

SRPKIN-1: A Covalent SRPK1/2 Inhibitor that Potently Converts VEGF from Pro-angiogenic to Anti-angiogenic Isoform

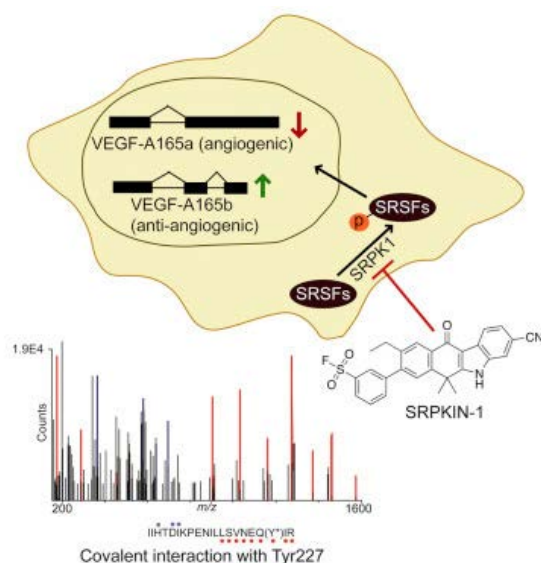
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ABSTRACT: The SRPK family of kinases regulates pre-mRNA splicing by phosphorylating serine/arginine (SR)-rich splicing factors, signals splicing control in response to extracellular stimuli, and contributes to tumorigenesis, suggesting that these splicing kinases are potential therapeutic targets. Here, we report the development of the first irreversible SRPK inhibitor, SRPKIN-1, which is also the first kinase inhibitor that forms a covalent bond with a tyrosine phenol group in the ATP-binding pocket. Kinome-wide profiling demonstrates its selectivity for SRPK1/2, and SRPKIN-1 attenuates SR protein phosphorylation at submicromolar concentrations. Vascular endothelial growth factor (VEGF) is a known target for SRPK-regulated splicing and, relative to the first-generation SRPK inhibitor SRPIN340 or small interfering RNA-mediated SRPK knockdown, SRPKIN-1 is more potent in converting the pro-angiogenic VEGF-A165a to the anti-angiogenic VEGF-A165b isoform and in blocking laser-induced neovascularization in a murine retinal model. These findings encourage further development of SRPK inhibitors for treatment of age-related macular degeneration.



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