between drug responders, non responders and controls. Also the epigenetic alterations were markedly associated with drug response rather than disease pathogenesis.

Discussion Our in-vitro data followed up with clinical data suggest that antipsychotic drugs can modulate the epigenome. The responsiveness to antipsychotic drugs shown by Schizophrenia patients is due to various epigenetic events induced by antipsychotic drugs, clearly suggesting the epigenetic mode of action of antipsychotic drugs. The study also highlights that the reported epigenetic alteration in schizophrenia may be influenced by antipsychotic drugs and not precisely for pathogenesis. The outcome of the study would help us to understand the role of epigenetic mechanisms in the pharmacological effects of antipsychotic medications and address the issue of interindividual variability in drug response.

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