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Dysfunctional epigenetic aging of the normal colon and colorectal cancer risk

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Abstract

Background: Chronological age is a prominent risk factor for many types of cancers including colorectal cancer (CRC). Yet, the risk of CRC varies substantially between individuals, even within the same age group, which may reflect heterogeneity in biological tissue aging between people. Epigenetic clocks based on DNA methylation are a useful measure of the biological aging process with the potential to serve as a biomarker of an individual's susceptibility to age-related diseases such as CRC.

Methods: We conducted a genome-wide DNA methylation study on samples of normal colon mucosa ($N = 334$). Subjects were assigned to three cancer risk groups (low, medium, and high) based on their personal adenoma or cancer history. Using previously established epigenetic clocks (Hannum, Horvath, PhenoAge, and EpiTOC), we estimated the biological age of each sample and assessed for epigenetic age acceleration in the samples by regressing the estimated biological age on the individual's chronological age. We compared the epigenetic age acceleration between different risk groups using a multivariate linear regression model with the adjustment for gender and cell-type fractions for each epigenetic clock. An epigenome-wide association study (EWAS) was performed to identify differential methylation changes associated with CRC risk.

Results: Each epigenetic clock was significantly correlated with the chronological age of the subjects, and the Horvath clock exhibited the strongest correlation in all risk groups ($r > 0.8$, $p < 1 \times 10^{-30}$). The PhenoAge clock ($p = 0.0012$) revealed epigenetic age deceleration in the high-risk group compared to the low-risk group.

Conclusions: Among the four DNA methylation-based measures of biological age, the Horvath clock is the most accurate for estimating the chronological age of individuals. Individuals with a high risk for CRC have epigenetic age deceleration in their normal colons measured by the PhenoAge clock, which may reflect a dysfunctional epigenetic aging process.

Keywords: Colorectal cancer, DNA methylation, Epigenetic clock, Biological/epigenetic age, Epigenetic age acceleration

Background

Colorectal cancer (CRC) is a leading cause of cancer-related death in the USA and arises via a polyp-to-cancer progression sequence. Virtually, all CRCs arise from adenomatous polyps or serrated polyps, although only 5–10% of colon polyps become CRC [1]. Advanced histologic features in the polyp (e.g., villous histology, high-grade dysplasia) and size of the polyp directly correlate with an increased risk of CRC [2]. A precise determination of the factors that mediate polyp initiation and progression would have a major impact on CRC prevention.

At the molecular level, CRC results largely from the progressive accumulation of genetic and epigenetic alterations in colon epithelial cells. DNA methylation alterations commonly occur in adenomas and CRCs and appear to cooperate with gene mutations to mediate field cancerization (also known as "field effect" or "field defect") in the colon and induce the initiation and progression of adenomas [3–9]. Previous studies evaluating methylation in the

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