

Epigenetic Regulation of MDR1 Expression in Human Blood-Brain Barrier Cells

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Clinically useful disease-modifying treatments for Alzheimer's disease have been elusive. Approved drug therapies have been useful providing symptomatic relief, but do not alter the course of the disease. A major pathological hallmark of Alzheimer's disease is the accumulation of neurotoxic amyloid- β peptides in the brain. The protein transporter P-glycoprotein (Pgp/ABCB1/MDR1) is an efflux pump found on the blood-brain barrier and has been shown to export amyloid- β from the brain into the blood. However, the activity of MDR1 decreases as the concentration of amyloid- β in the brain increases, as shown in rodents and humans. Treatment of hCMEC/D3 cells (human blood-brain barrier endothelial cells) with RG108 (N-Phthalyl-L-tryptophan), a DNA methyltransferase inhibitor, is expected to increase ABCB1 expression, suggesting that the expression of this transporter is regulated by DNA methylation. To study the effects of altered DNA methylation on the expression of ABCB1, western blot assays in hCMEC/D3 exposed to RG108 (0-25 μ M) for 24 hours. Finally, the ability of MDR1 transport to be altered by inhibition of DNA methylation was determined by measuring the ability of hCMEC/D3 cells to efflux the fluorescent dye rhodamine 123 after treatment with RG108. Preliminary data suggests that RG108 increases both the expression and function of MDR1 at the blood-brain barrier, laying the foundation of a novel therapeutic strategy for Alzheimer's disease. The findings also provide insight into the mechanisms by which epigenetic pathways regulate the expression of MDR1.

