**K811 acetylation regulates ZEB1 dimerization, protein stability, and NuRD complex interactions to promote lung adenocarcinoma progression and metastasis**

Mabel G. Perez-Oquendo, Roxsan Manshouri, Ph.D., Jared J. Fridette, Don L. Gibbons, M.D., Ph.D.

University of Texas MD Anderson Cancer Center UTHealth Graduate School of Biomedical Sciences

Department of Thoracic Head & Neck Medical Oncology

**Introduction**

Lung cancer is the leading cause of cancer-related death worldwide due to the ability of cancer cells to metastasize. Therefore, it is essential to expand our current knowledge of the biological processes that contribute to metastasis to guide the discovery of novel therapeutic modalities. The Epithelial-to-mesenchymal transition (EMT) is a mechanism for metastasis, which changes polarized epithelial cells into invasive mesenchymal cells. High expression of the Zinc finger E-box binding homebox 1 (ZEB1) transcription factor is correlated to poor outcomes in cancer, including therapeutic resistance and EMT-mediated metastasis. ZEB1 has a predicted molecular weight of 135kDa; however, multiple groups have reported discrepancies in the observed molecular weight (~190-250kDa). This has been attributed to dimerization mediated by post-translational modifications (PTMs). Therefore, we performed mass spectrometry and identified a novel PTM - K811 acetylation - that may regulate ZEB1 dimerization and function. To define the role of ZEB1 acetylation, we generated ZEB1 acetyl mimetic (K81Q) and deficient (K81R) mutants in a panel of lung adenocarcinoma cell lines. We aim to characterize a novel regulatory mechanism of the transcriptional repressor ZEB1 with the goal of identifying its functional and pathological relevance to the metastatic process.

**Lung Cancer is the leading cause of cancer-related deaths**

![Figure 1](image1.png)

**Mouse model of metastatic lung adenocarcinoma**

**Results**

**K811 acetylation site is a novel PTM in ZEB1 identified by mass spectrometry**

![Figure 2](image2.png)

**Hypothesis**

ZEB1 acetylation regulates dimerization and protein stability to promote lung adenocarcinoma progression and metastasis

**Dimerization facilitates ZEB1/NuRD complex interaction and binding at the promoter of its target genes**

![Figure 3](image3.png)

**K811 acetylation protects ZEB1 from proteasomal degradation by the action of the E3 Ubiquitin Ligase (UBL) SIAH1**

![Figure 4](image4.png)

**K811 acetylation promotes NSCLC invasion in vitro and metastasis in vivo**

![Figure 5](image5.png)

**Summary and working model**

- K811 acetylation regulates ZEB1 dimerization and protein stability.
- Acetylation protects ZEB1 from proteasomal degradation by the action of the UBL SIAH1.
- Dimerization facilitates recruitment of the NuRD complex to genomic promoters.
- ZEB1_K811ac promotes NSCLC metastasis via EMT

**Acknowledgements**

This research was funded by the Ruth L. Kirschstein National Research Service Award Individual Pre-doctoral Fellowship to Professor Dietrich (TIA0120287H). D. Frison and D. Orisack acknowledge Dr. I. Gibbons for helpful discussions. Additionally, the authors appreciate the assistance of the laboratories of Drs. M. Beltz and D. B. Kirschstein.