

KDR/VEGFR2 interacts with HTLV-1 Tax and prevents its autophagic degradation

Mohanty Suchitra¹, Lavorgna Alfonso², Ngouth, Nyater³, Jacobson, Steve³, Harhaj Edward W. ^{1,2*}

¹Penn State University College of Medicine, Department of Microbiology and Immunology, Hershey, PA, USA

²Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins School of Medicine, Baltimore, MD, USA

³Viral Immunology Section, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD, USA

Background: Human T-cell leukemia virus type 1 (HTLV-1) is the causative agent of adult T-cell leukemia/lymphoma (ATLL), and HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP). The HTLV-1 trans-activating protein Tax regulates viral gene expression and also triggers the aberrant activation of signaling pathways such as NF- κ B to drive clonal proliferation and survival of infected T cells. However, the regulation of Tax expression and protein stability by host cellular proteins is largely unknown. Hence, the identification of host proteins that control Tax expression and stability could potentially yield targets to develop novel therapeutic approaches for ATLL and/or HAM/TSP.

Methods: We have conducted a kinome-wide shRNA screen to identify host factors crucial for the survival of an HTLV-1-transformed T cell line, MT-2. The top hit in the screen was the tyrosine kinase receptor KDR/VEGFR2, which we have validated by using shRNAs and small molecule inhibitors by western blotting and flow cytometry. We examined the interaction between Tax and KDR by co-immunoprecipitation and proximity ligation assays in HTLV-1-transformed T cell lines. Viral gene expression was assessed by western blotting for Gag p19.

Results: Inhibition of KDR with shRNAs or small molecule inhibitors induced caspase-dependent apoptotic cell death selectively in Tax+ HTLV-1-transformed T cells. Furthermore, inhibition of KDR elicited the autophagic degradation of Tax resulting in diminished viral gene expression and NF- κ B activation. We found that Tax upregulated KDR expression and formed a complex with KDR in HTLV-1-transformed T cells.

Conclusion: Collectively, our results have revealed a critical role for KDR/VEGFR2 in protecting Tax from degradation by autophagy. This knowledge could be exploited as a potential strategy to target Tax in Tax+ ATLL and HAM/TSP patients.

Disclosure of interest: none