Riluzole Rescues Non-Canonical Akt Signaling and Improves Hereditary Hemorrhagic Telangiectasia Vascular Pathology

Patel, Radhika (School: Syosset High School)

Hereditary hemorrhagic telangiectasia (HHT, Rendu-Osler-Weber syndrome) is a genetic vascular disorder arising from endothelial cell proliferation and hypervascularization. Patients with HHT are at substantially increased risk of serious neurologic and hemorrhagic complications of the disease. Because diagnosis is associated with a significantly poorer survival compared with those who have no disease, evaluation of new strategies to improve clinical management is required. Genetic studies have revealed that most HHT patients carry mutations in ALK1 signaling, which subsequently increases Akt signaling, a central pathway in regulation of normal vascularization and pathological angiogenesis. This suggests that inhibitors of this pathway demonstrate potential as novel treatment for HHT. Therefore, the FDA-approved medicinal drug riluzole was used to observe its effect on the Akt signaling pathway. Riluzole was first found to improve vascular pathology by specifically reversing hyper-vascularization in the BMP9/10 immuno-blocked postnatal retina - a mouse model of HHT vascular pathology. Further experiments in C2C12 cells illustrated that riluzole does not directly participate in the canonical ALK1 signaling pathway, but does in fact block Akt signaling. It is thus proposed that riluzole repurposing has therapeutic potential in HHT. Future studies will continue to characterize cross-talk between riluzole and relevant signaling pathways.

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