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Development of a small mtDNA-encoded regulatory non-coding RNA region as a potential therapeutic agent to modulate mitochondrial bioenergetics

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Statement of the Problem: Mitochondrial malfunction is a hallmark of COPD. We identified an mtDNA-encoded small ncRNA, mito-ncR-805, that is upregulated in a cell-type specific manner in alveolar epithelial type II (AETII) cells during the stress of smoking. Mito-ncRNA-805 transcript functions as a retrograde signaling molecule between mitochondria and nucleus, with enhanced function during the adaptive stress response to smoking.

The purpose of this study: To study evolutionary conservation of mito-ncR-805, and interrogate the hypothesis that forced expression of synthetic oligos identical to evolutionary Conserved Region (CR) of mito-ncR-805 improves mitochondrial function.

Methodology and Findings: mito-ncR-805 is a mouse-specific transcript. We identified a region of mito-ncR-805 which is conserved in mammalian mitochondrial genomes, and generated shorter versions of mouse and human transcripts (mmu-CR805, and hsa-CR805), which differ in a few nucleotides. We called these small transcripts "functional bit". Over-expression of mmu-CR805 in MLE12 cells, led to increase in Krebs cycle, and in the activities of OXPHOS, stabilized mitochondrial potential, faster resumption of cell division following stress, and lower predisposition to apoptosis. Similarly, forced expression of hsa-CR805 in Beas-2B cells instigated faster proliferation compared to control cells. Although beneficial effects of respective ortholog oligos are less prominent than that of the species-specific oligo, both confer cross-species rescue during severe stress.

Conclusion & Significance: Our data indicate a high degree of evolutionary conservation of retrograde signaling via a functional bit of mito-ncR-805 in mammals. This emphasizes the importance of the pathway, and suggests a potential for the development of the functional bit of mito-ncR-805 into therapeutic agent that restores mitochondrial bioenergetics. Caution and awareness for the potential differences that may exist between forced over-expression of mito-ncR-805 during acute and chronic stress should be further investigated.

Biography

Anna Blumental Perry is a lung researcher at University at Buffalo. The focus of her research has been to understand proteostasis imbalance in lung disease, with a focus on endoplasmic reticulum and mitochondria malfunction in smokers. She investigates alveolar epithelial type II cells responses to cigarette smoke, because those cells are local progenitors with the ability to repair the damage and replenish the loss of alveolar epithelial type I cells. Anna developed the fascination to delineate the molecular mechanisms that confer survival advantages to type II cells in response to stressors and specifically, cigarette smoke stress. The approach has been multidisciplinary including protein chemistry, cell and molecular biology, genetic engineering, and animal models of disease.