RIT ME Virtual Seminar

How a somatic cancer mutation guides the modeling and therapeutics of lung diseases

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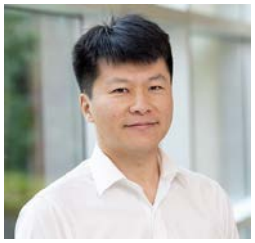
Abstract: Air pollution, smoking, viral infection cause damage to lung epithelium, whose repair process forces unscheduled proliferation of lung precursor cells, molecularly marked by premature shortening of telomeres - DNA repeats that protect the chromosomal ends from DNA damages and end-to-end fusion. Insufficient telomere maintenance provokes premature apoptosis or senescence of lung precursors, aggravating lung degeneration by excessive inflammation and fibrotic deposition. To revert telomere shortening as the early driver of precursor exhaustion, our long-term goal is to prolong telomeres by boosting telomerase – the specialized ribonucleoprotein enzyme that replenishes telomeric repeats. Specifically, we aim to 1) develop small molecule drugs or cell therapies that can boost telomerase in lung progenitor cells; 2) engineer human-like replicative senescence into a mouse model, where the aim1 approaches can be tested.

As the "immortalization" enzyme that reverts cellular aging, telomerase is universally activated in 90% of cancer cells; a somatic hotspot mutation (TPM) at the TERT gene promoter – encoding telomerase protein subunit - ranks as the no.1 frequent noncoding mutation across cancer genomes. In addition, TPM has been identified in tissues of cancer-free patients, as a compensational mechanism balancing certain germline loss-of-function mutations. Thus, engineering TPM into isolated human lung type2 precursor cells using CRISPR-base editing may present as a physiologically relevant vehicle to revert telomere shortening in the lung. Furthermore, we show that the TPM hijacks and amplifies a native promoter regulatory mechanism that is dominant-acting and is conserved among placental mammals. By CRISPR-engineering of mice – which contains 10x longer telomere and constitutive telomerase vs. human, we demonstrated that TPM-like cancer mechanism is evolutionarily selected by the germline of small-sized, short-lived mammals, and is selected against in larger, long-lived mammals. In sum, our work unrevealed an evolutionary parallel between somatic clonal expansion during carcinogenesis and germline selection during speciation, paving a way to fully engineer replicative senescence into lab mice for preclinical modeling of telomerase-modulating therapeutics.

Biography: Dr. Lu Chen is currently an assistant professor at the Cancer Signaling and Epigenetics Program and the Cancer Epigenetics Institute (CEI) of the Fox Chase Cancer Center in Philadelphia, Pennsylvania. Before joining Fox Chase, Chen was a postdoc fellow then an instructor in Stanford University. As a biochemistry and molecular biology expert, Chen has published high impact research in top journals such as *Nature, Cell, Molecular Cell, Cell Reports, Nucleic Acid Research, Proceedings of National Academy of Sciences*, and *Journal of Biological Chemistry*. Chen received the Stanford Cancer Institute Postdoctoral Fellowship, and ASBMB best poster award, and was selected as speaker in top research forums hosted by CSHL, EMBO, and NIH/NCI. Chen also serves on the editorial board of *Cancer Translational Medicine* and is a peer review board member for the *Journal of Visualized Experiments and Star Protocols*.



Lab Overview: The Lu Chen laboratory (luchenlab.org) studies molecular secrets underlying all things RNA biology – how RNAs are chemically modified, how their exact molecular forms are precisely defined, and how they cooperate with proteins to carry out molecular functions at specific cellular locations. We are translating our basic science discoveries into novel therapeutic options to combat cancer immortality, stem cell exhaustion, and degenerative diseases. We use diverse approaches, including protein-RNA reconstitution, Next-gen RNA structural profiling (icSHAPE-seq, nascent RNA-seq), CRISPR-engineering of human primary stem cell and mouse models, and single-molecule RNA imaging.