TRANSPIRTOME ANALYSIS REVEALS ADAPTIVE RESPONSES TO HYPOXIA IN THE CEREBRAL CORTEX OF CHOLESTATIC MICE

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Introduction

• Patients with cholestatic liver diseases (CLDs) commonly experience adverse disease-associated symptoms including altered mood, fatigue, cognitive dysfunction, decreased motivation, and social withdrawal that significantly diminish their quality of life.[1-3] (collectively termed sickness behaviors[4-6]).

• How CLD induces alterations in brain function, leading to sickness behaviors is poorly understood and represents a significant knowledge gap that impedes the development of new therapeutic approaches to treat them[7].

• Using near infrared spectroscopy (NIRS) we have shown frontal cerebral cortex (FC) hypoxia associated with significant dysregulation of cortical neurovascular coupling (mechanism linking transient nerve activity change in cerebral blood flow[8]) in patients with the CLD primary biliary cholangitis (PBC)[10]. Findings that remain unexplained.

• Pathways driving hypoxia-related changes in brain function may play a role in driving CLD-associated sickness behavior development. We have previously identified marked accumulation of activated monocytes in cerebral blood.[11]

• Therefore, we sued a mouse model of CLD to delineate whether cortical capillary plugging leads to brain hypoxia.

Methodology

• Brain intravital microscopy revealed a marked accumulation of monocytes in the cortical capillaries of CLD that are immobile, suggesting they may contribute to impaired cerebral blood flow.[9]

• RNAseq data defined ~3k significantly altered genes in the FC of BDL vs sham mice, a brain region highly relevant for sickness behavior development.

• BDL mice demonstrate gene expression changes in the FC suggesting tissue hypoxia – similar to findings in PBC patients.

• A therapeutic approach aimed at reducing leukocyte adhesion and capillary plugging could potentially reduce cortical hypoxia and reduce sickness behavior in patients.

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References


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