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ORIGINAL RESEARCH

Identification of Differentially-expressed Genes in Intestinal Gastric Cancer by Microarray Analysis

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KEYWORDS

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Abstract Gastric cancer (GC) is one of the most frequent malignant tumors. In order to systematically characterize the cellular and molecular mechanisms of intestinal GC development, in this study, we used 22 K oligonucleotide microarrays and bioinformatics analysis to evaluate the gene expression profiles of GC in 45 tissue samples, including 20 intestinal GC tissue samples,

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20 normal appearing tissues (NATs) adjacent to tumors and 5 noncancerous gastric mucosa tissue samples. These profiles allowed us to explore the transcriptional characteristics of GC and determine the change patterns in gene expression that may be of clinical significance. 1519 and 1255 differentially-expressed genes (DEGs) were identified in intestinal GC tissues and NATs, respectively, as determined by Bayesian analysis ($P < 0.001$). These genes were associated with diverse functions such as mucosa secretion, metabolism, proliferation, signaling and development, which occur at different stages of GC development.

Introduction

Gastric cancer (GC) is one of the most common malignant tumors. It is estimated that one million new cases are reported worldwide each year [1], with around two-thirds of GC occurring in developing countries. Although considerable effort has been directed toward the development of surgical and chemotherapeutic interventions, the prognosis for patients with advanced stages of GC remains poor. Thus, a major challenge toward assessing and, perhaps, improving the clinical outcome of the treatment of GC patients is to better understand the molecular basis of the disease and its development, *i.e.*, the key changes of gene expression patterns in gastric tumorigenesis. The relationship between specific gene expression patterns and certain properties of GC have been previously described, including resistance to chemotherapeutics [2], metastatic potential [3,4] and prognosis following a particular treatment [5,6]. However, to understand the underlying mechanisms of gastric tumorigenesis, it is essential to characterize the biological processes that initiate the development of GC and its subsequent progression, especially, to document the gene expression pattern from a high-risk population of GC. In this study, we have characterized the transcriptional profiles of GC in Chinese patients by using 22 K oligonucleotide microarrays and have identified differentially-expressed genes (DEGs) within GC, GC adjacent and normal tissues. These expression patterns were further examined by identifying molecular pathways associated with GC development.

Results

Genes differentially expressed between intestinal GC and normal gastric mucosa tissues

To understand the expression profile of intestinal GC, we collected 45 tissue samples, including 20 intestinal GC tissue samples, 20 normal appearing tissues (NATs) adjacent to tumors and five noncancerous gastric mucosa tissue samples, and performed microarray study to evaluate the gene expression profile. After normalization, a Bayesian analysis of gene expression level (BAGEL) was used to characterize differential gene expression between intestinal GC tissue samples and noncancerous gastric mucosa tissue samples with a significance cutoff of $P < 0.001$. A total of 1519 genes were recognized to be differentially expressed in intestinal GC when compared to normal gastric mucosa tissue (Figure S1). These included 593 upregulated and 926 downregulated genes. Hierarchical clustering of these DEGs demonstrated a dramatic variation in gene expression in tumors compared with normal gastric mucosa tissue. Tables S1 and S2 list P value, fold change and name of each DEG. Among these DEGs, 11 and 29 genes were upregulated and downregulated with fold change >10, respectively. The annotation analysis from GoMiner indicated that some of these genes were related with gastric physiological function, such as ATPase, somatostatin and gastrin.

Prediction of tumor-specific biological characteristics associated with DEGs in intestinal GC

Based on gene expression profile of GC, we were able to identify tumor-specific biological characteristics that correlate with DEGs. Using currently available chip annotation tools, including DAVID, SOURCE and the high-throughput GoMiner, we obtained the functional description, classification and location of the DEGs. Annotation results showed that these 1183 DEGs were known genes associated with a diverse set of biological pathways and functions in both cell- and organ-specific physiological processes (**Table 1**).

Prediction of tumor-specific pathways associated with gene expression profiling in intestinal GC

Signal transduction pathways associated with gene expression changes were analyzed and defined using the bioresource for array genes (BioRag, www.biorag.org). A total of 143 signal transduction pathways contained genes that were differentially expressed. Among them, 14 pathways showed altered expression of at least three up-regulated genes within each (**Table 2**). These pathways include the MAPK signaling pathway, inflammatory response pathway, TGF-β pathway and pathways associated with extracellular matrix synthesis and regulation of gluconeogenesis. Six pathways were changed with at least three downregulated genes (**Table 3**).

Genes differentially expressed between NATs and normal gastric mucosa tissues

Although NATs appear morphologically normal, Figure S2 demonstrated that the gene expression pattern of these tissues is very different from that of normal gastric mucosa tissues. A total of 1255 DEGs, including 561 upregulated and 694 downregulated genes, were identified with a $P < 0.001$ significance cutoff. The detailed information describing the upregulated and downregulated genes is presented in Table S3 and Table S4.

Comparison of gene expression patterns between GC tumors and NATs

The number of DEGs in GC and NATs is shown and clustered according to different fold changes in **Figure 1**. Our data above