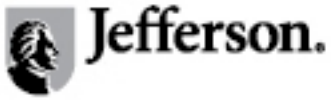

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Neoangiogenesis and Blood-brain Barrier Dysfunction in Human TSC Brain Lesions

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Neoangiogenesis and Blood-brain Barrier Dysfunction in Human TSC Brain Lesions

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Introduction: Tuberous sclerosis complex (TSC) is a genetic disorder characterized by the presence of multiple benign tumors throughout the body and brain. Patients with TSC experience severe cognitive dysfunction and therapy-resistant seizures, which can be associated with refractory epilepsy and poor developmental outcomes. We hypothesize that neoangiogenesis, disruption of the blood-brain barrier, and leakage of serum proteins into the brain parenchyma play vital roles in the pathogenesis of TSC.

Methods: In order to assess blood-brain barrier integrity, cortical tissue samples from TSC patients with intractable seizures, non-TSC patients with therapy-resistant epilepsy, and control subjects were immunolabeled for the serum protein fibrinogen, the adherens junction protein V-cadherin, and the tight junction protein occludin. Lectin was used to visualize blood vessels. Quantification was performed to assess average blood vessel segment length and branching. The fraction of membrane-associated V-cadherin and occludin, relative to the blood vessel surface area represented by lectin, was also analyzed.

Results: The average length of blood vessel segments and the average number of branch nodes were significantly increased in TSC compared to epilepsy and control. The average surface area fraction of V-cadherin and occludin was significantly decreased in TSC compared to control. In addition, fibrinogen staining outside of the blood vessels was extensive in both TSC and epilepsy. These results confirm our hypothesis, suggesting blood-brain barrier dysfunction in TSC, with disease-specific neoangiogenic mechanisms in TSC.

Discussion: Our results show increased blood-brain barrier permeability and increased vascular proliferation in TSC. These findings are likely due to decreased expression of tight junctions and adherens junctions in TSC cortical tissue. These results suggest that antiangiogenic therapies targeting the blood-brain barrier may offer a novel approach to preventing epileptogenesis in patients with TSC.