CANCER MUTATIONS OCCUR FREQUENTLY IN NORMAL ESOPHAGEAL EPITHELIUM

Somatic mutations occur in normal tissues throughout life. The majority of mutations are not pathogenic and accumulate passively, but mutations in key genes can confer a competitive advantage and induce tumorigenesis. The extent of somatic mutations in many normal tissues remains poorly understood. Sun-exposed skin has a high mutation rate and a large number of cells carrying tumor-driving mutations. Martincorena, Fowler, and colleagues sought to determine the mutational landscape of esophageal epithelium, which has a similar structure and tendency to develop squamous-cell cancers as skin epithelium but is exposed to different mutagens. Ultra-deep targeted sequencing of 74 cancer-associated genes was performed on 844 normal esophageal epithelium samples from nine deceased organ transplant donors ranging from 20 to 75 years of age. Further, 21 samples found to be dominated by large clones were also subject to whole-genome sequencing. The average number of somatic mutations present in healthy esophageal epithelial cells increased with age, with several hundred mutations per cell in people in their twenties, increasing to over 2,000 mutations per cell in older adults.

As expected, the mutation rate is lower than in sun-exposed skin (approximately 10-fold lower). However, there was a higher density of cancer-associated mutations in the normal esophagus than in sun-exposed skin, an unexpected finding suggesting stronger positive selection for cancer-associated mutations in the esophagus including NOTCH1 and TP53. TP53 mutations occurred in 5% to 10% of normal esophageal cells, a number variable across individuals and increasing with age, in contrast to esophageal squamous cell carcinomas (ESCC) where it has been reported to be mutated in over 90% of cells. Conversely, NOTCH1 mutations were detected in 30% to 80% of normal esophagus in middle-aged and elderly individuals, but are detected in only approximately 10% of ESCCs. In addition to characterizing the mutational landscape of normal esophageal epithelium, these findings provide insights into the mutational processes that underlie cancer and aging.

Cancer Mutations Occur Frequently in Normal Esophageal Epithelium

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