Review Article

A comprehensive review on biomarkers for detection of gastric cancer

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Abstract

Cancer is the second leading cause of mortality. It has been reported that cancer has caused 9.6 million mortalities, in which 1.03 million mortalities due to gastric cancer occurred worldwide in the year 2018. Gastric Cancer is a heterogeneous ailment, where every patient shows a different genetic and molecular profile. The biomarkers that are used for diagnosis of gastric cancer include carcinoembryonic antigen (CEA), specific carbohydrate antigens such as CA 19-9, CA 125, CA 72-4, CA 50, CA 24-2, HER-2, pepsinogen, fibroblast growth receptor factor 2 (FGRF-2), and E-cadherin. The traditional diagnosis methods of gastric cancer are of less utilization because of their low sensitivity. The traditional methods of diagnosis are unable to analyze the reappearance of cancer. Several studies have shown that cancerous cell secretes various molecules that can be an effective and sensitive method for detecting gastric cancer. These molecules can indicate gastric cancer in the acute stage and help to analyze the recurrence of cancer. This review gives detailed insight into the novel strategies and molecules for the diagnosis of gastric cancer.

Keywords: Gastric cancer, microvesicles, exosomes, microparticles, miRNA.

Introduction

World Health Organisation (WHO) has reported that cancer was the second leading cause of morbidity and mortality in 2018 worldwide. It has been estimated that cancer has caused approximately 9.6 million deaths, out of which 1.03 million deaths were reported due to gastric cancer. In India, 57394 cases of gastric cancer were reported in 2018 [1].

Gastric Cancer or stomach cancer develops due to the stomach's epithelial lining damage, and approximately 90% of gastric cancers are adenocarcinoma in nature. This adenocarcinoma can be allocated into cardia or non-cardia types, depending upon the site of initiation [2]. The causes of the damage of the protective covering of the stomach lining include *Helicobacter pylori* infection, dietary habits, obesity, tobacco and alcohol consumption, and NSAIDs use. Many risk factors affect gastric cancer incidences, such as age, gender, mutations in specific genes, race, or family history. The manifestations of gastric cancer include heartburn, nausea, vomiting, upper abdominal pain, viral infection, physical inactivity, and appetite loss. The chronic stage of gastric cancer shows symptoms like weight loss, yellowing of skin and whites of eyes, difficulties in swallowing, and blood in the stool [3].

There are various variants of gastric cancer that are more serious in comparison to the gastric adenocarcinoma. Several gastric cancer variants are Epstein-Barr virus-associated lymphoepithelioma like carcinoma, hepatoid adenocarcinoma, neuroendocrine cell carcinoma, squamous and adenosquamous carcinoma. A few others are choriocarcinoma, sarcomatoid carcinoma, acinar cell carcinoma, invasive micropapillary carcinoma, parietal cell carcinoma and oncocytic carcinoma. Among all of these, the Epstein-Barr virus-associated lymphoepithelioma-like carcinoma has the highest incidence rate, i.e., 4% [4].

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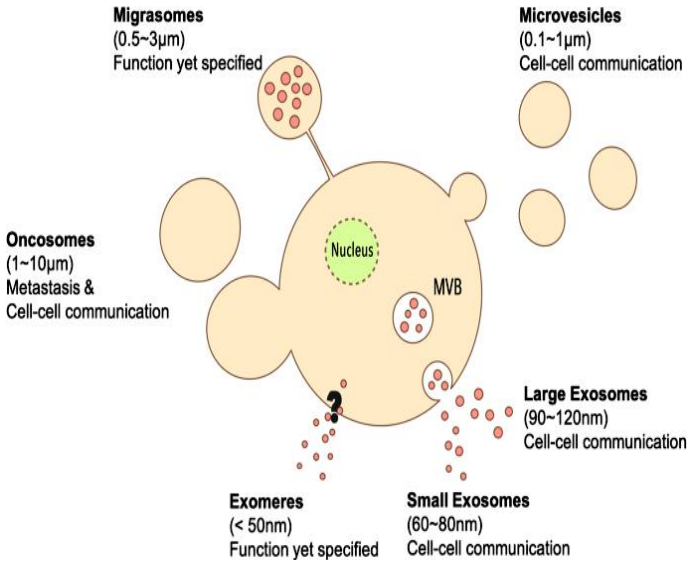

Figure: 1. Extracellular vesicles formation from the donor cell [14]

rate, i.e., 4% [4]. There are multiple pharmacological treatments available for gastric cancer, such as adjuvant therapy, cisplatin-5-fluorouracil, surgery, or anti-HER2 antibody trastuzumab. Nutraceuticals' consumptions help in the prevention of the development of stomach cancer. Physicians prescribe the nutraceuticals along with the anti-cancer drugs for the treatment of stomach cancer. They also prevent damaging the stomach's epithelial lining as they reduce gastric pH [5, 6].

Gastric or stomach cancer is a heterogeneous ailment that means every patient exhibits variation in the genetic and molecular profile. Detection of gastric cancer at its early stage can reduce the mortality rates among the population worldwide. Specific proteins play an essential role in cancer pathogenesis. The expression level of the receptor tyrosine kinase erbB-2 (ERBB2) has been found elevated in gastric cancer patients [7]. Sensitive and reproducible biomarkers related to gastric cancer can improve diagnosis, progression, recurrence of tumor, and response towards the anti-cancer treatment [8].

Biomarkers

Biomarkers are the molecules that can reveal the human body's condition and signify the actual medical state of the patient. The accepted meaning of biomarkers was framed by the National Institutes of Health Biomarkers Definition Working Group in 1998, states that "A biomarker is a characteristic element which objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention" [9]. The proteins, lipids, or nucleic acid can act as biomarkers. These molecules are synthesized either by the cancerous cell or by health cells in response to cancer development and reveal other disorders related to the cardiovascular system, autoimmune disorders [10].

Biomarkers can be collected from many sites such as blood and other body fluids, stools, urine, or site depending upon cancer type and size. These molecules play an essential role in the pathogenesis of cancer and intracellular communication between the cells. The internalization process supports tumor growth factors responsible for angiogenesis, invasion, and metastasis of cancers. Different biomarkers play different roles in cancer development, and they are an essential aspect of any clinical research success. These biological markers aids in the diagnosis of the disease, staging the disease, indicate disease prognosis, help the physician develop the treatment plan, and monitor progress [11].

Biomarkers of Gastric Cancer

Biomarkers in gastric cancer are useful for diagnosis, developing treatment strategy, monitoring, and screening for recurrence. Gastric cancer is a heterogeneous condition, and markers that are used clinically for diagnosis of stomach cancer include carcinoembryonic antigen (CEA), fibroblast growth receptor factor 2 (FGRF-2), specific carbohydrate antigens such as CA19-9, CA 50, CA 72-4, CA 24-2, CA125, HER-2, pepsinogen, and E-cadherin. A traditional biomarker, cytokeratin has been used as the diagnostic biomarker of gastric cancer. It is a type of keratin protein found on the intracytoplasmic cytoskeletal of the epithelial cells, which helps diagnose the circulating tumor cells (CTCs) within the blood. Cytokeratin is present on the surface of the CTC's that circulate through the blood for metastasis. These can only be collected from the plasma or serum. The traditional biomarkers are insufficient for the early diagnosis of recurrence of tumors [10, 12]. The low sensitivity of the existing biomarkers developed a need for new strategies that are effective and sensitive for diagnostic purposes. Recent studies have suggested that the tumor tissue secretes specific molecules to circulate biomarkers to diagnose gastric cancer. These include extracellular vesicles such as microvesicles, exosomes, microparticles, microRNA, and long non-coding RNA molecules [13].

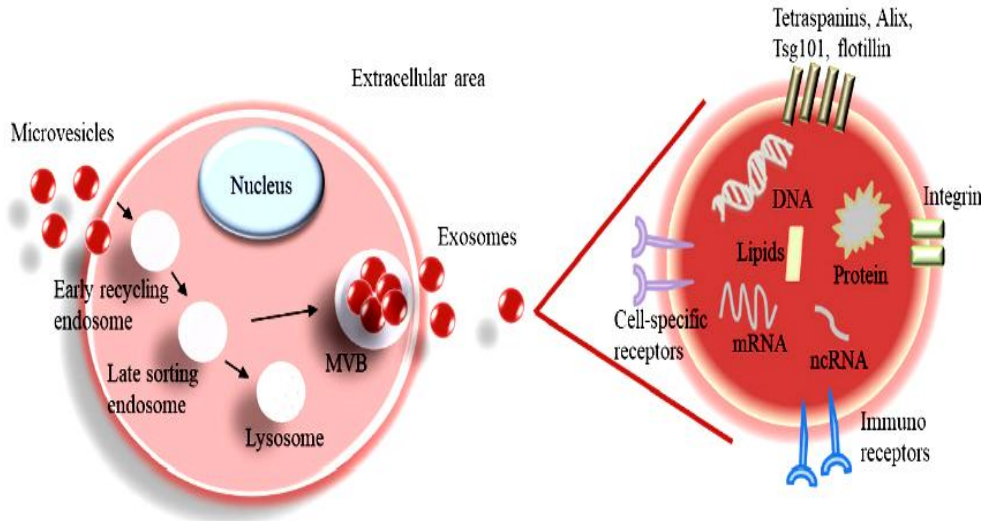

Figure: 2 Biogenesis and components of exosomes [20]

Extracellular vesicles

Extracellular vesicles (EV) are the vesicles that play an essential role in intercellular communication between cells [Figure 1]. These are the membrane-bound vesicle, and the size ranges from 30nm to µm. The composition of the extracellular vesicles is proteins, lipids, and nucleic acids. EV can be classified into different types depending upon the size, such as microvesicles (100nm to 1µm), exosomes (40nm to 120nm), oncosomes (1µm-10µm), and apoptotic bodies (50nm-2µm). Various techniques are available to isolate the extracellular vesicles, such as density gradient or cushion centrifugation, immunoaffinity-based capture, and differential centrifugation. EVs are collected for the supernatants of the cell culture in the fetal calf serum. These extracellular vesicles have an essential part to play in cancer progression as well as pathogenesis. They also help cancer cells in invasion and metastasis [15].

Exosomes

The exosome is a type of extracellular vesicles formed by the fusion of the plasma membrane and multivesicular bodies. These are smaller in size ranges from 40nm to 120nm. The three most essential components of vesicles are protein, nucleic acid, and lipids. These extracellular vesicles are involved in the pathogenesis of many diseases such as HIV infection, cancer, heart diseases, and also play an essential role in intracellular communication. The vesicles can be collected from body fluids such as blood, plasma membrane, CSF, or breast milk. Exosomes have been proven to be useful for diagnosis, monitoring the development and prognosis of cancer, response to treatment, and recurrence of cancer [16].

Composition of exosomes

Exosomes are made up of proteins, lipids, and nucleic acids. The exosomal membrane is a lipid bilayer consisting of gangliosides and sphingomyelin. Exosomes can be easily internalized by the recipient cells due to phosphatidylserine in the membrane's outer surface and contain various proteins such as Integrin, Selectin, Rab proteins, SNAREs, tetraspanins like-CD9, CD8, and CD63. Exosomes consist of miRNA, siRNA, DNA, growth receptors, and some soluble factors [17].

Biogenesis and isolation of exosomes

Exosomes are forms by the formation of buds of the plasma membrane of the early endosomes. The endosomes divide into two forms, the degradative multivesicular bodies the exocyclic multivesicular bodies. The degradative multivesicular bodies form the lysosomes [Figure 2]. These multivesicular bodies merge with the plasma membrane and form exosomes released into the extracellular fluid (ECF) for intracellular communication [18]. Exosomes can be isolated by several techniques such as density gradient or cushion centrifugation, immunoaffinity based capture, and differential centrifugation. A series of centrifugation removes debris and dead cells from the sample, and ultracentrifugation results in the separation of pure exosomes pellets. The differential ultracentrifugation obtains the highest yield of the exosomes [19].

Exosomes targeted towards gastric cancer

Cancerous cells secrete exosomes into the extracellular fluid for intercellular gesturing. Many studies have suggested that exosomes play an essential role in the development, angiogenesis, metastasis, invasion, and drug resistance in gastric cancer. Exosomes are responsible for the cellular molecules' transportation, which causes progression, metastasis, and invasion of the tumor cells. The tumor-targeting proteins, peptides, or antibodies, make exosomes suitable for a specific drug, therapeutic target drug delivery, and a cancer-targeting agent. Exosomes are also capable of neutralizing antibody-based drugs and help to reduce antibody-dependent cytotoxicity [21].
Many studies have suggested unique properties of the exosome

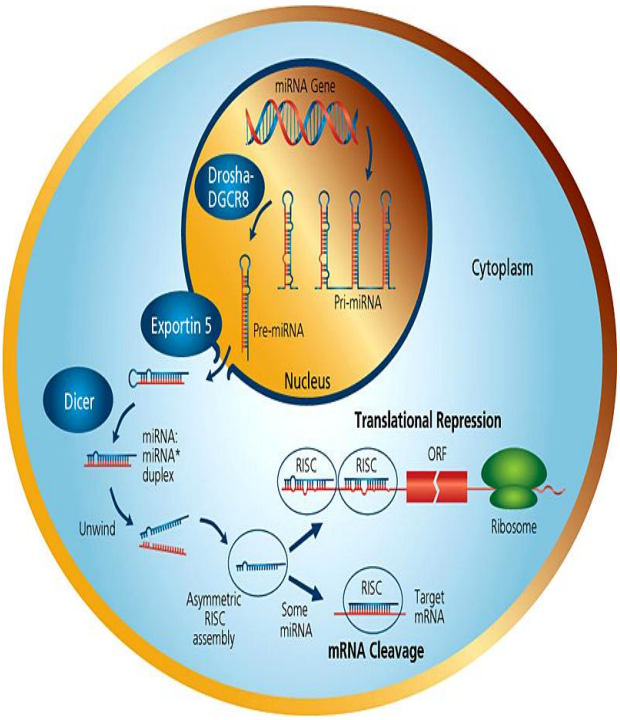

Figure: 3 Biogenesis of the microRNA (miRNA) [26]

of carrying cancer oriented RNA, stability, and reproducibility makes it a better contender for cancer diagnosis. The early gastric cancer exosomal IncUEGC1 is a sensitive, non-invasive, and stable biomarker for diagnosing gastric cancer [22]. The exosomal DNA derived from the gastric juice also diagnose stomach cancer in its acute stage. The levels Gastrokine 1 (GKN1) and TRIM3 exosomal protein derived from serum exosomes were found to be lower in gastric cancer patients compared with the healthy person. Exosomes can also act as potential drug targets for gastric cancer. The proton pump inhibitors prevent the formation and release of exosomes in the extracellular fluids by the gastric cancer cells, thus interrupting cellular communication among cancerous cells. Exosomes can also be used for the delivery of RNA based cancer therapies. The anti-miR-214 loaded exosomes have been shown to reverse the resistance against cisplatin in gastric cancer patients [23].

MicroRNA (miRNA)

As many biomarkers detect gastric cancer, such as MG7-AG, CEA, CA1999, and CA50, all of which are not very effective and specificity. Along with this, some gene-related biomarkers and miRNAs are other forms of biomarkers that can detect human disease and have a very close association with cancers. The miRNA is non-coding ribonucleic acids containing approximately 19-25 nucleotides that alter the translation of the targeted genes [Figure 3]. The deregulation of miRNA has correlated with cancer development and tumor progression and helps regulate the body's biological processes like ontology, stress, apoptosis, migration, and cell proliferation [24].

Like in zebrafish, miR430 helps develop the brain, while miR181 helps differentiate the regulation of B-cells. While two other biomarkers- miR221 and miR222 are involved in the regulation of angiogenesis [25]

Many investigations have described the up-regulation and down-regulation of miRNA as gastric cancer that acts as a tumor suppressor gene. LATS2, a tumor suppressor gene of miR373, controls cancer cell growth and cell cycle by down-regulation mechanism, whereas overexpression of miR650 also promotes cancer cell growth and the proliferation of gastric cancer. [27] Non-coding RNA is detected in the blood, and many studies suggested that miRNA is a remarkably stable protein component and releases by the cancerous cells undergoing apoptosis or necrosis [28]. They are also secreted due to the chronic inflammation of the damaged tissue. Immune cells are present in cancer cells that secrete active miRNA that is either attached to the microvesicle or are independent in a specific manner [29].

Clinical application of miRNA

The diagnosis of gastric cancer in the acute stage is a very challenging aspect. Specific strategies have been reported that can be used for the detection of gastric cancer in its early stage. The expression of miRNA can be used to diagnose stomach cancer in acute stage disease. Solexa sequencing and qRT-PCR is the best-suited method for identifying five contrasting archetypes of serum microRNA like miR1, miR20a, miR27a, miR34, and miR423-5p related to tumor stage, could act as detective biomarkers of gastric cancer. The diagnostic biomarkers have reported various samples of miRNA. Sample 60GC (46A, 6M, 8S)/18C was used as a diagnostic biomarker of miRNA as miR-421 using the qRT-PCR technique. Sample 63GC/10C was used as a diagnostic biomarker of miRNA as miR-31 using the real-time qRT-PCR (RNU6B) technique.

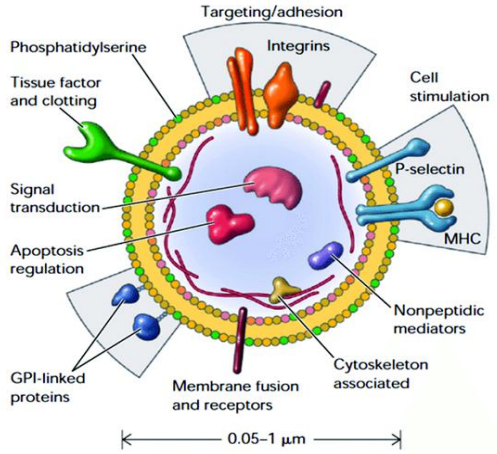

Figure: 4. Cellular microparticle and its composition [39]

Sample 37GC/37C was used as a diagnostic biomarker of miRNA as miR-21 using the qRT-PCR (U6) technique. Sample 72GC/72C was used as a gastric cancer biomarker of miRNA as miR-196a using the qRT-PCR technique. Sample 20GC/20C was used as a diagnostic biomarker and target biomarker of miRNA as miR-146a using the qRT-PCR technique. Sample 4GC cell lines, 106GC/106C used as a diagnostic biomarker of miRNA as miR-148b using real-time qRT-PCR(U6). Sample 101GC (341,67B)/101CC/ used to detect gastrointestinal cancer by miRNA biomarker as miR-148a and miR-152 using real-time qRT-PCR technique [30].

miRNA in gastric cancer therapy

The proliferation and progression of stomach cancer are relatively high. The detection of cancer development in the stomach in the early stage can reduce the associated morbidity and mortalities [31]. The miR-421 has been reported to be overexpressed in gastric cancer patients as compared to healthy ones. The analysis of the expression level of the miR-421 was proven to be a better diagnostic strategy compared to the CA125 and CEA methods [32].

The miRNA based drugs inhibit onco-microRNA, which further inhibits the tumor progress by suppressing the signal pathway process. For example, miR-34 inhibits microRNA in certain tumors like gastric cancer, breast cancer, lung cancer, and liver cancer. The miR-34 has been reported to increase the expression of the tumor-suppressor genes p53, which results in inhibition of gastric cancer growth and development. miRNA therapy also helps to reduce the resistance against anti-cancer drugs [33].

Certain studies have reported that miRNA therapy increases nuclear receptors' expression, drug transporters, transcriptions factors, and drug-metabolizing enzymes. Along with the advantages, particular miRNA also possesses some unwanted activities. Specific microRNA has been reported to alter the transcription of genes other than the targeted ones [34].

Microparticles

Microparticles are a type of extracellular vesicles ranges from 0.1 to 1.0 µm. Microparticles are secreted by the donor cells due to cell injury or stress conditions into the extracellular fluid. Microparticles can be isolated from body fluids, and the levels of circulating microparticles may get altered in diseased conditions such as cancer, diabetes, cardiovascular disorders. The altered level of the microparticles can act as the diagnostic tool. Studies have suggested that microparticles are also responsible for the development of any disease state [35].

Composition and Biogenesis of microparticles

Microparticles are the antigenic component, are functional cytoadhesions, bioactive phospholipids, and cytoplasmic cellular components that form by the budding of the plasma membrane [36]. Microparticles are extracellular vesicles forms by the budding of the plasma membrane [37]. In the cell plasma membrane, the phosphatidylserine residue is present in the internal surface, while the formation of the microparticles, this phosphatidylserine residue undergoes a flip-flop movement [Figure 4]. The membrane of microparticles contains the phosphatidyl residue on the external surface [38].

Microparticles in gastric cancer

The plasma level of platelet microparticles (PMP) has been reported to increase in gastric cancer patients. The plasma microparticles levels can distinguish between the acute and metastatic stages of stomach cancer [40]. Platelet activation markers include beta-thromboglobulin, platelet factor 4, or thrombosporidin be elevated in patients with different cancer [41].

Discussion

Gastric Cancer is the most common cause of mortalities around the world. The diagnosis of stomach cancer in the early stage can help select appropriate treatment strategies, and proper monitoring can reduce the mortalities and morbidities caused by gastric cancer. Several gastric cancer markers are used for diagnosis and analysis of the response towards therapy. The biomarkers can also act as the anti-tumor therapeutic agent. Many biomarkers are used in gastric cancer, and they are carbohydrate antigen CA-724, CA-125, SLE, BCA225, and

pepsinogen-1st/2nd. Carcinoembryonic antigen (CEA) and CA-199 are the most accepted tools for diagnosing gastric cancer. These traditional tools' major disadvantage is lesser sensitivity and inability to diagnose cancer in its acute stage. The discovery of the more sensitive and accurate biomarkers can prove a remarkable success in oncology. The most accepted novel biomarkers have the potential of overcoming the limitations of the conventional biomarkers. They can help diagnose gastric cancer in its early stage and the recurrence of cancer.

Microparticle contributes to the pathogenesis of cancer and also be used in the context of cancer management. The detection of microparticles in body fluid provides significant meaning for the diagnosis and surveillance of cancer patients. Platelet biomarkers such as as-beta-thromboglobulin, platelet factor-4, or thrombosporidin levels are elevated in cancer patients. Patients have a reduced count of PMPs leading to bleeding disorders.

In gastric cancer, miRNA also plays a vital role as the biomarker of gastric cancer; miR-125a-5p (a biomarker of miRNA) functions as a crucial malignancy conquer in human gastric cancer. The microarray analysis or deep sequencing of cell-free miRNA can detect their presence even in small quantities. miRNA can be collected from the patient's blood, urine, or saliva [42]. The novel biomarkers can distinguish between the subtypes of cancer. Studies have reported that the level of novel biomarkers such as miRNA and microparticles are found different in adenocarcinoma and squamous cell carcinoma [43].

Conclusion

Gastric Cancer is the second leading cancer that caused 9.6 million deaths worldwide, out of which 1.03 million deaths were reported due to gastric cancer. The stomach lining cause includes helicobacter pylori infection, dietary habits, obesity, tobacco, alcohol consumption, and NSAIDS use. Biomarkers can reveal the exact medical state of the patients. Some proteins, lipids, and nucleic acids can act as biomarkers. These biological markers aid in the diagnosis of the disease, staging of disease, indicating disease of prognosis, and helps physicians develop the treatment plan and monitor the progress of patients. Many studies have suggested that exosomes as a biomarker help in angiogenesis, metastasis invasion, and drug resistance of gastric cancer. Exosomes also are used for the delivery of RNA-based cancer therapies. The anti-miR-214 loaded exosomes have been shown to reverse the resistance against cisplatin in gastric cancer. While circulatory miRNA act as a biomarker and detect tumor cells' growth at an early stage in cancer, miR-34 impedes gastric cancer by upregulating the expression of the tumor-suppressor genes p53. The novel technology for the diagnosis of gastric cancer is more sensitive and reproducible. These techniques can diagnose cancer at the early stage, cancer progression, response towards cancer therapy, and recurrence of cancer.

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