Epigenetic regulation of the Klotho/Miz1 axis promotes cigarette-smoke extract (CSE)-induced alveolar epithelial cell (AEC) mtDNA damage and apoptosis

Seok-Jo Kim PhD1,2, Paul Cheresh, PhD2,3, Liu Jing PhD1, Benjamin D. Singer MD2, Ravi Kalhan MD1, Karen Ridge PhD1, John Varga MD1, David Kamp MD2,3

1Department of Medicine, Division of Rheumatology, 2Department of Medicine, Division of Pulmonary & Critical Care Medicine, Feinberg School of Medicine, Northwestern University, Chicago, IL
3Department of Medicine, Division of Pulmonary & Critical Care Medicine, Jesse Brown VA Medical Center, Chicago, IL; 4Department of Surgery/Cancer Center, College of Medicine, University of Illinois at Chicago, Chicago, IL

ABSTRACT

INTRODUCTION

- Age-related lung diseases, such as emphysema/COPD, continue to pose serious health concerns yet the pathophysiology is incompletely understood. (3-5).
- The anti-aging gene Klotho has an extra-cellular domain that circulates providing important endocrine and paracrine functions impacting anti-oxidant and anti-fibrotic functions in distal organs, including the lungs.(6,7). We recently showed that Klotho preserves AEC mtDNA integrity, a key intracellular target that integrates cell survival/death signaling following oxidative stress.(1). The attenuation of Klotho expression after renal injury is mediated in part by epigenetic modification of the Klotho promoter causing transcriptional repression (8,9).
- Miz1 has a critical role in regulating cell proliferation, differentiation, cell-cycle progression and apoptosis through the transcriptional activation and repression of its target genes (10-13). Miz1 is a key negative regulator in constraining LPS-induced inflammation and acute lung injury response.(14). Also, alveolar epithelial cell specific Miz1-deficient mice spontaneously develop emphysema with aging (ATS 2018).
- We reason that Klotho is crucial for maintaining AEC mtDNA integrity and preventing apoptosis following tobacco exposure preventing epigenetic hypermethylation of the Klotho promoter that reduces Miz1 binding in the pathophysiology of COPD/emphysema.

HYPOTHESIS

Tobacco-induced reductions in Klotho expression result from hypermethylation of the Klotho promoter that reduces Miz1 binding

RESULTS

1. CSE induces AEC mtDNA damage, apoptosis and Klotho/Emphysema (Figure 1).
2. Miz1, which co-locates at AT2 cells, binds on the significant methylation-enrichment locus of Klotho proximal promoter sequence (Figure 2-4).
3. CSE decreases Miz1 expression, and AT2 cell specific Miz1-deficient mice (Spc-Cre+/Miz1(POZ2)) have decreased Klotho mtDNA and serum levels as well as age-dependent AT2 cell mtDNA damage (Figure 5).

CONCLUSIONS

1. Klotho plays an important role in mitigating oxidant-induced AEC mtDNA damage and mitochondria-regulated apoptosis.
2. Our findings suggest that Miz1 is a novel regulator of the Klotho/Miz1 axis that is susceptible to CSE-induced epigenetic methylation that promotes AEC mtDNA damage and apoptosis.
3. Collectively, these data firmly support our understanding of the epigenetic regulation of the Klotho/Miz1 axis in mediating AEC injury as a potentially innovative therapeutic target for preventing smoking-related lung diseases of aging (i.e. COPD, lung fibrosis, lung cancer, etc.).

BIBLIOGRAPHY