cmgh
CELLULAR AND MOLECULAR GASTROENTEROLOGY AND HEPATOLOGY

REVIEW

Genomics, Endoscopy, and Control of Gastroesophageal Cancers: A Perspective

Brian J. Reid

Divisions of Human Biology and Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, Washington; and Department of Genome Sciences, University of Washington, Seattle, Washington

SUMMARY

Esophageal adenocarcinoma (EA) is remarkably similar to gastric adenocarcinoma CIN subtype. Current enthusiasm for endoscopic control of EA has little impact on mortality. Current strategies need to be revisited given emerging evidence that many cancers develop rapidly by punctuated and catastrophic genome evolution.

In The Cancer Genome Atlas the goals were to define how to treat advanced cancers with targeted therapy. However, the challenges facing cancer interception for early detection and prevention include length bias in which current screening and surveillance approaches frequently miss rapidly progressing cancers that then present at advanced stages in the clinic with symptoms (underdiagnosis). In contrast, many early detection strategies detect benign conditions that may never progress to cancer during a lifetime, and the patient dies of unrelated causes (overdiagnosis). This challenge to cancer interception is believed to be due to the speed at which the neoplasm evolves, called *length bias sampling*; rapidly progressing cancers are missed by current early detection strategies. In contrast, slowly or non-progressing cancers or their precursors are selectively detected. This has led to the concept of cancer interception, which can be defined as active interception of a biological process that drives cancer development before the patient presents in the clinic with an advanced, symptomatic cancer. The solutions needed to advance strategies for cancer interception require assessing the rate at which the cancer evolves over time and space. This is an essential challenge that needs to be addressed by robust study designs including normal and non-progressing controls when known to be appropriate.
(Cell Mol Gastroenterol Hepatol 2017;3:359–366; http://dx.doi.org/10.1016/j.jcmgh.2017.02.005)

Keywords: Barrett's Esophagus; Biomarkers; Chromosome Aberrations; Esophageal Neoplasms; Gastroesophageal Reflux; Genomic Instability; Genomics; Stomach.

Cancer is a disease of the genome.

Francis Collins

I was trained as a geneticist.[1] The National Cancer Act was passed in 1971 while I was a graduate student in the University of Washington's Department of Genetics. It was during this period that I first learned the concept of cancer as a disease that develops and progresses by somatic genomic evolution as later proposed eloquently by Dr Peter Nowell[2] in his 1976 *Science* classic. I became interested in this concept as a graduate student, but it was difficult to identify a research pathway for a basic PhD geneticist to study cancer as an evolutionary process. I therefore changed my plans for a postdoctoral fellowship and instead entered medical school to learn how to study early stages of neoplasia and their relationship to development of cancer. In the medical school "Gut Course" taught by Dr David Saunders, I realized that the advent of modern endoscopy would allow direct access to premalignant lesions such as those in the stomach and esophagus. This concept was reinforced in my gastrointestinal (GI) rotation with Dr Sidney Truelove at Oxford, who taught me to establish cohort studies for long-term follow-up of GI diseases.

In medical school I was taught then existing concepts of cancer, many of which have subsequently been proven to be outdated or even wrong. One prominent example was the concept that cancer develops by gradual linear accumulation of genetic alterations, which was derived from earlier disease models that have been deeply embedded in medical thought for decades.[3] However, gradual linear evolution of cancer has not been proven rigorously, and a significant amount of recent genomic data support the concept that neoplastic evolution is branched, and some steps in neoplastic evolution occur much more rapidly than others.[4–6] For example, evidence for development of whole genome doublings (WGDs) (near tetraploidy) has only been possible with advances first in cytometric technologies[7] and cytogenetics[8] and more recently in genomic technologies.[9]

With the advent of modern genomic technologies, it has been well-established that cancers evolve from premalignant fields over time and space in tissues of the body, including Barrett's esophagus (BE).[10–17] Cancer is more accurately described as a complex, evolutionary process

Abbreviations used in this paper: **BE, Barrett's esophagus; CIN, chromosome instability; EA, esophageal adenocarcinoma; GI, gastrointestinal; PCGA, pre-cancer genome atlas; TCGA, The Cancer Genome Atlas; WGD, whole genome doubling.**

Most current article

2352-345X
http://dx.doi.org/10.1016/j.jcmgh.2017.02.005

than a molecular disease because of its ability to acquire characteristics that allow it to expand, invade surrounding tissues, metastasize to different parts of the body, and eventually kill the patient.[18] It has consistently evaded attempts at control by therapy, early detection, and prevention.

The 25th anniversary of the Funderburg Research Award comes at a time when recent advances in genomic technologies have made it possible for comprehensive studies such as The Cancer Genome Atlas (TCGA) to be completed in a large number of cancers, including those of the stomach and esophagus.[19–23] These comprehensive studies have provided potential paths forward and insight into the large reservoir of genomic diversity within advanced cancers that could lead to evolution of resistance to cancer therapies,[24] as well as potentially to endoscopic therapies. This effort has provided an atlas of genetic and genomic alterations as well as other measures such as expression and DNA methylation in addition to other characterizations to improve targeted therapy for advanced cancers. The results of TCGA combined with recent advances in immunotherapy have revolutionized approaches to patients who present with advanced malignancies of the upper GI tract.

The 25th Funderburg anniversary also comes at a time when the National Cancer Moonshot Task Force is releasing reports on achievements and strategies. These and other advances may lead to a future in which the longstanding poor outcomes of gastric and esophageal adenocarcinomas (EAs) could radically improve through implementation of new therapeutic strategies including immunotherapy,[25] targeted therapy based on the known genomic profile of the cancer,[20] and combinatorial therapies.

These advances have been a long time coming, and we need to be careful to match our optimistic predictions with reality-based results. We have learned many things since the passage of the National Cancer Act of 1971. Perhaps the most important thing we have learned during these 45 years is that cancer fights back. Therefore, predictions of victory should include plans to overcome evolution of resistance to therapeutic strategies.

Recently, a novel strategy of cancer interception has been proposed to overcome current limitations to early detection and prevention that are imposed by different trajectories of neoplastic evolution.[26] It has been recognized for decades that early detection and prevention strategies miss cancers that evolve so rapidly that they become detectable only after or between screening and surveillance intervals, respectively (Figure 1). Conversely, current strategies will selectively detect non-progressing conditions because they will remain stable for prolonged periods. This concept has been referred to as length bias sampling in the literature, but relatively little progress was made during the pre-cancer genome era (PCGA) because the mechanisms driving "fast" and "slow" or "indolent" tumors were not understood.[27]

The challenges facing cancer interception are different from those involved in deciding treatment for an advanced cancer. In considering a patient with an advanced, symptomatic cancer, the question is how do we treat? In contrast, when we consider cancer interception, we need to decide whether or not to treat and when and how to treat in those who need therapy. To do this with the required precision, the trajectory of somatic genome evolution in time and space must be assessed to determine whether a premalignancy will progress and to determine the "window of opportunity" during which those patients who will progress can be identified, diagnosed, and treated appropriately when they need therapy. Although many insights can be gained about cancer evolution from "cancer only" study designs,[28] non-progressing controls and temporal data from progressors will be required to determine the window of opportunity for cancer interception studies.[9]

Gastroenterologists currently play critical roles in screening, surveillance, diagnosis, and treatment of gastric and esophageal cancers, but current approaches are far from "precision" medicine in BE.[29,30] Physicians also face the full spectrum of ways in which cancer evades attempts at control: (1) failure to detect rapidly evolving cancers that kill patients (underdiagnosis), (2) detection of patients with slowly or non-progressing neoplasms who will never die of esophageal or gastric cancer (overdiagnosis), and (3) initial treatment response followed by evolution of resistance to therapy as a result of branched evolution or other mechanisms.[27,31] For example, there was high hope that endoscopic ablation would be durable,[32] but multiple studies have shown rapid, substantial rates of recurrence ranging from 9% to 33% with radiofrequency ablation.[33] Another study using argon plasma coagulation and multipolar electrocoagulation with a mean follow-up of 6.4 years reported >70% cumulative incidence of relapse of BE.[34] A recent registry follow-up study reported that 100 patients treated with radiofrequency ablation (from a total of 4982) developed EA during follow-up, 9 of whom died of the cancer.[35] The biological bases for recurrence of BE and EA after ablation in some patients are currently unknown.

Inherited mutations that predispose to gastric cancer[36] or to EA[37,38] offer the greatest window of opportunity for cancer interception and prevention. In some cases, especially those without a family history, the interpretation of the genetic variants with regard to the risk posed to the patient may be unclear, even including germline variants. It is likely that many practitioners will choose to have such variants evaluated by a medical geneticist. The American College of Medical Genetics and Genomics also provides recommendations,[39] but this will likely be a rapidly evolving field in which many gastroenterologists may well seek the opinion of a medical geneticist.

Multiple EA sequencing studies have also reported mutation signatures including 1 signature that has been reported only in gastric and esophageal adenocarcinomas.[19,20,40–42] Mutation signatures are the result of biological processes that produce mutations. Each signature has both DNA damage and DNA repair components.[43] The signature shared by gastric and esophageal adenocarcinomas may be critical to developing prevention strategies for these cancers. TCGA and other data indicate that EA is genomically similar to the chromosome instability (CIN) subtype of gastric adenocarcinoma with high rates of