Cancer Research

Implications of Epigenetic Drift in Colorectal Neoplasia

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Abstract

Many normal tissues undergo age-related drift in DNA methylation, providing a quantitative measure of tissue age. Here, we identify and validate 781 CpG islands (CGI) that undergo significant methylomic drift in 232 normal colorectal tissues and show that these CGI continue to drift in neoplasia while retaining significant correlations across samples. However, compared with normal colon, this drift advanced (~3–4-fold) faster in neoplasia, consistent with increased cell proliferation during neoplastic progression. The observed drift patterns were broadly consistent with modeled adenoma-to-carcinoma sojourn time distributions from colorectal cancer incidence data. These results support the hypothesis that, beginning with the founder premalignant cell, cancer precursors frequently sojourn for decades before turning into cancer, implying that the founder cell typically arises early in life. At least 77% to 89% of the observed drift variance in distal and rectal tumors was explained by stochastic variability associated with neoplastic progression, whereas only 55% of the variance was explained for proximal tumors. However, gene–CGI pairs in the proximal colon that underwent drift were significantly and primarily negatively correlated with cancer gene expression, suggesting that methylomic drift participates in the clonal evolution of colorectal cancer. Methylomic drift advanced in colorectal neoplasia, consistent with extended sojourn time distributions, which accounts for a significant fraction of epigenetic heterogeneity in colorectal cancer. Importantly, these estimated long-duration premalignant sojourn times suggest that early dietary and lifestyle interventions may be more effective than later changes in reducing colorectal cancer incidence.

Significance: These findings present age-related methylomic drift in colorectal neoplasia as evidence that premalignant cells can persist for decades before becoming cancerous.

See related commentary by Sapienza, p. 437

Introduction

Colorectal cancers arise along alternative pathways through an accumulation of mutations and epigenetic alterations accompanied by clonal expansions, along with random and selective drift (1–5). Several mutations or epigenetic changes are thought to be necessary (e.g., biallelic inactivation of *APC*, epigenetic silencing of *MLH1*) to initiate premalignant clonal growth (6). Occult premalignant clones that do not undergo extinction may grow into observable adenoma while accumulating (epi)genetic alterations, with some developing genomic instability, undergoing malignant transformation, and invasive growth (7–9). Rates for these processes may be influenced by obesity, diet, genetics, the microbiome, and other factors (3, 10–12). Although colorectal cancer genomes have been extensively profiled for somatic mutations, chromosomal abnormalities, and epigenetic alterations (3, 9), little is known about the dynamics of the carcinogenic process, including the sojourn time distribution from the time when a premalignant founder cell is born to when the descendent cancer becomes clinically identifiable (13). Here, we aim to better understand these dynamics and the role of epigenetic drift in the

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