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MicroRNAs (miRNAs) as Biomarker(s) for Prognosis and Diagnosis of Gastrointestinal (GI) Cancers

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Abstract: Gastrointestinal (GI) cancers remain one of the most common malignancies and are the second common cause of cancer deaths worldwide. The limited effectiveness of therapy for patients with advanced stage and recurrent disease is a reflection of an incomplete understanding of the molecular basis of GI carcinogenesis. Major advancements have improved our understanding of pathology and pathogenesis of GI cancers, but high mortality rates, unfavorable prognosis and lack of clinical predictive biomarkers provide an impetus to investigate new sensitive and specific diagnostic and prognostic markers for GI cancers. MicroRNAs (miRNAs) are short (19-24 nucleotides) noncoding RNA molecules that regulate gene expression at the posttranscriptional level thus playing an important role in modulating various biological processes including, but not limited, to developmental processes, proliferation, apoptosis, metabolism, differentiation, epithelial-mechenchymal transition and are involved in the initiation and progression of various human cancers. Unique miRNA expression profiles have been observed in various cancer types at different stages, suggesting their potential as diagnostic and prognostic biomarkers. Due to their tumor-specific and tissue-specific expression profiles, stability, robust clinical assays for detection in serum as well as in formalin-fixed tissue samples, miRNAs have emerged as attractive candidates for diagnostic and prognostic applications. This review summarizes recent research supporting the utility of miRNAs as novel diagnostic and prognostic tools for GI cancers.

Keywords: Gastrointestinal cancers, diagnosis, prognosis, miRNAs.

INTRODUCTION

Gastrointestinal cancers refer to malignant conditions of the gastrointestinal tract (GI tract) and digestive tract associated organs including the esophagus, stomach, biliary system, pancreas, small intestine, large intestine, rectum and anus. The GI cancers are collectively the major cause of cancer related morbidity and mortality worldwide [1]. Prognosis of patients with GI cancers remains largely unsatisfactory due to loco-regional recurrence [1]. Despite improvements, the current treatment strategies including surgery, radiotherapy (RT) and/or chemotherapy (CT) have marginally improved the curative expectations and the quality of life of patients; however, the effectiveness of these new tools depends largely on the stage in which tumors can be detected. Therefore, these cancers can be managed by developing biomarkers, which could enhance early detection, improve patient stratification and therapy response prediction resulting in a more favorable disease outcome. Currently, the most important conventional prognostic factors for survival of GI patients are histological tumor grade and tumor stage at the time of diagnosis, including depth of tumor invasion and involvement of regional lymph nodes. In addition to these clinicopathological parameters, biomarkers are being intensively sought and validated for GI cancers. However, low sensitivity and specificity of available biomarkers limit their utility particularly in screening for early stages or in distinguishing aggressive and indolent tumors [2]. Currently, the relative abundance of several proteins is used as an indicator for diagnostic and prognostic potential. However, complexity of protein composition, diversity of posttranslational modifications, low relative abundance of many proteins and difficulties in developing suitable high-affinity detection agents hinder the development of new protein-based biomarkers. This has prompted investigators to identify more specific and sensitive novel markers, which can supplement or complement existing detection methods for better diagnosis and management of lethal GI cancers.

In recent years, miRNAs present in the body fluids such as plasma, serum, urine, saliva, etc. and tissues have been utilized as biomarkers in various diseases including many cancers [3]. These miRNAs are short noncoding RNA molecules of approximately 19–24 nucleotides (nt), involved in post-transcriptional regulation of gene expression. miRNAs bind to the 3' untranslated region of mRNA, which leads to either translational repression, or mRNA degradation initiated by miRNA guided rapid deadenylation [4]. They act as master regulators for many important biological processes including ontogeny, cell proliferation, apoptosis, migration, differentiation, metabolism, stress, viral infection, cancer initiation and progression and drug resistance [5-8]. Although hundreds of miRNAs have been shown to be deregulated in cancers, the group of miRNAs actually playing any pathogenic role in cancer has not yet been fully defined [9]. However, recent high throughput screening studies have documented several miRNA expression signatures as promising biomarkers in a wide array of human cancers that are potentially capable of predicting favorable prognosis or exhibit association with tumor development, progression and response to therapy [10-12]. In cancers, approximately half of the deregulated miRNAs have been located near fragile sites, in loci associated with loss of heterozygosity or with DNA amplification, and in common breakpoints [13]. Being physiologically important and deregulated in several malignancies, miRNAs are considered to carry important information about the pathophysiological status of cancer patients.

While the majority of miRNAs are intracellular, in recent years extracellular circulating miRNAs have been detected in a variety of biological fluids, such as blood, serum and plasma, saliva, urine, breast milk, seminal plasma, tears, amniotic fluid, colostrum, bronchial lavage, cerebrospinal fluid, peritoneal fluid, and pleural fluid [14-17]. Although Lawrie *et al* identified miRNAs from serum of diffused B cell lymphoma patients; it remained unknown whether the miRNAs detected originated from tumor cells or from nonma-

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