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Identification of a key role of widespread epigenetic drift in Barrett's esophagus and esophageal adenocarcinoma

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Abstract

Background: Recent studies have identified age-related changes in DNA methylation patterns in normal and cancer tissues in a process that is called epigenetic drift. However, the evolving patterns, functional consequences, and dynamics of epigenetic drift during carcinogenesis remain largely unexplored. Here we analyze the evolution of epigenetic drift patterns during progression from normal squamous esophagus tissue to Barrett's esophagus (BE) to esophageal adenocarcinoma (EAC) using 173 tissue samples from 100 (nonfamilial) BE patients, along with publically available datasets including The Cancer Genome Atlas (TCGA).

Results: Our analysis reveals extensive methylomic drift between normal squamous esophagus and BE tissues in nonprogressed BE patients, with differential drift affecting 4024 (24%) of 16,984 normally hypomethylated cytosine-guanine dinucleotides (CpGs) occurring in CpG islands. The majority (63%) of islands that include drift CpGs are associated with gene promoter regions. Island CpGs that drift have stronger pairwise correlations than static islands, reflecting collective drift consistent with processive DNA methylation maintenance. Individual BE tissues are extremely heterogeneous in their distribution of methylomic drift and encompass unimodal low-drift to bimodal high-drift patterns, reflective of differences in BE tissue age. Further analysis of longitudinally collected biopsy samples from 20 BE patients confirm the time-dependent evolution of these drift patterns. Drift patterns in EAC are similar to those in BE, but frequently exhibit enhanced bimodality and advanced mode drift. To better understand the observed drift patterns, we developed a multicellular stochastic model at the CpG island level. Importantly, we find that nonlinear feedback in the model between mean island methylation and CpG methylation rates is able to explain the widely heterogeneous collective drift patterns. Using matched gene expression and DNA methylation data in EAC from TCGA and other publically available data, we also find that advanced methylomic drift is correlated with significant transcriptional repression of ~ 200 genes in important regulatory and developmental pathways, including several checkpoint and tumor suppressor-like genes.

Conclusions: Taken together, our findings suggest that epigenetic drift evolution acts to significantly reduce the expression of developmental genes that may alter tissue characteristics and improve functional adaptation during BE to EAC progression.

Keywords: Barrett's esophagus (BE), Esophageal adenocarcinoma (EAC), Tissue age, Epigenetic drift, DNA methylation, Neoplastic progression, Transcriptional repression in cancer, Endogenous retroviruses (ERVs)

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