

Assessment of gene expression profiles of peripheral blood mononuclear cells from patients with a history of carbamazepine hypersensitivity

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Abstract

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Background Carbamazepine (CBZ) therapy is associated with hypersensitivity reactions, which can be multisystemic and sometimes fatal. The pathogenesis of these reactions is incompletely understood but heterologous immunity generated to viral antigens has been proposed as a potential mechanism. Our aim was to investigate changes in gene expression profiles of peripheral blood mononuclear cells (PBMCs) from patients with CBZ hypersensitivity to characterise the pathways involved in immune activation.

Methods PBMCs were isolated from five individuals with a history of hypersensitivity to CBZ. The PBMCs were incubated for 24 h with CBZ, carbamazepine 10,11-epoxide (CBZE), cell culture medium, or tetanus toxoid. Expression profiles for mRNA and microRNA were generated with microarrays (Affymetrix, Santa Clara, CA, USA). Differential gene expression was undertaken by limma analysis in the R statistical software. Ingenuity pathway analysis (IPA) was used to define the molecular mechanisms in development of CBZ hypersensitivity.

Findings Incubation of PBMCs with CBZ, CBZE, and tetanus toxoid led to significant differential expression (\log_2 -fold change >1 or <-1 , $p<0.05$) of multiple mRNA ($n=204$) and microRNA ($n=148$) transcripts with little overlap between the different incubation conditions. The top differentially expressed genes for CBZ-treated and CBZE-treated cells identified in IPA analysis were *COX8A*, *IFI35*, *IFIT3*, *PARP9*, *PARP12*, *PTGES*, *RSAD2*, *USP18*, *USP41*, *miR433*, *miR455*, *miR3194*, *miR4723*, and *miR345*. These genes were highly interconnected in functional networks and defined five top functional categories—namely, viral infection, psoriasis, inflammation of body region or organ, and antiviral response.

Interpretation Incubation of PBMCs from CBZ hypersensitive individuals with CBZ or CBZE led to treatment-specific changes in gene expression associated with activation of antiviral and inflammatory pathways. These CBZ-specific and CBZE-specific mRNA and microRNA changes could potentially act as novel diagnostic biomarkers and treatment targets for CBZ hypersensitivity reactions, but further validation and confirmation of specificity in larger numbers of patients are needed.

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Contributors

VY, KP, DN, and MP conceptualised the study. VY, EZ, KC, FF, OV, and MP were responsible for methodology. VY, EZ, and LR conducted investigations. VY, EZ, KC, BF, and OV analysed the data. VY and MP acquired funding and drafted the abstract. VY, EZ, BF, OV, DN, and MP reviewed and edited the abstract. FF, OV, KP, and MP supervised the study.

Declaration of interests

We declare no competing interests.