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RIOK2 transcriptionally regulates telomerase activity to prevent telomere shortening

Abstract: Telomere shortening is a characteristic feature of tissues derived from aging individuals and from patients diagnosed with idiopathic pulmonary fibrosis (IPF) or blood cancers such as myelodysplastic syndrome (MDS). Although telomerase activity tightly controls telomere length homeostasis, the upstream regulation of telomerase holoenzyme subunits has remained largely elusive. Also, the intriguing association between telomere shortening and anemia in aged individuals is poorly understood. We have previously reported that RIOK2 (right open reading frame kinase 2) functions as a master transcription factor in human blood cell development1, and loss of RIOK2 impairs erythroid differentiation, thus causing anemia1,2. Here, we show that RIOK2 transcriptionally regulates key telomerase subunits (TriC and Dyskerin complexes) to maintain telomere length homeostasis in several different cell types using gene expression analyses, fluorescence in situ hybridization, chromatin immunoprecipitation, reconstitution experiments, and TRAP assays3. Interestingly, RIOK2's expression is downregulated in aged individuals and IPF patients, and its mRNA levels significantly correlate with the expression of TriC and Dyskerin complex subunits in samples derived from MDS and IPF patients as well as aging individuals. Most importantly, ectopic expression of RIOK2 significantly alleviates telomere shortening and associated DNA damage responses in primary lung fibroblasts isolated from IPF patients3. Collectively, our findings demonstrate that RIOK2 governs both telomere length homeostasis and blood cell development, highlighting it as an unprecedented connecting link between anemia and telomere shortening in aging individuals. Thus, RIOK2-driven transcriptional programs have potential therapeutic implications in MDS, IPF and aging.

Keywords: RIOK2, telomere shortening, telomerase activity, MDS, IPF.

Biography: Dr. Shrestha Ghosh earned her PhD in Biochemistry from the University of Hong Kong (HKU) after having completed her bachelor's in biotechnological engineering from India. She received the best thesis award in the medicine faculty of HKU, published several first-author papers, and her thesis has been published as a book by Springer Nature. Dr. Ghosh then joined Dana- Farber Cancer Institute, Harvard Medical school, where she started studying hematopoietic differentiation in the context of blood cancers. She is now an Instructor of Medicine, has published several first author papers in reputed journals like Nature Immunology, Nature Communications, and has recently cofounded a biotech startup. Today she'll speak about her recent work on exploring the link between telomere shortening and anemia.

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