

Active mutation of the genome in human somatic cells by LINE-1 mobile elements

Principal Investigator
Young Seok Ju

Department
Graduate School of Medical Science and Engineering

Co-Investigators
Chang Hyun Nam, Jeonghwan Youk, Joonoh Lim, Hyein Won, Yunah Lee, Jinju Han

Homepage
<http://julab.kaist.ac.kr>

With approximately 500,000 copies – accounting for 17% of the human genome – LINE-1 retrotransposons have long been recognized for their contribution to the evolution of the human species by introducing “disruptive innovation” to genome sequences. Until now, it was believed that most LINE-1 elements had lost their ability to jump in normal tissues of modern humans. In this study, using whole-genome sequences of 899 single-cells collected from 28 individuals, we revealed that some LINE-1 jumping genes can be widely activated in normal cells, resulting in the gradual accumulation of genomic mutations over time during aging and tumorigenesis. The study provides novel insights into the aging process and the development of diseases in human colorectal tissues.

Background

The L1 jumping genes, accounting for 17% of the human genome with approximately 500,000 copies, have long been recognized for their contribution in the evolution of the human species through ‘disruptive innovation’ of the genome sequences. Until recently, the conventional wisdom has been that most L1 jumping genes have lost their jumping activity in the cells of modern humans, particularly in normal tissues. However, this study revealed that some L1 jumping genes can be widely activated at least in the colorectal epithelial cells, resulting in the accumulation of genomic mutations over an individual’s lifetime.

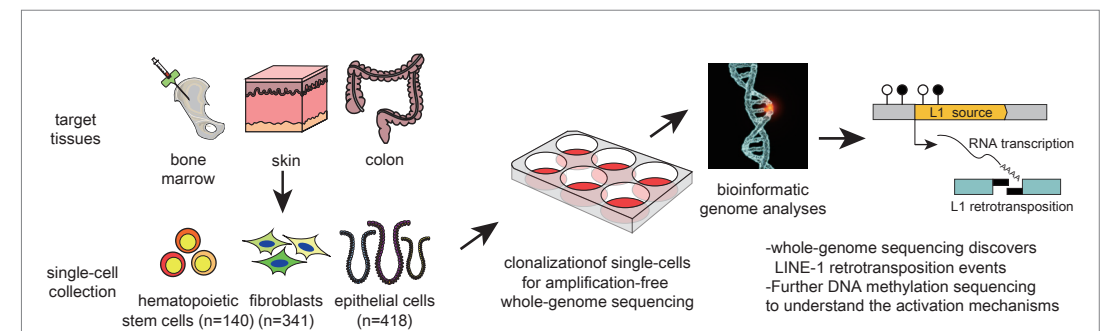
Description

The research analyzed 899 whole-genome sequences obtained from single-cells of the skin (fibroblasts), blood, and colon epithelial tissues collected from 28 individuals. The rate of L1 jumping and resulting genomic alterations varied among different cell types, with a notable concentration observed in aged colon epithelial cells. The study reveals that the activation of L1 jumping genes in normal cells initiates during the early stages of embryogenesis and persists throughout a human lifetime. It also suggests that on average, every colonic epithelial cell accumulates an L1 jumping event by the age of 30. This study clearly demonstrates that L1 jumping genes are our “internal carcinogen” that can mutate our genomic sequences. Additionally, the study explored epigenomic (DNA methylation) and transcriptomic (RNA) changes together with genomic mutations in the same cells to understand the mechanism underlying L1 jumping gene activation. Activated L1 jumping genes exhibited demethylated promoters, suggesting the critical role of epigenetic changes in regulating L1 jumping gene activity in normal cells. Surprisingly, most of these epigenomic alterations occurred during the early stages of embryogenesis rather than being acquired during the aging of the cells in the lifetime.

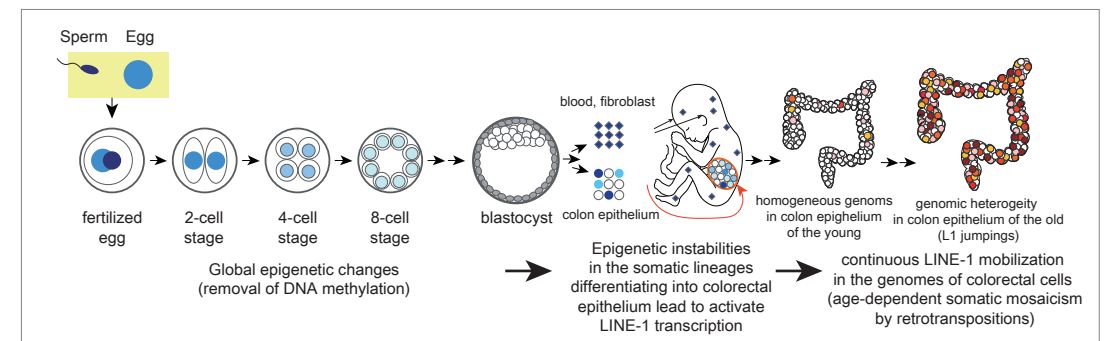
Implications

This study leveraged sequencing data and bioinformatics approaches to shed light on biological phenomena that are challenging to observe in the human body. Even in normal cells, genomic mutations are identified and gradually accumulate through various mutagenic processes. Notably, the activation of L1 jumping genes and resulting genomic alterations were clearly demonstrated in normal human cells, especially in the colorectal epithelium. Moreover, this study suggests, for the first time, the contribution of epigenomic alterations during early embryogenesis in the activation of L1 jumping genes. These findings pave the way for further studies on the role of L1 jumping gene activation in aging and disease development, as well as for developing technologies aimed at controlling aging and disease by suppressing L1 jumping gene activity.

a. Methods



b. Findings



Research outcomes

[Publication] Nam C. et al., Widespread somatic L1 retrotransposition in normal colorectal epithelium. *Nature* 617, 540-547 (2023)
[Publicity] Domestic, Chosunbiz, May 15th, 2023 etc; International, Science Daily, May 25th, 2023 etc.
[Award] The 19th Kyung-Ahm Prize (2023)

Research funding

Leader Researcher Program of the National Research Foundation of Korea (NRF-2020R1A3B2078973), Young Investigator Program of the Suh Kyungbae Foundation (SUHF-18010082), and MD-PhD/Medical Scientist Training Program of the Korea Health Industry Development Institute