Evolution of Genomic Abnormalities Determines Progression to Cancer

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Cancer progression is thought to proceed through multiple stages of genomic mutation, beginning with genomic instability, which gives rise to populations of cells with diverse genomic abnormalities. Natural selection then acts on these populations of altered cells and some progress to cancer. The prevailing model assumes that these mutations accumulate linearly over time, giving a prolonged window of opportunity for cancer detection. However, this model does not hold true for all cancers. Barrett's esophagus (BE) is a premalignant change to the esophageal mucosa induced by chronic acid exposure from gastric reflux, and it is the only known precursor of esophageal adenocarcinoma (EA), an aggressive cancer that has a particularly high level of genomic instability. Early detection screens for EA have met with limited success, because they tend to detect the more benign Barrett's esophagus, which does not always progress to cancer over the patient's lifetime ("overdiagnosis"), and fail to reliably detect the sudden appearance of esophageal adenocarcinoma ("underdiagnosis", see figure). In a recent report published in *Cancer Prevention Research*, Dr. Xiaohong Li, Patricia Galipeau, and Drs. Thomas Paulson and Brian Reid (Human Biology and Public Health Sciences Divisions), and their collaborators demonstrated that the chromosomal abnormalities in patients with BE who do not progress to EA tend to be stable over time, while patients who develop EA rapidly evolve extensive additional genomic abnormalities within a timeframe of four years prior to EA diagnosis.

The authors employed single nucleotide polymorphism (SNP) arrays to identify genetic changes in temporal biopsies from patients with BE who either progressed or did not progress to EA. At all time points examined, non-progressors typically had relatively small chromosomal changes involving ~12% of the genome, often at known fragile sites and on specific chromosomes. Patients that progressed to EA tended to have slightly higher levels of somatic chromosome alterations (SCA) than non-progressors at time points more than 48 months prior to a diagnosis of EA (299.7 Megabases (Mb) of SCA vs. 178.6 Mb, p=0.007), although the landscape of changes was similar to non-progressors. However, over time this difference became more marked (602.5 Mb vs. 179.8 Mb, p=5.4×10-7 within 2 years of EA diagnosis) and involved larger, more variable regions of the

patient's genome, including changes involving chromosome arms, whole chromosomes, and genome doublings.

Based on these results, Li, *et al*. next sought to determine how SCA evolved in the esophagus over space and time. The team found that non-progressors had similar patterns of SCA regardless of how far apart two biopsies within the BE tissue were sampled. There was very little difference in spatial patterns of SCA between non-progressors and progressors at timepoints more than 48 months before EA diagnosis. However, the spatial divergence in SCA patterns increased over time in progressors. Within 24 months of EA diagnosis the divergence in SCA patterns was elevated between two biopsies regardless of their distance from each other. Overall, at any given timepoint 56% of progressors had different SCA patterns in >15% of their genome between any two biopsy sites while nonprogressors were much more stable.

Taken together, the results of this study demonstrate that genomic abnormalities in patients that progress to EA develop surprisingly rapidly in the background of relatively stable BE-associated SCA. These genetic abnormalities form a non-linear mosaic of SCA in the esophagus with some regions having low SCA and other regions possessing much more dramatic SCA. Rather than the prevailing model of gradual accumulation of specific changes on the pathway to cancer, this study supports the hypothesis that the evolution of SCA during progression to EA is a much more dynamic and stochastic process. "Similar sequences of chromosome alterations have been inferred in a number of other types of cancers for which early detection has been [challenging…] including those of the ovary, breast, lung and colon. Our research provides a mechanism for rapid and slow neoplastic evolution that can be investigated in these other types of cancers to identify windows of opportunity for early detection of cancers when they can be cured by resection," said Dr. Reid.

Li X, Galipeau PC, Paulson TG, Sanchez CA, Arnaudo J, Liu K, Sather CL, Kostadinov RL, Odze RD, Kuhner MK, Maley CC, Self SG, Vaughan TL, Blount PL, Reid BJ. 2014. Temporal and Spatial Evolution of Somatic Chromosomal Alterations: A Case-Cohort Study of Barrett's Esophagus. *Cancer Prev Res (Phila).* (1):114-27.

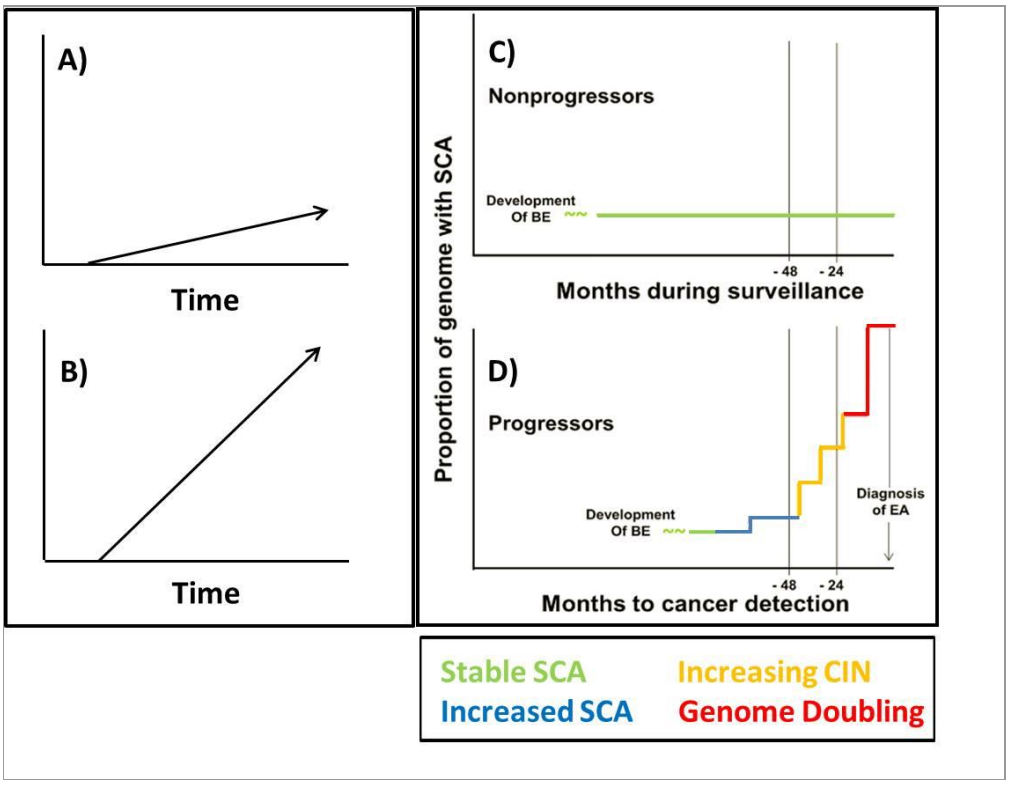

Image courtesy Brian J. Reid

Progression to esophageal adenocarcinoma is characterized by dynamic, stochastic increases in somatic chromosome alterations (SCA). The prevailing scientific paradigm is that cancer develops by linear accumulation of mutations over decades, which would provide a long "window of opportunity" for early detection. In some people, progression is believed to be so slow that the individual dies of other causes (A) whereas others are characterized by more rapid linear evolution (B). However, data from Li, et al. indicate that the population of patients with nonprogressing Barrett's genomes has a low level of SCA that typically remains relatively stable over prolonged periods of time (C). In contrast, the population of BE patients that progress to EA develop increasing levels of SCA largely in the 48 months prior to detection of cancer, characterized by an increased background of gains and losses of whole chromosomes or chromosome arms (blue), followed by increasing chromosome instability (CIN) with selection and co-selection of gains and losses of specific chromosomes and chromosome arms beginning 48 months before the diagnosis of cancer (yellow) and catastrophic genome doublings within 24 months of the diagnosis of cancer (red).