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MiR-200c as a biomarker and therapeutic target for gastric cancer

Abstract

Gastric cancer (GC) continues to be a major health problem worldwide. This article discusses the role of the miRNA-200 family, especially miR-200c, in GC. The miR-200 family plays essential managing role in processes including epithelial-mesenchymal transition (EMT), cell proliferation, apoptosis, and metastasis. miR-200c can reduce cellular invasion and increase the susceptibility of cancer cells to chemotherapeutic drugs by increasing E-cadherin levels. Several studies have shown that low expression of miR-200c in GC negatively affects the prognosis of the disease and is associated with resistance to chemotherapy. It has also been indicated that miR-200c has great potential as a biomarker for early diagnosis of GC and a therapeutic target for enhancing response to chemotherapy. According to the current findings, further studies needed to understand the role of miR-200c in GC.

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Introduction

Gastric cancer (GC) is the fifth most frequent cancer all around the world and its incidence appears to be increasing according to recent data. In 2020, approximately 1.1 million new cases and 800,000 deaths were reported. The incidence of GC is 1.7 times higher in male than in females.[1] Risk factors of GC can be environmental, such as *Helicobacter pylori (H.pylori)* infection, high consumption of salty foods, tobacco and alcohol or familial, such as genetic predisposition.[2,3] Familial predisposition accounts for approximately 10% of the cases while 1-3% involve germline mutations.[4] The histopathology of GC has a crucial impact in the diagnosis and treatment of the disease. There are many histopathological classifications for the disease. This classification may be related to the appearance of the tissue, as in the Borrmann classification.[5] This old classification is still useful, and the macroscopic growth pattern is related to the microscopic allocation systems. The World Health Organization (WHO) classification system classified GC into four categories as tubular, papillary, mucinous and signet ring cell subtypes.[6] In 1965, according to the Lauren classification, GC was defined as intestinal and diffuse type. Both forms were thereafter categorized as adenocarcinomas.[7] Adenocarcinoma is the most common histological form of GC, accounting for over 90% of all cases.[8,9] Adenocarcinomas have histologically two main subtypes including differentiated (benign) and undifferentiated (malignant) adenocarcinomas. Differentiated adenocarcinomas generally have a better prognosis, while undifferentiated types are more aggressive and have a higher risk of metastasis.[9]

MicroRNA (miRNA) is a small, single-stranded RNA form, 18-25 nucleotides length. It is transcribed by DNA and regulates the functions of genes involved in protein synthesis.[10] Aberrant miRNA expression is a key factor in the development of conditions such as cancer, heart disease, diabetes and schizophrenia. Also, dysregulation of miRNA expression has been associated with cell proliferation, apoptosis, migration, epithelial mesenchymal transition (EMT), metastasis and angiogenesis.[11] Among the various miRNA families, the miRNA-200 (miR-200) family stands out for its critical involvement in cancer development. The miR-200 family, consisting of five members, miR-200a, miR-200b, miR-200c, miR-141, and miR-429.[12] Here in this review, we emphasize that miRNA 200c can be used as a potential biomarker for early diagnosis of GC. This molecule may hold significant potential in the detection of cancer at early stages. Furthermore, they might have the capability as an important tool in the development of personalized medicine approaches, especially in individualized cancer treatment.

MiRNA-200 family in cancer progression

The miRNA-200 (miR-200) family has a fundamental role in regulating various hallmarks of cancer. In particular, it is involved in numerous cellular processes that contribute to the development of cancer, including epithelial-mesenchymal transition (EMT), apoptosis, invasion, and metabolic changes.[12] EMT is the process of epithelial cells showing mesenchymal cell characteristics and migrating to other tissues and organs in cancer invasion. This mechanism is mediated through multiple signaling pathways, such as TGF-a and Wnt/β-catenin. MiR-200 family is known to recognize the zinc finger E-box binding homeobox (ZEB) and suppress EMT.[13] MiR-200a affects EMT by first inhibiting β-catenin. After that, Wnt/β-catenin signaling pathway is blocked in renal cell carcinoma via that molecule.[14] On the other hand, it is found that miR-200a targets Catenin β1 and trigger the proliferation and invasion in esophageal squamous cell carcinoma cells.[15] MiR-200b contributes significantly to the EMT process. It promotes E-cadherin expression by inhibiting transcription factors including ZEB1 and ZEB2, which are implicated in EMT. This limits the transition of cells to mesenchymal cell type while retaining epithelial characteristics. This mechanism diminishes the metastatic potential of cells.[16,17] miR-200c, another member associated with E-cadherin, is increased in pancreatic cancer cells. This increase may reduce cell invasion and raise the E-cadherin levels.[18]

MiR-200c in gastric cancer

Studies have shown that miR-200c is associated with many types of cancer, especially gastric cancer, and plays an important role in overcoming chemotherapy resistance.[19,20] miR-200c can suppress the proliferation, cell cycle, and migration of gastric cancer cells by downregulating invasion-related proteins MMP9 and VEGFR. Moreover, it has the potential to increase cell sensitivity to cisplatin by inhibiting RhoE. These findings suggest that miR-200c expression

levels can be regulated to increase its efficacy in cancer treatment. As a result, it has been suggested that miR-200c can effectively eliminate treatment resistance and improve response to chemotherapy.[19] In a study examining the potential functions of miR-200b and miR-200c in the onset and progression of GC, miR-200b and miR-200c expression was evaluated in 36 non-cancerous and GC samples and cell lines. PCR analyses revealed that these molecules were expressed at low levels in GC cell lines and samples. In addition, miR-200b and miR-200c degrees were found to related to TNM classification and patient survival. These findings suggest that miR-200b and miR-200c may be useful biomarkers in determining the prognosis of GC and may offer a potential treatment strategy.[21,22]

Other MiRNAs used as biomarkers in gastric cancer

The role of microRNAs in gastric cancer diagnosis can be quite different. Due to regulations such as DNA methylation, overexpression and supressions,[23] miRNAs can act either as oncogenes or tumor suppressors. According to their dual functions, miRNAs are seen as potential biomarkers for cancer diagnosis and prognosis.[24] While miR-21 stands out as an important diagnostic biomarker in GC, as in many other types of cancer, it is found that miR-18a, miR-106a and miR-106b (all upregulated) can also be used as biomarkers in GC.[25]

MiR-200c as a biomarker and therapeutic target

MiR-200c is being evaluated as a potential biomarker in the diagnosis and prognosis of cancer. Serum miR-200c levels can be used to monitor the course of the disease in gastric cancer patients. For example, high levels of miR-200c have been associated with better prognosis in some types of cancer.[26] It has also been reported that miR-200c can be used to predict response to cancer treatment.[27] Reexpression of miR-200c can increase the sensitivity of cancer cells to chemotherapy. Under cisplatin treatment, high levels of miR-200c enhance the response of cancer cells to therapy.[28] It has also been shown that miR-200c can reduce tumor growth by inhibiting the invasion of cancer cells.[29]

Limitations of miRNAs in GC treatment

Although miRNA appears to be an effective method for diagnosis, it has some limitations. First of all, miRNA's are difficult to find stable in the blood stream, plasma or other body fluids. Sensitive methods are required for detecting the correct amount of miRNAs in body fluids. Also, there is a lack of standardization in techniques used to measure miRNAs. Inadequate normalization methods used in measurement techniques and inconsistent estimation of miRNA amounts may affect the results.[30] The expression levels of miRNAs may vary in different individuals and tissues. This is due to biological heterogeneity and may reduce their reliability as a biomarker. The roles of miRNAs in cancer cells (oncogenic or tumor suppressive) may vary depending on the cancer type and microenvironment.[31] Consequently, further studies are needed to evaluate their biomarker potential.

Conclusion

Gastric cancer poses a serious health burden worldwide with both high incidence and mortality rates. In this context, the effects of miRNAs, especially the miR-200 family, on GC have increasingly attracted attention. It has been demonstrated that low expression of miR-200c contributes to the progression of GC and negatively affects the prognosis of patients. It has been shown that this molecule suppresses cellular invasion and metastasis by promoting E-cadherin expression, and also improves patients' treatment responses by increasing sensitivity to chemotherapy. Current literature suggests that miR-200c should be considered not only as a biomarker for early diagnosis of GC, but also as a promising therapeutic target for treatment-resistant patients. Serum miR-200c levels may be an effective indicator for clinical follow-up of GC patients. However, understanding how re-expression of miR-200c may play a role in overcoming chemotherapy resistance will be an important step in developing personalized treatment approaches. However, larger clinical studies and in vivo models are required to understand the precise effects of miR-200c on GC. Such studies may offer new and effective approaches to improve both GC prognosis and treatment strategies. In this context, miR-200c offers innovative potential as both a diagnostic and therapeutic tool in GC management.

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Conflicts of interest

The authors declared that there are no conflicts of interest.

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