Derepression of endogenous retroviral elements promotes extracellular matrix remodeling and immune cell evasion in prostate cancer

Emily C. Williams[1,2], Anelia Horvath[2,3], Katherine B. Chiappinelli[2,4] and Maho Shibata[1,2]

[1]Department of Anatomy and Cell Biology, The George Washington University School of Medicine and Health Sciences, Washington, DC 20052, USA
[2]The George Washington University Cancer Center, The George Washington University School of Medicine and Health Sciences, Washington, DC 20052, USA
[3]McCormick Genomics and Proteomics Center, Department of Biochemistry and Molecular Medicine, The George Washington University School of Medicine and Health Sciences, Washington, DC 20037, USA
[4]Department of Microbiology, Immunology and Tropical Medicine, The George Washington University School of Medicine and Health Sciences, Washington, DC 20052, USA

Endogenous retroviral elements (ERVs) are remnants of viral elements that make up 8-10% of the human and mouse genomes, and their expression is tightly regulated in differentiated cell types. ERV expression has been reported in multiple cancers, including prostate cancer, yet how ERVs promote tumor progression is not well understood. Tripartite motif-containing 28 (TRIM28/TIF1b/KAP1) is a key transcriptional co-repressor protein that represses ERV expression in many cell types, including embryonic stem cells, neural progenitor cells, differentiated adult cells, and cancer cells. We recently developed a unique *in vivo* genetic mouse tumor model where deletion of *Trim28* in prostate epithelial cells results in tumors with decreased cellular plasticity and increased apoptosis. However, long-term *Trim28* deletion unexpectedly alters the tumor microenvironment and promotes tumor progression (Yende, Williams et al., 2023). In this study, we investigated the effect of *Trim28* deletion on the expression of ERVs using this immune competent genetically engineered mouse model for prostate cancer.

Analysis of bulk RNA sequencing data revealed that *Trim28* deletion in prostate tumors led to derepression of ERVs in prostates from both hormonally intact and castrated mice. ERVs can regulate the expression of neighboring genes, and we detected increased expression of several protein-coding genes near derepressed ERVs. *Trim28* deletion in prostate tumor epithelial cells promoted an immune response but also led to excessive deposition of tumor extracellular matrix (ECM). Our findings suggest that ECM alterations downstream of ERV derepression affect immune cells in the tumor microenvironment and may promote tumor progression.

Altogether, our study suggests that ERV derepression and chronic inflammation promote fibrosis and changes to the extracellular matrix in tumors, as observed in kidney and lung disease. Our findings of increased collagen formation and extracellular matrix remodeling at 1 month after tumor induction indicate that these tumor extracellular matrix changes precede the increase in CD206-expressing macrophages, and likely enhance tumor progression by preventing immune cell infiltration and promoting immune suppression. Overall, these findings have wider implications for understanding the association between ERV expression, chronic inflammation, and cancer.

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Reference: Yende, A., Williams, E.C., Pletcher, A., Helfand, A., Ibeawuchi, H., North, T.M., Latham, P.S., Horvath, A., and Shibata, M. (2023). TRIM28 promotes luminal cell plasticity in a mouse model of prostate cancer. *Oncogene.* 42(17):1347-1359. PMID: 36882525; PMCID: PMC10122711.