BIOSENSOR BASED ADVANCED CANCER DIAGNOSTICS

FROM LAB TO CLINICS

EDITED BY

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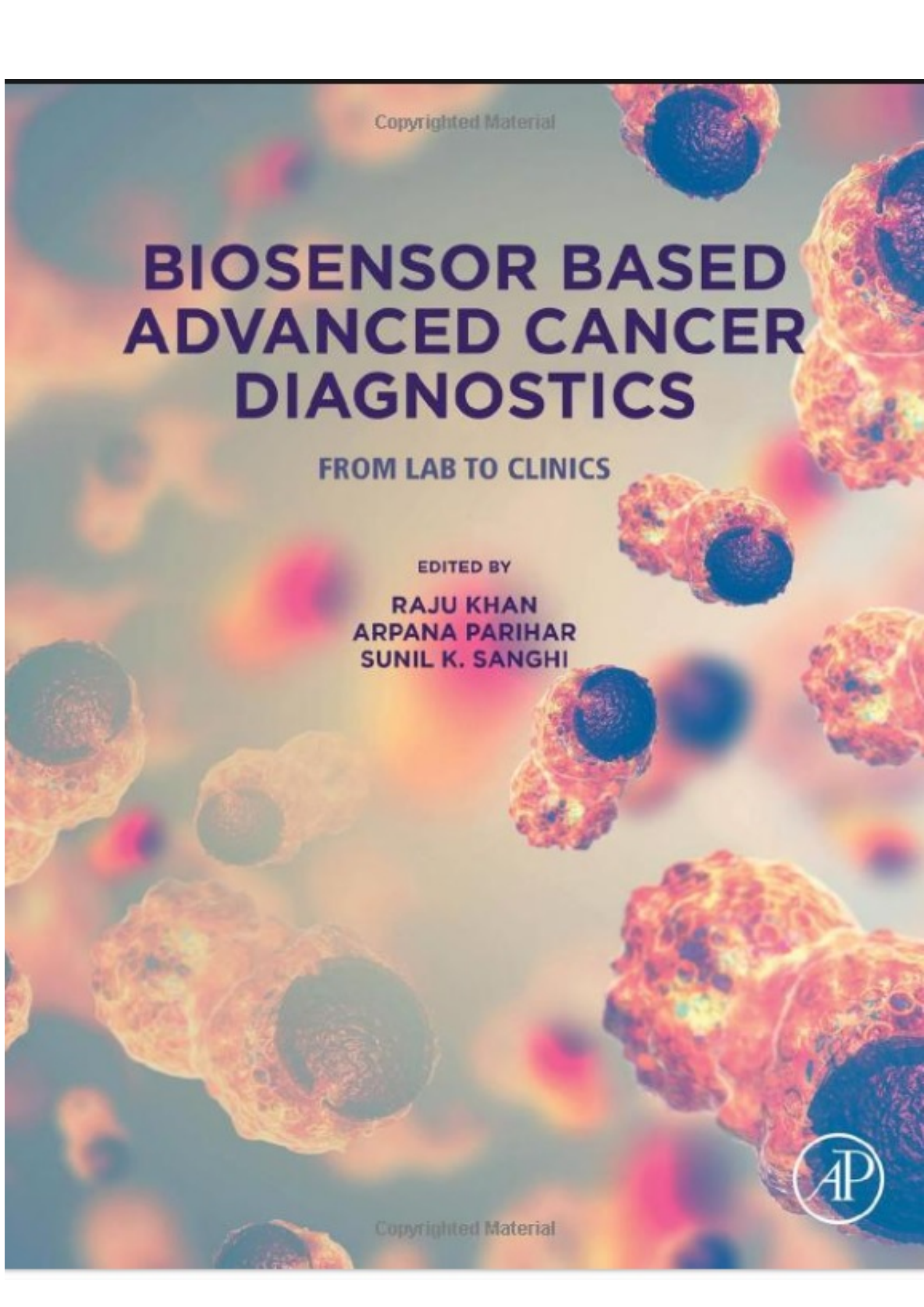

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Academic Press is an imprint of Elsevier
125 London Wall, London EC2Y 5AS, United Kingdom
525 B Street, Suite 1650, San Diego, CA 92101, United States
50 Hampshire Street, 5th Floor, Cambridge, MA 02139, United States
The Boulevard, Langford Lane, Kidlington, Oxford OX5 1GB, United Kingdom

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British Library Cataloguing-in-Publication Data
A catalogue record for this book is available from the British Library

Library of Congress Cataloging-in-Publication Data
A catalog record for this book is available from the Library of Congress

ISBN: 978-0-12-823424-2

Publisher: Mara Conner
Acquisitions Editor: Carrie Bolger
Editorial Project Manager: Sara Valentino
Production Project Manager: Prem Kumar Kaliamoorthi
Cover Designer: Mark Rogers

Typeset by MPS Limited, Chennai, India

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Contents

Chapter 15

Biosensor-based early diagnosis of gastric cancer

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15.1 Introduction

Gastric cancer is one of the most commonly found cancers worldwide (Kono, 2016). Gastric adenocarcinomas constitute most of the stomach cancer or gastric cancer, and based on the anatomical location of the tumor, it is sub-divided into cardia (gastro-esophageal junction) and noncardia (true gastric) tumors (Van Cutsem, Sagaert, Topal, Haustermans, & Prenen, 2016). Gastric cancer is uncommon in all populations below the age of 50, and the incidence rate increases with the increase in age, reaching its peak at the age of 55–80 years. The frequency of gastric cancer is two- to threefold higher in men than in women. The age-standardized incidence rate is 15.7 per 1,000,000 men and 7 per 1,000,000 women in 2018 (Thrift & El-Serag, 2020). The highest incidence rate was seen in the high-income Asia Pacific region (29.5 per 100,000 population, age-standardized), especially Japan, South Korea, and East Asia (28.6 per 100,000 population). In East Asia, China contributed about half of the global incident in 2017, followed by Eastern Europe and Andean Latin America. Other than these regions, Mongolia and Afghanistan had the overall highest age-standardized incidence rates. Southern and eastern sub-Saharan Africa and high-income North America experienced the lowest incidence rates. The highest age-standardized death rate is experienced by East Asia, followed by Andean Latin America and central Asia (Etemadi et al., 2020). India falls in the low incidence category in the context of gastric cancer. There is a huge regional difference in gastric cancer occurrence across India. According to the national cancer registries, gastric cancer is the leading problem in the northeastern and southern states of the Indian subcontinent. As per the available report, Aizawl, Mizoram, has the highest recorded incidence of gastric cancer followed by Tamil Nadu. The lowest incidence of gastric cancer in India is reported in Gujrat. Gastric cancer is the fifth most frequent cancer among men and sixth among women in India. It is also the second most common reason for cancer-associated death in Indian men and women among the age group of 15–44. Detection of gastric cancer in the advanced stage in most of the patients leads to a decrease in the 5-year survival rate in comparison with the countries where early diagnosis is made. The treatment standard and protocol in most of the institutions are good as any other country, although it is not observed evenly across the country (Dikshit, Mathur, & Mhatre, 2011; Servarayan Murugesan et al., 2018; Sharma & Radhakrishnan, 2011). The incidence of stomach cancer remarkably decreases in the last half century. Nonetheless, stomach cancer is in the fifth and third positions of cancer incidence and deaths due to cancer, respectively, all over the world (Balakrishnan, George, Sharma, & Graham, 2017).

Helicobacter pylori (*H. pylori*) infection is the most important risk factor which causes a prolonged inflammatory reaction of the immune response (Crew & Neugut, 2006; Rawla & Barsouk, 2019). Salt and salt preserved food may also increase the threat of stomach cancer. A decrease in stomach cancer is associated with a reduction of *H. pylori* infection (Cisco, Ford, & Norton, 2008). The decline in infection rate is due to better sanitation, hygienic practice, and better food preservation methods (Sharma & Radhakrishnan, 2011). Stomach cancer epidemiology has significant geographical diversity leading to at least a 10-fold variation of incidence worldwide (Servarayan Murugesan et al., 2018). Part of this variation is related to *H. pylori* infection frequency throughout the population, and environmental factors which are also responsible for stomach cancer (Etemadi et al., 2020). Cigarette smoking is a risk factor for both the type of cancer. Because of the higher occurrence of risk factors such as smoking or hormonal factors, both the cancers are more common in males.

Biosensor Based Advanced Cancer Diagnostics. https://doi.org/10.1016/B978-0-12-823424-2.00023-5

The decline in gastric cancer is not universal (Balakrishnan et al., 2017). Reduction in the incident cases and deaths in East Asia will lead to a decrease in absolute incident cases and death, as half of the incident cases and death occur there. Migrant studies and secular trends in stomach cancer rates reveal that environmental factors play a significant role in the pathogenesis of stomach cancer. In contrast, only about 1–3% are known to be hereditary syndromes (Thrift & El-Serag, 2020; Van Cutsem et al., 2016). Reduction in high salt food consumption in Asian countries is an approach to decrease stomach cancer since lifestyle, particularly high sodium diets in East Asian peoples and smoking in males, plays a significant part in stomach cancer burden. The main focus is on preventing *H. pylori* infection, since it is the most crucial element of danger for stomach cancer.

Gastric cancer is grouped into two: (1) early gastric cancer (EGC, stages I and II) defined as the malignant tumor confined to the mucosa and submucosa irrespective of lymph node metastasis; and (2) advance gastric cancer (AGC, stages III and IV); there is lack of a homogeneous definition of advance gastric cancer. However, gastric cancer is a cancer that has attacked the muscularis propria or gastric wall (Cisco et al., 2008; Ooki et al., 2009; Saragoni, 2015). Surgery can treat EGC, but AGC usually requires multidisciplinary treatment. Early diagnosis and careful staging can reduce mortality. Despite all this, gastric cancer staging is facing difficulties because of the lack of defined risk factors. Thus, late diagnosis and inadequate staging arrangements may cause an increase in mortality. So a fast and noninvasive method is needed for early diagnosis and staging of gastric cancer.

General cancer treatment procedures are related to characterizing the cancer cells at the early stages, like chemotherapy, surgery, and radiation. So the diagnosis of cancer is essential for timely individuating a viable cancer treatment. Existing tumor diagnosis depends on an assortment of complicated clinical settings, which include x-ray, magnetic resonance imaging (MRI), computerized tomography (CT), endoscopy, positron emission tomography (PET), cytology, sonography, thermography, and biopsy. In addition, both genomic- and proteomic-based molecular tools are progressively used, such as polymerase chain reaction (PCR), radioimmunoassay (RIA), enzyme linked immunosorbent assay (ELISA), immunohistochemistry (IHC), and flow cytometry (Altintas & Tothill, 2013; Mittal, Kaur, Gautam, & Mantha, 2017; Prabhakar, Shende, & Augustine, 2018). The current technologies and methods are proficient, but most of them are invasive, costly, time-consuming, and restricted to laboratory centers in big hospitals (Cui, Zhou, & Zhou, 2019). For instance, an invasive method biopsy is a medical process that needs the insertion of the medical tool into the patient's body to deduce specific tissues to be examined to find the presence of cancer cells. Such a procedure is tedious, and further, has numerous constraints. Patients experiencing biopsies complain of weak health, nausea, sleeping disorder with further postbiopsy impacts. Therefore, the requirement for noninvasive detection has come into significance in the present time. Also, rapid detection is needed to give patients instant results to start treatment without wasting any time. So the requirement of rapid noninvasive detection of cancer has driven the researchers to develop instruments that would identify cancer early without an invasive technique. This lead to the development of biosensors for noninvasive early detection of cancer (Devi & Laskar, 2018).

15.2 Biomarker for gastric cancer

Researchers and scientist from all around the world have turned their attention to the noninvasive diagnosis of cancer using cancer biomarkers due to numerous drawbacks of the invasive process of cancer detection (Devi & Laskar, 2018; Grossmann, Avenarius, Mastboom, & Klaase, 2010; Wu & Qu, 2015). Cancer biomarkers are essential indicators of cancer status (Karley, Gupta, & Tiwari, 2011). They are utilized not only to analyze and monitor disease but also to provide a prognostic approach to deal with treatment (Chatterjee & Zetter, 2005; Mayeux, 2004). The National Cancer Institute (NCI) (Park, Ross, Klagholz, & Bevans, 2018) defines a biomarker as "a biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process or a condition or disease." A biomarker may be used to see how well the body responds to a treatment for a disease or condition (Biomarkers Definitions Working Group, 2001). Biomarkers can be of several molecular origins, counting DNA (i.e., specific mutation, translocation, amplification, and loss of heterozygosity), RNA, or protein (i.e., hormone, antibody, oncogene, or tumor suppressor). The existence of biomarkers in blood or some other body fluid confirms the presence of cancer cells in the body (Tothill, 2009). There are different biomarkers for different types of cancers (Meyer & Rustin, 2000; Smith, Humphrey, & Catalona, 1997; Tothill, 2009). The maximum of these biomarkers still has to exhibit adequate sensitivity and specificity for translation into routine clinical use or treatment monitoring. This is an area that biosensor technology can improve upon (Bohunicky & Mousa, 2011).

There are several biomarkers available for the early diagnosis of gastric cancer (Fu, 2016). Fig. 15.1 displays the summary of gastric cancer biomarkers. Serum protein biomarkers of gastric cancer are gastric tissue specific or related to gastric-specific infections and divided into two types: gastric cancer-specific markers, and general tumor markers. Proteins such as pepsinogen I (PGI or PGA), pepsinogen II (PGII or PGC), and gastrin 17 are considered specific markers of gastric cancer

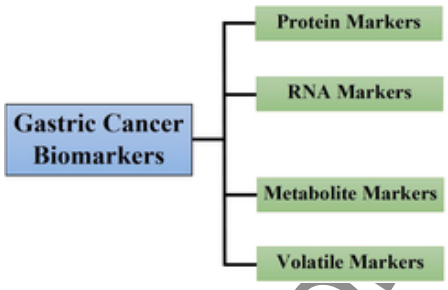

FIGURE 15.1 Summary of gastric cancer biomarker.

because of their gastric specific gene expression (Hallissey, Dunn, & Fielding, 1994; Shiotani et al., 2005). Antibodies linked to gastric specific infections such as *H. Pylori*, CagA, and antiparietal cell antibodies, which reflect current or past gastric infections associated with gastric cancer growth, are useful biomarkers for assessing gastric cancer risk (Kaise et al., 2013; Kikuchi, Crabtree, Forman, & Kurosawa, 1999; Sugiu et al., 2006). Many proteins are regarded as gastric cancer screening markers, although most of them are not gastric cancer specific. These proteins comprise carcinoembryonic antigen (CEA), pyruvate M2 kinase, cancer antigen 125 (CA125), cancer antigen 19-9 (CA19-9), Alpha-fetoprotein (AFP), serum amyloid A, macrophage migration inhibitory factor, leptin, dickkopf (Dkk), olfactomedin 4, VAP-1, UPA, cathepsin B, HMW kininogen, P53 antibody, cytokeratin 18, RegIV, IPO-38, S100A6, thrombin light chain, fibrinopeptide A, angiopoietin-like protein 2 (Capelle et al., 2009; Chan et al., 2007; Ebert et al., 2005, 2006; Gao, Xie, Ren, & Yang, 2012; Ghosh et al., 2013; Hao et al., 2008; Harbeck et al., 2008; Herszenyi et al., 2008; Ick et al., 2004; Kaplan et al., 2014; Kumar, Tapuria, Kirmani, & Davidson, 2007; Lee et al., 2012; Liu, Sheng, & Wang, 2012; Mitani et al., 2007; Suppiah & Greenman, 2013; Tas, Karabulut, Serilmez, Ciftci, & Duranyildiz, 2014; Umemura et al., 2011; Yu, Wang, & Chen, 2011; Zhang, Zhang, Jiang, & Zhang, 2014). Among them, carcinoembryonic antigen (CEA) and cancer antigen 19–9 (CA19–9) are most commonly used. CEA was firstly recognized by Gold and Freedman in 1965 (Gold & Freedman, 1965) and was first used for the diagnosis of early gastric cancer in 1980 (Tatsuta et al., 1980). CEA is currently regarded as the most valuable serum protein marker for identifying patients at risk of developing gastric cancer and for the diagnosis of early-stage gastric cancer (Jin, Jiang, & Wang, 2015). CEA was observed to improve colon carcinoma cells' metastasis with its sialofucosylated glycoforms which function as selecting ligands (Deng et al., 2015; Kikuchi et al., 1999). CEA is produced in a high amount of carcinomas in numerous different organs (Kikuchi et al., 1999; Kumar et al., 2007). CEA significantly affects the tumor prognosis because of its effect on tumor metastasis and may be connected with gastric cancer prognosis. Gastric cancer patients show expanded CEA levels, which are associated with patient survival based on an organized analysis of serum markers for gastric cancer (Sugiu et al., 2006). As per literature, preoperative CEA levels could predict gastric cancer (Ick et al., 2004; Schneider & Schulze, 2003), yet few reports deny this thought (Chan et al., 2007; Kumar et al., 2007; Moshkovskii, 2012). There is still discussion encompassing gastric cancer patients' prognosis with expanded CEA levels (Gao et al., 2012; Lee et al., 2012). Henceforth, it is important to build up a state-of-the-art, highly specific, and sensitive CEA detection technique for clinical examination and diagnostics (Tao, Du, Cheng, & Li, 2018). CA19–9 is a glycoprotein highly associated with malignant tumors and a commonly used marker in gastrointestinal cancer; however, it is present in some cancer types, particularly pancreatic, colorectal, and gastric cancer. The CA 199 test combined with the CEA test is a beneficial aide for observing carcinoma of the stomach; though, the sensitivity of performing these tests concurrently is similar to performing the CEA test alone in gastric carcinoma (Szymendera, 1986).

Warburg effect (i.e., cancer cells' dependence on glycolysis for energy and normal cell dependence on oxidative phosphorylation) is the most important difference between cancer cells and normal cells (Vander Heiden, Cantley, & Thompson, 2009; Liberti & Locasale, 2016). In gastric patient's serum or tissue samples, level of lactate which is a result of glucose glycolysis was found to increase constantly (Abbassi-Ghadi et al., 2013; Hirayama et al., 2009). Besides, cancer cells have a high protein synthesis rate. Hence, in gastric cancer patients, numerous metabolic studies showed an increase of amino acids; for example, glycine, asparagine, methionine, tyrosine, and aspartate. Moreover, cancer cells have a high nucleotide synthesis rate for the growing demands of DNA synthesis and DNA repair. Reports also suggested altered nucleotide metabolites in a certain type of cancers. Some of the researchers studied the fatty acid metabolism metabolites in gastric cancer patients. Though both increased fatty acid synthesis (FASN) and fatty acid oxidation (CPT1A) have been related to cancer growth. Fatty acid oxidation metabolites, such as β-hydroxybutyrate and acetone, have been recognized as possible biomarkers of gastric cancer (Fu, 2016).

Usually, RNA is inappropriate for cancer as biomarkers since it is an unsteady species of biomolecules. But current research proposed that certain serum non-coding RNA could also be possible gastric specific markers, for example, RNA HULC and H19 were favorable novel biomarkers in plasma of gastric cancer patients (Abbassi-Ghadi et al., 2013). MicroRNA (miRNA) is a comparatively stable type of RNA in the serum. In gastric cancer, 21 individual miRNAs and six miRNA clusters are consistently upregulated, while miR29c, miR30a5p, miR148a, miR375, and miR638 are usually downregulated (Tatsuta et al., 1980). The most frequently used tumor markers, such as CEA and CA19–9, have limited application in early diagnosis of gastric cancer since they have insufficient sensitivity and specificity. Thus, the foundation of novel robust definite biomarkers with adequate sensitivity is a perfect approach for improving the early detection and the cure rates for gastric cancer patients. Also, these biomarkers should be easy to estimate and consistently linked with clinical results. miRNAs are seen as a desirable cancer biomarker because of the acceptance of their part in tumorigenesis. Discovery of miRNAs and the approval of their role in tumorigenesis and the development of various cancers have presented them as suitable cancer biomarkers. There is also developing evidence that miRNAs exist in cells as well as in an assortment of body fluids, counting blood, saliva, and urine. Those miRNAs that can be found in the circulation system are called circulatory miRNAs. They are generally cancer-specific, and their expression patterns are incredibly comparable among healthy persons and patients. The circulatory miRNAs are remarkably resistant to RNase digestion, non-physiologic pH values, and high temperature. Henceforth, these miRNAs have been considered as a capable biomarker for early detection of cancer (Daneshpour, Omidfar, & Ghanbarian, 2016). But the selection of a high reference gene is an essential element in using miRNA as a tumor biomarker.

Volatile organic compounds (VOCs) released from cancer cell metabolism are considered significant markers for biochemical procedures are happening in cancer cells. The study of VOCs may be capable of predicting and diagnosing early cancer. Volatile metabolites associated with genomics and proteomics represent pathway feedback mechanisms, which positively point out the possible pathophysiological growth in cancer cells. To a certain point, volatile metabolites embody the status of cancer cells. Considering volatile biomarkers from gastric cancer cells and creating an ultrasensitive detection method will help early warning and diagnosis of gastric cancer (Capelle et al., 2009; Chan et al., 2007; Ebert et al., 2005, 2006; Gao et al., 2012; Ghosh et al., 2013; Hao et al., 2008; Harbeck et al., 2008; Herszenyi et al., 2008; Ick et al., 2004; Kaplan et al., 2014; Kumar et al., 2007; Lee et al., 2012; Liu et al., 2012; Mitani et al., 2007; Suppiah & Greenman, 2013; Tas et al., 2014; Umemura et al., 2011; Yu et al., 2011; Zhang et al., 2014).

15.3 Biosensor and gastric cancer

Evidence recommends that a growing amount of attention have been focused on developing rapid techniques named "biosensor technology" for the identification, detection, and checking of human health-related conditions (Islam & Uddin, 2017). A biosensor is an analytical device used to identify biological analytes, be it environmental or biological in the source (i.e., inside the human body). A usual biosensor contains a recognition element, a transducer, and a signal-processing unit (Qian et al., 2019). The signal in the form of an analyte is detected by a molecular recognition component converted into an electrical signal by a transducer (Bohunicky & Mousa, 2011). Cammann used the word "biosensor" first (Cammann, 1977), and the International Union of Pure and Applied Chemistry (IUPAC) introduced its definition (Thévenot, Toth, Durst, & Wilson, 2001) and Clark and Lyonsin started biosensor application journey in 1960s (Clark & Lyons, 1962). Biosensors' applications for cancer diagnosis are very promising for conventional methods since it provides better performance in terms of speed, flexibility, automation, and costs (Balaji & Zhang, 2017; Bohunicky & Mousa, 2011; Jainish & Prittesh, 2017; Li, Li, & Yang, 2012; Mittal et al., 2017; Pasinszki, Krebsz, Tung, & Losic, 2017). The recognition of cancer biomarkers present in the blood is the most challenging task because of the low biomarkers' concentration in early-stage patients. A biosensor can measure shallow levels of biomarkers in physiological samples, which can help diagnose cancer at an early stage (Choi, Kwak, & Park, 2010).

Fig. 15.2 demonstrates the working procedure of biosensors for the detection of cancer. The process comprises three key steps: discovery of biomarker, biomarker detection with biosensors, and analysis of data. Every stage plays a vital role and decides the outcomes of the biosensor device (Qian et al., 2019).

15.3.1 Role of electrochemical biosensors in early detection of gastric cancer

Among all biosensors, electrochemical sensors have been of great interest, mainly because they are simple, portable, sensitive, inexpensive, and offer a fast response (Topkaya, Azimzadeh, & Ozsoz, 2016). Electrochemical biosensors use electrochemical transducers that transfer a biological entity (i.e., protein, RNA, and DNA) into an electrical signal that can be analyzed and detected (Qian et al., 2019; Wang, 2006). Amperometric and potentiometric transducers are most commonly

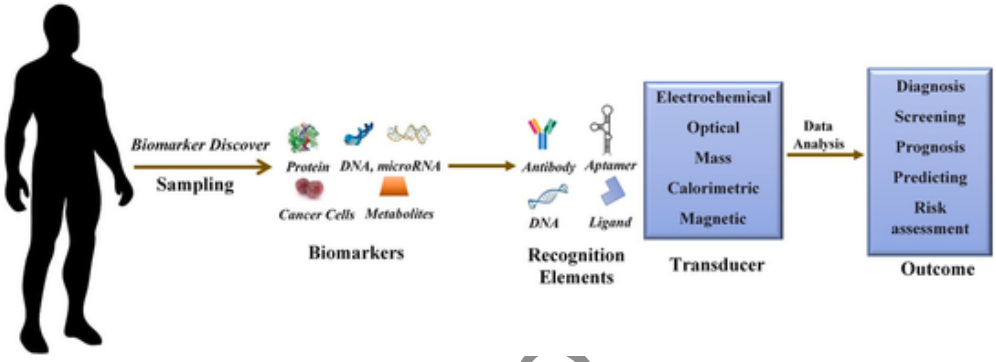

FIGURE 15.2 Working procedure of biosensors for cancer diagnosis.

used in conjunction with electrochemical biosensors. In potentiometric devices, the analytical information is obtained by converting the biorecognition process into a potential signal in connection to the use of ion selective electrodes (ISE). Amperometric biosensors operate by applying a constant potential and monitoring the current associated with the reduction or oxidation of an electroactive species involved in the recognition process. An amperometric biosensor may be more attractive because of its high sensitivity and wide linear range (Wang, 2006). Electrochemical impedance spectroscopy (EIS), differential pulse voltammetry, square wave voltammetry, capacitance measurement, and dielectrophoresis spectroscopy have also been used to measure biosensor response to biomarkers.

Daneshpour et al. (2016) fabricated a novel electrochemical nano biosensor using a double-specific probe approach and a gold-magnetic nanocomposite as tracing tag to detect miR-106a gastric biomarker. EIS and cyclic voltammetry (CV) approaches were used to confirm the electrode's successful modification and hybridization with the target miRNA. For quantifiable estimation of miR-106a, recording the reduction peak current of gold nanoparticles DPV approach was used. The proposed biosensor showed notable selectivity, high specificity, linearity ranging from 1×10^{-3} p.m. to 1×10^{3} p.m., agreeable storage stability, and great performance in real sample investigations and offered a promising application to be used for medical early detection of gastric cancer. B. Li et al. (Balaji & Zhang, 2017; Bohunicky & Mousa, 2011; Jainish & Prittesh, 2017; J. Li et al., 2012; Mittal et al., 2017; Pasinszki et al., 2017) carried out a two-stage cyclic enzymatic amplification method (CEAM) to determinate miRNA-21in in the blood serum of gastric cancer patients. The electrochemical biosensor exhibits a low detection limit of 0.36fM with notable specificity. Most importantly, it can be employed to study the expression level of miRNA in the gastric cancer patient blood serum. Tao et al. (2018) developed a selective and sensitive sandwich-type electrochemical aptasensor based on Pt/Au/DN-graphene-CEAapt2-Tb bioconjugate to detect gastric cancer. The proposed method was demonstrated to be sensitive, as indicated by the improved electrochemical response, since the dendritic Pt/Au/DN-graphene showed peroxidase-mimic activity for the reduction of H_2O_2 introduced into the electrolytic cell, thereby confirming its desirable catalysis capacity. Since dendritic Pt/Au/ND-graphene is very conductive and possesses peroxidase-mimic activity, the electrochemical response signal and the charge transfer were promoted through catalysis of H_2O_2 reduction introduced into the electrolyte cell. Hence, aptasensor was found to enhance analytical capacity and attained desirable sensitivity. Amouzadeh Tabrizi et al. (Amouzadeh Tabrizi, Shamsipur, Saber, Sarkar, & Sherkatkhameneh, 2017) also fabricated a sandwich type electrochemical aptasensor for the sensitive detection of adenocarcinoma gastric cell AGS cancer cells in the presence of H_2O_2 by using MWCNT-Aunano as a nanoplatforms and the secondary aptamer-Au@Ag nanoparticles as the labeled aptamers. The aptasensor was also used in the detection of AGS cancer cells in a human serum sample. The developed aptasensor showed a wide linear range and good stability and selectivity. Ilie and Stefan-van Staden (2019) developed a graphite paste modified with 2, 6-bis((E)-2-(furan-2-yl) vinyl)-4-(4,6,8-trimethylazulen-1-yl) pyridine based electrochemical sensor for the detection L-tryptophan gastric cancer biomarker, which is an amino acid in real whole blood samples. The proposed gastric cancer sensor exhibits a high sensitivity with a low limit of detection. Zhang, et al. (Y. Zhang et al., 2014) developed an ultrasensitive electrochemical biosensing interface based on Au-Ag Alloy coated MWCNTs to detect volatile biomarkers of gastric cancer cells. Results displayed that eight various volatile biomarkers were screened out between MGC-803 and GES-1 gastric cancer cells. Fig. 15.3 shows cyclic voltammogram of MWNTs/AU-Ag/GCE was exposed to the head space of MGC-803 gastric cancer cells, GES-1gastric mucosa cells, and cell-free medium. The particular volatile biomarkers of MGC-803 gastric cancer cells and the well-adapted electrochemical system have substantial potential in the near future for applications, for example, screening and warning of early gastric cancer. Rahman et al. fabricated an Ag-Cu bimetallic alloy nanoscale based electrochemical sensor (Rahman et al.,

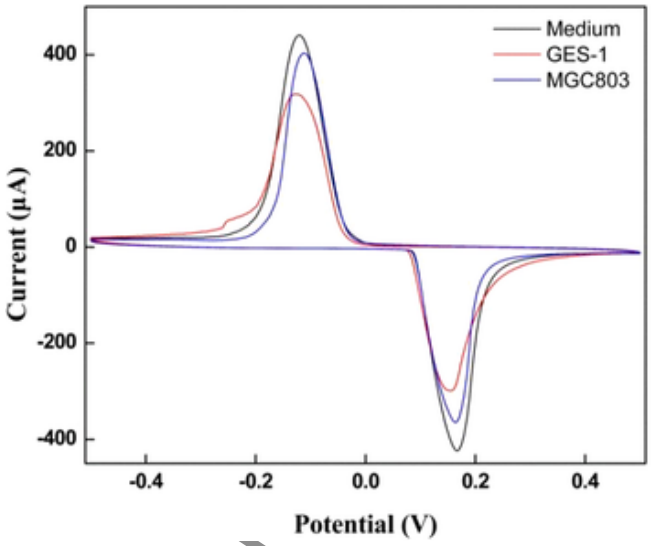

FIGURE 15.3 CVs of MWNTs/AU-Ag/GCE exposed to the head space of MGC-803 gastric cancer cells, GES-1gastric mucosa cells, and cell-free medium.

2015) for the monitoring of 2-butanone. The sensor showed the best sensing properties for the detection of 2-butanone with 0.1 μM detection limit. It was expected that the designed sensor could effectively be applied to detect the early stages of gastric and lung cancer caused by 2-butanone. Wu and Qu developed a novel and sensitive nonenzymatic sandwich type electrochemical immunosensor (Devi & Laskar, 2018; Grossmann et al., 2010; L. Wu & Qu, 2015) for the detection of gastric cancer biomarker CA72–4 using dumbbell-like PtPd-Fe_3O_4 nanoparticles (NPs). The immunosensor was fabricated by modifying the glassy carbon electrode by rGO-TEPA for effective immobilization of primary anti-CA72–4 antibody, and the secondary anti-CA72–4 antibody was adsorbed onto the PtPd-Fe_3O_4 NPs. The proposed immunosensor showed wide linearity ranging from 0.001–10 U/mL with a low detection limit of 0.0003 U/mL and possessed outstanding clinical value in cancer screening along with suitable point-of-care diagnostics. To meet the clinical demands for early detection of gastric cancer, Yao et al. (Yao et al., 2015) developed a disposable easy-to-use electrochemical microfluidic chip combined with multiple antibodies against six kinds of biomarkers. The electrochemical microfluidic chip showed linearity ranging from 0.37–90 ng mL^{-1}, 10.75–172 U mL^{-1}, 10–160 U L^{-1}, 35–560 ng mL^{-1}, 37.5–600 ng mL^{-1}, and 2.5–80 ng mL^{-1} for CEA, CA19–9, HP, P53, PG I, and PG II biomarkers, respectively (Fig. 15.4). This method showed improved sensitivity compared with ELISA results of 394 specimens of gastric cancer sera. The electrochemical microfluid chip is a promising candidate for early screening of gastric cancer, therapeutic evaluation, and real-time dynamic review of gastric cancer advancement in the near future. Mohammad Shafiee and Parhizkar (2020) successfully fabricated Au nanoparticles/g-C_3N_4 modified electrochemical gastric cancer biosensor for the detection of miRNA. The sensor used a hairpin locked nucleic acids probe and Zn^{2+} functionalized TiP nanospheres labels. The sensor showed linearity ranging from 0.6 nM to 6 nM with a limit of detection to 80 pM. For the detection of miR-100 in the sera gastric cancer patients, Zhuang, Wan, and Zhang (2021) developed a rapid, selective, and sensitive biosensor based on Au electrode (AuE) modified with gold nanoparticle (AuNP) which was attached with DNA capture probes (CPs) (CPs/AuNP-AuE). The range of detection and detection limit of the biosensor for miR-100 was 100 a.m. to 10 p.m. 100 a.m. respectively.

15.3.2 Role of SPR biosensor in early detection of gastric cancer

In recent decades, various optical biosensor approaches have been established, counting surface plasmon resonance (SPR) (Nelson, Grimsrud, Liles, Goodman, & Corn, 2001), ellipsometry (Arwin, Poksinski, & Johansen, 2004), and quartz crystal microbalance (QCM) (Frank, Elke, Neil, Kenichi, & Yoshio, 1997). Amongst them, the SPR-based method is a representative type of label-free procedure for checking biomolecular interactions in a real-time (Nguyen, Park, Kang, & Kim, 2015). SPR is an optical phenomenon take place in the overall internal reflection of light at a metal film-liquid interface (Van Oss & van Regenmortel, 1994; Raether, 1988). At the point when the incident light is completely reflected, a part of the incident light momentum named as evanescent wave penetrates the liquid medium near the metal (generally Au)

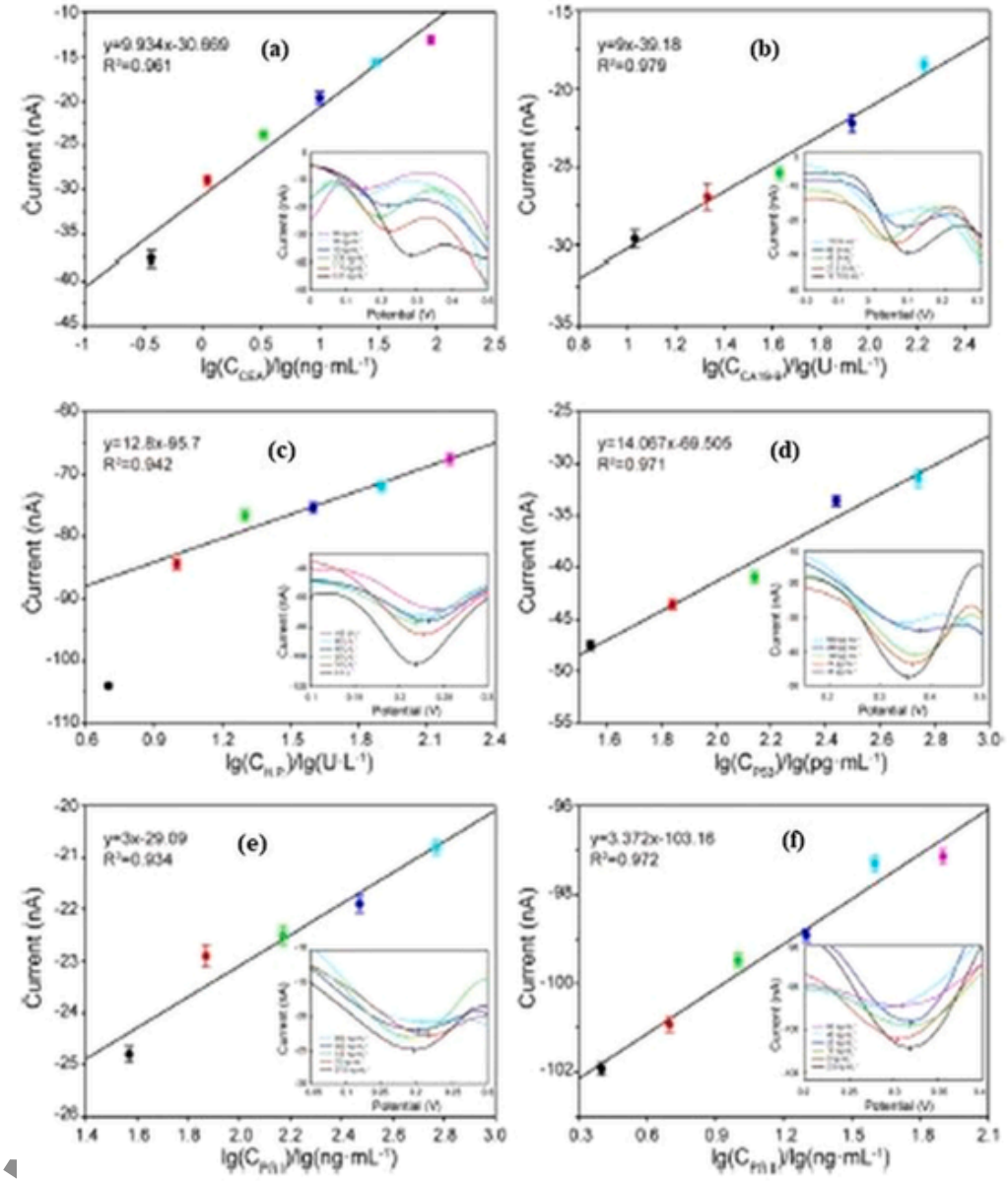

FIGURE 15.4 Linear detection ranges of six kinds of biomarkers (A) CEA, (B) CA19–9, (C) HP, (D) P53, (E) PG I, and (F) PG II by differential pulse voltammetry.

surface. In the thin metal film surface, the evanescent wave interacts with longitudinally oscillating free electrons termed surface plasmon. During SPR, metal film absorbed the energy of incident light, decreasing the light intensity. While the angle of incidence is fixed, the resonance phenomenon happens only at an accurately defined wavelength, which depends upon the medium's refractive index (RI) near the metal surface. RI changes in a direct extent to the mass and dielectric permittivity of the present medium. Immobilization of antibodies on the metal surface causes the corresponding antigen to bond on the surface when it touches the liquid samples. The binding method can be observed via observing the SPR wavelength which depends on the quantity of antibody-antigen binding. The SPR biosensor is sensitive to refractive index adjustments or thickness of biomaterials at the interface between a metal thin film and a surrounding medium. Therefore, using antibodies peculiar to pathogens of interest can measure the number of pathogenic bacteria existents in a sample by quantifying the

change in refractive index and characterize interactions of biomolecules on the surface in real time without labeling (Brockman, Nelson, & Corn, 2000; Fang et al., 2010; Green et al., 2000)

For the early diagnosis of gastric cancer, Fang et al. (2010) fabricated a SPR sensor based on the detection of MG7-Ag, a gastric cancer-specific tumor-associated antigen in human sera. The measurements contained two cases of healthy blood donors, nine cases of gastric cancer patients, and an MKN45 cancer cell lysate sample solution for positive control. Results showed the binding of MG7-Ag onto the sensor surface was observed from SPR spectra. The prepared SPR biosensor showed potential for the early diagnosis of gastric cancer, but the limit of detection and measure for cancer risk assessment in early diagnosis was not confirmed. F. Liu (Capelle et al., 2009; Chan et al., 2007; Ebert et al., 2005, 2006; Gao et al., 2012; Ghosh et al., 2013; Hao et al., 2008; Harbeck et al., 2008; Herszenyi et al., 2008; Ick et al., 2004; Kaplan et al., 2014; Kumar et al., 2007; Lee et al., 2012; Liu et al., 2012; Mitani et al., 2007; Suppiah & Greenman, 2013; Tas et al., 2014; Umemura et al., 2011; Yu et al., 2011; Zhang et al., 2014) used surface plasmon resonance phase sensing to detect EGFR on active human gastric cancer BGC823 cells. The results showed that the SPR phase sensing is proficient of real-time recognition of molecular interactions and cellular responses on living cells. It also proposed that more studies on the mechanism and method might let SPR sensing become a useful tool for the essential research of cell biology, yet also for medical diagnosis and drug development.

15.3.3 Role of surface-enhanced Raman spectroscopy sensor in early detection of gastric cancer

Amongst optical nano biosensors, those established on surface-enhanced Raman scattering (SERS) spectroscopy have been drawing significant attention. It is because of the combination of the intrinsic prerogatives of the technique, such as structural specificity and sensitivity, and the high degree of modification in nano-manufacturing, which translates into consistent and robust real-life applications. In SERS, the excitation of localized surface plasmon resonances (LSPR) at the surface of nanostructured metals with light induces the massive intensification of the Raman scattering from molecules located close to the metallic surface. This effect yields an ultrasensitive plasmon-enhanced spectroscopic technique that retains Raman spectroscopy's intrinsic structural specificity and experimental flexibility. As impressive advances in instrumentation and nanofabrication techniques enabling the engineering of finely tuned plasmonic nanomaterials continue, SERS is progressively expanding into the realm of viable biomedical applications (Guerrini & Alvarez-Puebla, 2019).

There are 14 VOC biomarkers in human breath used for differentiating gastric cancer patients from healthy persons. Chen et al. (2016) fabricated a SERS sensor based on breath analysis to identify VOC biomarkers to distinguish EGC and AGC cancer patients from healthy persons. They prepared a clean SERS sensor using hydrazine vapor adsorbed in graphene oxide (GO) film by in situ formations of gold nanoparticles (AuNPs) on reduced GO (RGO) deprived of any organic stabilizer. The SERS sensor effectively analyzed and distinguished various simulated breath samples and 200 breath samples of medical patients with over 83% and 92% sensitivity and specificity, respectively. Yunsheng Chen et al. (2018) fabricated non-invasive, cheap, fast SERS sensors based on salivary analysis to screen early and advance gastric cancer patients. The developed graphene oxide nanoscrolls wrapped with gold nanoparticle (A/GO NSs)-based SERS sensors detect the biomarkers in 220 clinical liquid saliva. These sensors successfully analyzed and distinguished various stimulated and medical patients' samples with sensitivity and specificity greater than 80% and 87.7%, respectively. For the detection of miR-34a biomarker, Lee et al. (Capelle et al., 2009; Chan et al., 2007; Ebert et al., 2005, 2006; Gao et al., 2012; Ghosh et al., 2013; Hao et al., 2008; Harbeck et al., 2008; Herszenyi et al., 2008; Ick et al., 2004; Kaplan et al., 2014; Kumar et al., 2007; Lee et al., 2012; Liu et al., 2012; Mitani et al., 2007; Suppiah & Greenman, 2013; Tas et al., 2014; Umemura et al., 2011; Yu et al., 2011; Zhang et al., 2014) fabricated a uniform, highly robust, and ultra-sensitive surface-enhanced Raman scattering substrate by using silver nanostructures grown in gold nanobowls (SGBs). They were accomplished by consistent and direct detection of miR-34a in human gastric cancer cells by applying the advantages of SGBs in SERS sensing. An essential chemokine named interleukin 8 (IL-8) plays a vital part in tumor growth and angiogenesis and has been found in various human tumors, counting gastric and breast cancer. Zhen-yu Wang et al. (Qian et al., 2019; Wang, 2006) fabricated a double antibody sandwich format-based SERS immunosensor for the determination of IL-8. The immunosensor showed high sensitivity, selectivity, and low detection limits for the detection of IL-8 in PBS and human serum, hence, providing a great possibility for application in clinical diagnosis.

15.3.4 Role of GMI-based biosensing system in early detection of gastric cancer

In recent times, the giant magnetoimpedance (GMI) effect has attracted considerable attention due to its possible application in magnetic field sensing (Wang et al., 2017). The GMI effect is the change of complex impedance of soft magnetic mate-

rials conveying alternating current upon the use of the external magnetic field in Beach and Berkowitz (1994), Knobel and Pirota (2002), Phan and Peng (2008), and Panina and Mohri (1994)

Kurlyandskaya et al. (2003) introduced a GMI sensor into the field of biosensors. A GMI-based biosensing system linking with the magnetic labeled technology was used to distinguish gastric cancer cells (Chen et al., 2016). For the recognition of functional nanoparticles-probed gastric cancer cells, Lei Chen et al. (2011) planned, fabricated, and tested a GMI-based biosensing system with a Co-based ribbon sensing element. Functionalized nanoparticles were structured by coating Fe_3O_4 with chitosan and conjugating with cyclic RGD peptides. This fabricated system can recognize the dissimilarities among targeted and nontargeted cells.

15.3.5 Other types of biosensor in early detection of gastric cancer

Different types of biosensors can also detect gastric cancer related biomarkers. Stefan-van Staden et al. (Stefan-Van Staden, Ilie-Mihai, Pogacean, & Pruneanu, 2019) developed an exfoliated graphene (E-NGr) based high sensitive stochastic sensor used for pattern recognition of CEA, CA19-9, and p53 in whole blood and urine samples of patients found in very early and later gastric cancer stages.

15.4 Conclusion and future perspectives

Due to the numerous limitations in conventional detection methods of cancer, scientists and researchers are showing their attention to biosensors' development for effective rapid noninvasive detection of cancer markers. In the body, presence of cancer cells is confirmed by cancer markers. These markers exist in saliva, blood, or some other body fluids. As a complex heterogeneous disease, gastric cancer is one of the most widely recognized malignancies around the world. Gastric malignant growth is the fifth most regular kind of disease and the subsequent driving reason for the third leading malignant growth-related mortality (accounted for 8.2%) overall (Sitarz et al., 2018; Zhou et al., 2018). Early gastric cancer can be cured with surgery. In contrast, advanced gastric cancer often needs combined multidisciplinary therapy, and delayed diagnosis and inadequacies of the staging system may increase mortality. Therefore, it is very demanding to develop a rapid and noninvasive diagnosis technique to realize early detection of gastric cancer and simultaneous staging. Consequently, it is challenging to create a rapid and noninvasive diagnosis technique to realize early detection of gastric cancer and simultaneous staging. Early detection of gastric cancer prominently increases the probabilities for effective treatment and survival rates of cancers. Several types of biosensors have been proposed to detect gastric biomarkers and have shown an excellent opportunity for the early diagnosis of gastric cancer.

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