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Mini Review

Molecular classification and prediction in gastric cancer

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ABSTRACT

Gastric cancer, a highly heterogeneous disease, is the second leading cause of cancer death and the fourth most common cancer globally, with East Asia accounting for more than half of cases annually. Alongside TNM staging, gastric cancer clinic has two well-recognized classification systems, the Lauren classification that subdivides gastric adenocarcinoma into intestinal and diffuse types and the alternative World Health Organization system that divides gastric cancer into papillary, tubular, mucinous (colloid), and poorly cohesive carcinomas. Both classification systems enable a better understanding of the histogenesis and the biology of gastric cancer yet have a limited clinical utility in guiding patient therapy due to the molecular heterogeneity of gastric cancer. Unprecedented whole-genome-scale data have been catalyzing and advancing the molecular subtyping approach. Here we cataloged and compared those published gene expression profiling signatures in gastric cancer. We summarized recent integrated genomic characterization of gastric cancer based on additional data of somatic mutation, chromosomal instability, EBV virus infection, and DNA methylation. We identified the consensus patterns across these signatures and identified the underlying molecular pathways and biological functions. The identification of molecular subtyping of gastric adenocarcinoma and the development of integrated genomics approaches for clinical applications such as prediction of clinical intervening emerge as an essential phase toward personalized medicine in treating gastric cancer.

Contents

1. Introduction

Gastric cancer (GC) is the second leading cause of cancer death and the fourth most prevalent malignancy worldwide, accounting for 8% of cancer incidence and 10% of cancer deaths [1]. In the United States,

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about 21,000 cases of gastric cancer (61% are men and 39% are women) were diagnosed and about 10,000 patients died from this disease in 2012 [2]. Many factors such as ineffective screening, diagnosis, and treatment approaches contribute to the high incidence and mortality rates of GC [3,4].

Tumor staging has been established and validated as the best predictor of patient survival. Besides tumor node metastasis (TNM) staging, gastric cancer clinic has two well-recognized classification systems, the Lauren classification that subdivides gastric adenocarcinoma into intestine and diffuse types and the alternative World Health Organization system that divides gastric cancer into papillary, tubular, mucinous (colloid), and poorly cohesive carcinomas. Both classification systems enable a better understanding of histogenesis and biology of gastric cancer yet have a limited clinical utility in guiding patient therapy, especially when dealing with the molecular heterogeneity of gastric cancer [5,6]. The TNM classification is the most important tool for planning treatment in oncology and for assessing the patient's prognosis. However, even the latest edition of the TNM classification has limited power to capture the complex cascade of progression events that derived from the heterogeneous clinical behavior of GC [7].

In the past decade, much progress has been made in identifying more accurately molecular GC subtypes by gene expression profiling based on microarray technologies [8]. Such advances hold a great promise in improving prognosis and identifying more appropriate therapies [9]. High-throughput large-scale molecular profiling data provide rich information that is unobtainable from morphological or clinical examinations alone. Unprecedented whole-genome-scale data have been catalyzing and advancing the molecular subtyping approach.

Here we cataloged and compared published gene expression profiling signatures in GC as well as more integrated genomic features of GC from gene expression, somatic mutation, chromosomal instability, Epstein–Bar Virus (EBV) virus infection, and DNA methylation. We highlighted the consensus patterns across these signatures, identified their associated molecular pathways, and underscored their prediction power of GC stratification and chemotherapy sensitivity. Fig. 1 outlines the contents of this review which focuses on applications of gene expression profiling in diagnosis, prognosis, and therapeutic intervention of GC.

2. Molecular diagnosis of GC

Gene expression signatures have successfully been identified to determine, differentiate, and categorize subtypes of GC as well as to solve some diagnostic dilemmas [8]. In early gastric cancer (EGC), tumor invasion is confined to the mucosa or submucosa regardless of the presence of lymph node metastasis or not [10]. Gene expression analysis identified a signature that differentiated EGC from normal tissue [10]. Boussioutas et al. analyzed 124 tumor and adjacent mucosa samples and explored the molecular features of gastric cancer, which could be discerned that readily defined premalignant and tumor subtypes, using DNA microarray-based gene expression profiling [11]. The identification of molecular signatures that are characteristic of subtypes of gastric cancer and associated premalignant changes should enable further analysis of the steps involved in the initiation and progression of gastric cancer. Vecchiet al. derived 1024 genes (52% up-regulated and 48% down-regulated) that were differentially expressed in 19 EGC samples when compared with 9 normal tissues [12]. The up-regulated genes are involved in cell cycle, RNA processing, ribosome biogenesis, and cytoskeleton organization, while the down-regulation genes are implicated in specific functions of the gastric mucosa (digestion, lipid metabolism, and G-protein-coupled receptor protein signaling pathway). Nam et al. [13] also identified a 973-gene signature to differentiate EGC from normal tissue using the microarray data from the matched tumor and adjacent non-cancerous tissues of 27 EGC patients [13]. They further demonstrated that the up-regulated genes in EGC tissues were correlated with cell migration and metastasis. Kim et al. demonstrated that 60 genes were gradually up or down-regulated in succession in normal mucosa, adenoma, and carcinoma samples by comparing the expression profiles of these tissues from eight patient-matched sets. Thus, molecular classification seems very promising for molecular diagnosis of EGC [14].

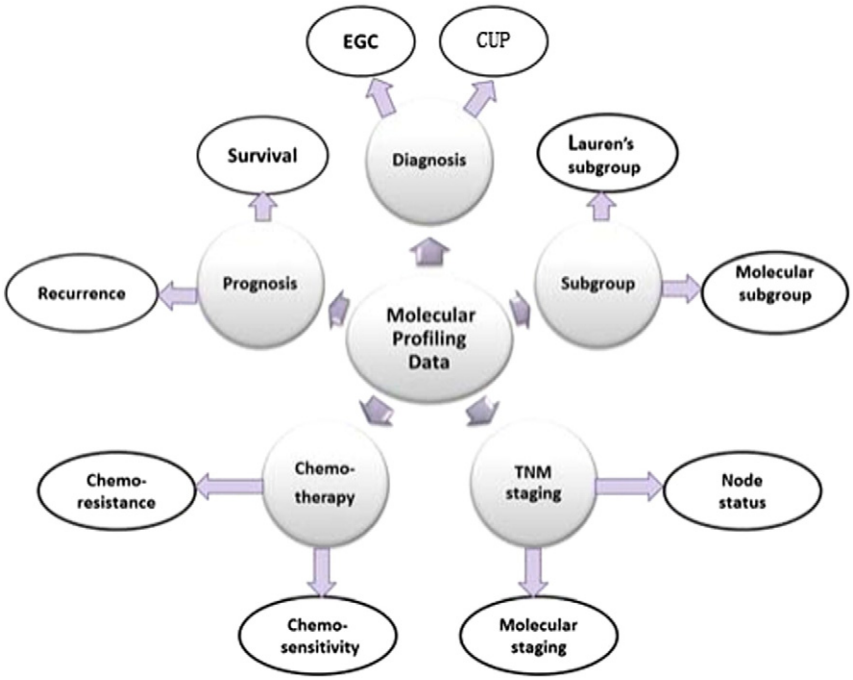

Fig. 1. Applications of molecular profiling in diagnosis and treatment of GC. The applications of gene expression profiling in GC include diagnosis, subgroup, TNM staging, treatment, and prognosis evaluation. EGC: early gastric cancer; CUP: cancer of unknown primary site.