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The Functionality of Nano Biosensors in Detecting Lung Cancer: A Review

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Abstract:
Nowadays, lung cancer is one of the most common diseases worldwide and has the highest mortality rate among all types of cancers. Therefore, early diagnosis of this disease is of special importance. Due to the high cost and time requirements of traditional lung cancer detection methods, there has been a recent emphasis on developing more affordable and efficient alternatives. In recent years, significant progress in nanotechnology and the development of various nanomaterials has led to increased activity in the field. Recent studies suggest that graphene oxide nanomaterials have high potential for designing bio-nano sensors to detect lung cancer due to their unique properties. This research presents a biosensor based on a graphene oxide-DNA nanohybrid for identifying deletion mutations that cause lung cancer. The mutations are identified using a FAM-labeled DNA probe and fluorescence spectroscopy. Additionally, graphene oxide was synthesized based on Hamer's method and verified using FT-IR, UV-Vis, and TEM imaging."

Keywords:
Graphene oxide, bio-Nano sensor, lung cancer, DNA, deletion mutation.

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Introduction

Cancer is a genetic disease caused by the uncontrolled growth and division of cells in a part of the body, resulting from a combination of environmental factors and genetic disorders. Specifically, cancer arises from a series of successive mutations in human genes. There are over 200 types of cancer, and lung cancer is one of the most common. It is the second most frequent cancer among both men and women and is highly preventable. There are two main types of lung cancer: small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). These types differ in their growth and spread in the body, as well as their treatment approaches. NSCLC can be further divided into three categories based on their cell types (1-3): Superficial tissue cancer, Cancer of glands secreting mucus and lymphatic vessels (glandular epithelium) and Lung cancer with large cells.

Of all people diagnosed with lung cancer, approximately 85-90% have NSCLC, while about 10-15% have SCLC. The most common clinical symptoms of lung cancer include persistent and chronic cough, chest pain, anorexia, weight loss, bloody sputum, shortness of breath, respiratory infections such as bronchitis, and the onset of wheezing, which usually does not appear in the early stages of the disease. Therefore, the death rate from this type of cancer is very high (4-6).

Risk factors of Lung Cancer

The most significant risk factor for lung cancer is smoking, particularly cigarette smoking. Nearly 90% of patients with lung cancer have a history of smoking, and smokers are 20-40 times more likely to develop lung cancer than non-smokers. Approximately 79% of women and 90% of men diagnosed with lung cancer have a history of smoking. In fact, 90% of lung cancer deaths are caused by smoking(7). Radon gas is the second leading cause of lung cancer. This radioactive gas is odorless, tasteless, and colorless and is formed naturally from the breakdown of uranium in soils and rocks(8). Other things that increase the risk of this type of cancer and exist in the workplace include. polycyclic aromatic hydrocarbons, arsenic, asbestos, cadmium, beryllium and compound materials containing nickel and chromium as well as chloromethyl ethers. In addition to the above-mentioned factors, other reasons such as air pollution, family history of lung cancer, lung radiation therapy, poor diet, advanced age, and hereditary or acquired genetic changes can also contribute to the development of lung cancer(9).

Genetic Changes as a Causative Factor of Lung Cancer

Lung cancer is often the result of a series of genetic changes, including the activation of proto-oncogenes, which transform into oncogenes, and the inactivation of tumor suppressor genes (TSGs), where the latter plays a crucial role in slowing down cell division and determining the time of cell death, and their lack leads to uncontrollable cell division(10). Proto-oncogenes are genes that normally regulate cell division and growth, but when they undergo genetic mutations, they become oncogenes with significantly increased gene expression.

Oncogenes that lead to lung

cancer include c-myc, mutated KRAS, overexpressed EGFR gene, cyclin D1, and BCL2. Tumor suppressor genes (TSGs) involved in most cases of lung cancer include p53, p16, hTR, and hTERT genes that are expressed in almost all types of lung cancer as an immortal mechanism (10, 11).

Lung Cancer Detection Methods

According to global statistics, more than one million people die from this type of cancer every year, which accounts for about 27% of all cancer deaths. More than 80% of lung cancer patients die in less than five years from the time of diagnosis, mostly due to being diagnosed during advanced stages of the disease where treatment options are limited. Therefore, early detection of lung cancer is of utmost importance(1, 6). Until now, in the field of medicine, various methods have been used to identify lung cancer, among which we can refer to chest X-ray, CT scan, MRI, bone scan, bronchoscopy, and sputum test(12, 13). In the case of lung cancer, several biomarkers have been identified, such as carcinoembryonic antigen (CEA), cytokeratin fragment antigen 21-1 (CYFRA 21-1), neuron-specific enolase (NSE), and pro-gastrin-releasing peptide.

(ProGRP)(14). However, these biomarkers are not specific to lung cancer and can also be found in other diseases, which may lead to false positive results. Therefore, there is a need for more specific and accurate biomarkers for the early detection of lung cancer. Recent studies have focused on the use of nanomaterial-based biosensors for the detection of lung cancer biomarkers with high sensitivity and specificity. These biosensors use nanomaterials as transducers that can convert the

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biomolecular interactions into measurable signals, such as electrical, optical, or mechanical signals (15). The biosensors can detect the biomarkers in various samples, such as blood, urine, and breath, which makes them non-invasive and easy to use. Moreover, the biosensors can detect the biomarkers at low concentrations, which is crucial for the early detection of lung cancer(16, 17).

Nano Biosensor for Cancer Detection

Nano biosensors or micro biosensors are one of the recent advances in biotechnology. Totally Nano sensors are very accurate, sensitive, and specific measurement systems. The term of Nano biosensor actually means that biological materials such as an antibody, nucleic acid, pathogens,
and their metabolites can be detected by nanotechnology (18). Nanoparticles have been shown to be effective in addressing the tendency and low capacity of connection in biosensors. This is due to their unique manufacturing ability, where their small size does not affect their biological properties and their ability to connect to the target. In fact, their small size has actually increased their tendency to connect(19).

The use of Nano biosensors is important for disease diagnosis, as they can detect several pathogenic and dangerous factors in a system and even differentiate between them. They have the ability to detect very low concentrations of biomarkers, making them highly sensitive tools for disease detection (20). In this review, we investigated the principles and structure of these micro sensors in the detection of biological factors in the lung cancer. This can help researchers and healthcare professionals to better understand the potential of nanotechnology in disease diagnosis and to develop more effective diagnostic tools for lung cancer and other diseases. Nanobiosensors are analytical tools that utilize biological materials to identify compounds and create a chemical, optical, or electrical signal. The biosensor works by converting the biological reaction into a signal that can be measured. A nanobiosensor is typically composed of three parts: a bioreceptor or receiver, a transducer, and a detector. The bioreceptor component of a nanobiosensor is responsible for recognizing the target compound or analyte. This may include enzymes, antibodies, cell receptors, nucleic acids, or microorganisms. When the bioreceptor interacts with the analyte, it creates physical or chemical changes that are then detected by the transducer component of the sensor(18, 21).

The transducer component of a nanobiosensor converts the physical or chemical changes into a measurable signal. This may include electrochemical, optical, or thermal transducers. The detector component of the sensor then measures the signal and provides information about the presence or concentration of the analyte(15). These tools play a role in a wide range of analytical applications, such as medical diagnosis, veterinary medicine, laboratory science, environmental control and industrial process control. Overall, nanobiosensors offer high sensitivity and
selectivity for the detection of target compounds, making them a promising tool for disease diagnosis and monitoring especially in cancers(22).

The use of nanobiosensors in the field of medicine can have numerous applications beyond just the detection of diseases. For instance, nanobiosensors can be used to study the mechanisms of diseases and disorders, identify potential drug targets, and evaluate the efficacy and safety of new drugs. In addition, nanobiosensors can be used in drug delivery systems to improve the targeted delivery of drugs to specific cells or tissues, and to monitor the release of drugs in real- time. Finally, the use of nanobiosensors in medicine has great potential to advance our understanding and treatment of various diseases and disorders(23). Nowadays, nanostructures are being utilized in biosensors for various reasons, resulting in valuable progress in this field.

The purpose of using nanomaterials in the structure of biosensors is to increase the surface area required to stabilize biological materials, which in turn increases sensitivity and catalyzes the process. Biosensors can be classified based on the type of transducer or bioreceptor used. (Figure 1).

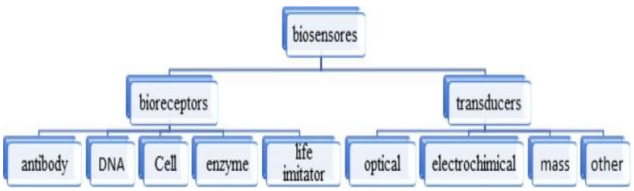

Figure 1: types of transducers and bioreceptors

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Transducer Classification Based on the Type of Bioreceptors

The specificity of a biosensor is determined by the nature of the bioreceptor and its ability to selectively interact with the analyte of interest. The bioreceptor must be carefully chosen to ensure that it only interacts with the target analyte and not with other molecules that may be present in the sample matrix. This is particularly important in complex biological samples where there may be many different molecules present that could potentially interfere with the sensor's performance(16). Antibody-based biosensors are among the most commonly used bioreceptors due to the high specificity and affinity of antibodies for their target antigens. However, nucleic acid-based biosensors, enzyme-based biosensors, and cell-based biosensors are also widely used and offer unique advantages for specific applications. Biomimetic or synthetic bioreceptors are also gaining popularity due to their ability to be tailored to specific analytes and their potential for high sensitivity and stability(24). Overall, the choice of bioreceptor depends on the specific application and the characteristics of the analyte being measured, as well as the desired sensitivity and specificity of the biosensor.

Classification of Biosensors Based on Transduction System

The transducer is a critical component of a biosensor, as it converts the signal generated by the bioreceptor-analyte interaction into a measurable physical phenomenon that can be detected and quantified. The transducer can be based on various types of physical measurements, and biosensors can be classified based on the type of transduction system used(25). Optical biosensors are commonly used and are based on the measurement of changes in light properties such as luminescence, absorption, and surface plasmon resonance. Electrochemical biosensors are also widely used and are based on the measurement of changes in electrical properties such as impedance, current, and potential. Mass-sensitive biosensors, such as quartz crystal microbalance (QCM) biosensors, are based on the measurement of changes in the mass of the bioreceptor-analyte complex, which can be detected as changes in resonance frequency or bending(26). There are also hybrid biosensors that use a combination of different transduction systems to improve the sensitivity and selectivity of the sensor. For example, an optical-electrochemical biosensor may use surface plasmon resonance to detect the bioreceptor-analyte interaction and an electrochemical transducer to amplify the signal (27, 28). Collectively, the choice of transduction system depends on the specific application and the characteristics of the analyte being measured, as well as the desired sensitivity and selectivity of the biosensor.

Application of Biosensors

Biosensors have been successfully employed in the identification of various viruses, including Newcastle disease(29), Dengue fever, foot-and-mouth disease, and hepatitis B (30). For example, a piezoelectric biosensor with an antibody coating on a quartz crystal covered with gold has been used to detect foot-and-mouth disease virus. When antigens bind to the antibodies on the crystal, the frequency of the biosensor changes, allowing for the identification of the virus. next- generation biosensing technologies that offer better sensitivity and selectivity, and easy handling for end- users are highlighted. An emerging example of these next-generation biosensors are those powered by novel synthetic biology tools, such as clustered regularly interspaced short palindromic repeats (CRISPR) with CRISPR-associated proteins (Cas), in combination with integrated point-of-care devices (31, 32). However, these biosensors are not solely limited to viral identification and have a wide range of potential applications in various fields.

The identification of hepatitis B virus relies on the hybridization of the virus DNA with labeled nucleotide acid that comes into contact with gold electrodes. In 2004, Dinhs-Vo and colleagues (33) used biosensors for diagnosing and treating cancer cells. The detection of chemical and biological species is crucial in the fields of biological sciences, veterinary medicine, and medicine. Therefore, the development of a tool that can provide direct, sensitive, and rapid analysis of these species can be a significant advancement for diagnostic methods(34). Moreover, nanobiosensors have been developed to detect herpes simplex virus, influenza type A virus, and adenoviruses (35, 36).

Some functional nano-biosensors:

Silica nanowires

Silica nanowires are one-dimensional nanostructures that are smaller than one hundred nanometers in two

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dimensions and larger in one dimension(37). In order to detect lung cancer using silica nanowires, the first step is to produce free NH2 groups. Silica nanowires are then functionalized with APTMS, and specific antibodies against cancer antigens or receptors are immobilized on the surface of the silica nanowires, as shown in Figure 2.

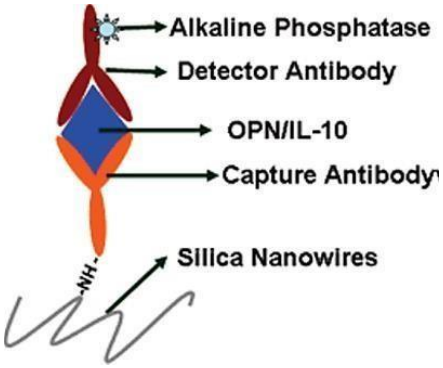

Figure 2. Silica nanowires for establishing an antigen-antibody structure to detect biological molecules like cancer antigens, cytokines.

- **Gold nanoparticles**

Detection of lung cancer using gold nanoparticles has been done in several stages. In the first stage, the exhaled air of cancer patients was collected, and in the second stage, volatile organic compounds (VOCs) in the exhaled air of cancer patients, which were considered lung cancer biomarkers, were identified using special methods. In the next steps, sensors based on gold nanoparticles have been designed, and in these sensors, gold nanoparticles with a thickness of five nanometers have been functionalized by various organic groups such as decanethiol,1-butanethiol, 2-ethyl hexane thiol, hexanediol,2-ercaptobenzoxazole, and then functionalized gold nanoparticles are placed on the surface of ID electrodes. In the final stages, the designed sensors are installed in a circuit and inside a chamber where the exhaled air is directed into this chamber. When the sensors are exposed to exhaled air, they cause a reversible change in the resistance of the circuit(38, 39).

- **Carbon nanotubes**

Carbon nanotubes, first discovered in 1991 by Eijima(40), are composed of sheets of graphene formed into an integrated tubular structure. These nanotubes are structurally classified into two categories:
Single-walled carbon nanotubes (SWCNTs) and Multi-walled carbon nanotubes (MWCNTs)(41). SWCNTs consist of a tubular graphene sheet, while multi-walled nanotubes are composed of several concentric tubular graphene sheets. To detect lung cancer, a biosensor based on single-walled carbon nanotubes has been designed. First, the nanotubes are functionalized with a non-polymeric organic substance, such as Pentadecane (C15H32) or Trixane (C23H48), to increase the biosensor's selectivity. Then, the functionalized nanotubes are placed on the surface of ID electrodes and assembled into a biosensor device. Volatile organic compounds (VOCs) present in the exhaled air of lung cancer patients are considered biomarkers, and since carbon nanotubes have a high surface absorption capacity, they can detect VOCs present in the exhaled air of cancer patients and cause a change in resistance in the system(42, 43).

- **Quantum dots**

Quantum dots are small semiconductor crystals that emit light when stimulated. They are typically very small, with a diameter of 2-10 nm and are composed of 100 to 100,000 atoms. In this context, they are being used to detect lung cancer by designing an ECL (electrochemiluminescence) sensor to detect a specific biomarker for lung cancer, called embryonic carcinogen antigen (CEA). To create the sensor, the researchers synthesized Fe3O4/CdSe-CdS/APS nanocomposites. First, a layer of polyallylamine hydrochloride (PAH) was added to the surface of the Fe3O4 magnetic nanoparticles. Then, CdSe-CdS quantum dots were added on top of the PAH layer. Finally, 3-aminopropyltriethoxysilane (APS) was added to form a layer on the surface of the Fe3O4/CdSe-CdS nanoparticles. APS is an important agent in this process because it binds to biomolecules and helps to stabilize the nanocomposites on the electrode surface. The resulting nanocomposites are then used in the ECL sensor to detect CEA as a biomarker for lung cancer (44-46).

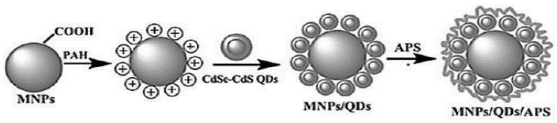

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Figure 3. Structure of the Fe_3O_4/CdSe–CdS/APS nanocomposites

In the next step, a magnetic electrode is designed by placing a magnet inside a gold electrode. Fe3O4/CdSe- CdS/APS nanocomposites are then fixed on the surface of this electrode using magnetic attraction, and gold nanoparticles are accumulated on the electrode. The electrode is then used to detect CEA, a biomarker for lung cancer, by binding CEA antibodies to the gold nanoparticles on the electrode surface. The electrode is then placed in a phosphate buffer containing K2S2O8, and bovine serum albumin (BSA) is used to block any non-specific binding sites on the sensor. The identification method used in this process is based on electrochemiluminescence (ECL). ECL is a type of luminescence that is produced during electrochemical reactions. In other words, it is a method of producing light using electrochemical reactions to produce reactive species on the surface of the electrode. The possible mechanism of the ECL process is described by equations (1) to (4). First, an electron is transferred to the CdSe-CdS nanocomposite to form a negatively charged species, CdSe-CdS-. Then, the electron is transferred to the K2S2O8 in the phosphate buffer, producing SO42- and SO4- species. The CdSe-CdS- species then reacts with the SO4- species to form an excited state, CdSe-CdS*. Finally, the CdSe-CdS* species relaxes to the ground state, releasing energy in the form of light (hv) and regenerating the CdSe-CdS nanocomposite(47).

(1) CdSe-CdS + e- → CdSe-CdS-
(2) S2O82- + e- → SO42- + SO4-
CdSe–CdS- + SO4- → CdSe-CdS* + SO42-
CdSe-CdS* → CdSe-CdS + hv

The cancer detection method described using Fe3O4/CdSe-CdS/APS nanocomposites and ECL has high sensitivity and selectivity, with a detection limit of fgml-1 32. This method has been shown to have a lower detection limit compared to other methods, including the ESEIA (enzyme-linked immunosorbent assay)
method. It is important to note that this method is not specific to the detection of lung cancer, but can also be used to detect other types of cancer. This is because the same ECL method can be used with different antibody biomarkers that are specific to different types of cancer. This makes it a versatile and potentially useful method for cancer diagnosis and screening(48).

- **Graphene**

Graphene is a two-dimensional planar sheet of carbon atoms arranged in a hexagonal configuration, where the atoms are sp2-bonded. Each carbon atom in a graphene sheet is tetravalent and is connected to three other carbon atoms with three covalent bonds, all on the same plane and with angles of 120 degrees between them. Graphene is a two-dimensional nanomaterial (D2) and the newest member of the family of multidimensional carbon materials, which also includes zero-dimensional fullerenes, one-dimensional single-walled carbon nanotubes, and three-dimensional graphite. Graphene is an allotrope of carbon that has a thickness of only one atom and has a honeycomb structure. In terms of strength, graphene is one of the strongest materials known to date, and it is the basic building block of carbon nanotubes and large fullerenes. Because of its unique properties, graphene has attracted a great deal of interest in various fields, including electronics, photonics, energy, and biomedicine(49, 50).

- **Graphene oxide**

Graphene oxide (GO) is a derivative of graphene that consists of a two-dimensional atomic layer of carbon atoms with sp2 hybridization in a hexagonal configuration, with additional carbon atoms that have sp3 hybridization and are attached to oxygenated functional groups. The most common method of producing graphene oxide is by oxidizing graphite using strong oxidizing agents, which introduces oxygenated functional groups into the graphite structure and produces graphite oxide. GO has a variety of functional groups, such as hydroxyl, carboxyl, and epoxide groups, which can interact with other molecules and enable various applications in fields such as biomedicine, catalysis, and energy storage. GO can also be reduced back to graphene, which can restore its electrical and mechanical properties(51, 52).

Some Applications of Graphene Oxide

One of the major challenges in using nanomaterials in

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biological and medical applications is their poor solubility and stability in biological solutions such as blood or cell culture media. This can limit their effectiveness and safety, as well as their ability to interact with biological systems. However, Graphene oxide's hydrophilic (COOH) groups and hydrophobic flat surface make it more soluble and stable in biological solutions compared to other nanomaterials. The hydrophilic nature of GO, along with the COOH groups present on its surface, enables easy functionalization with peptides or other biomolecules. The unique properties of graphene oxide have led to its application in various fields, including biomedical applications(49, 52, 53).

Biological application:

Apoptosis is a highly regulated process that eliminates unwanted or damaged cells in the body. It plays a crucial role in maintaining normal tissue homeostasis and preventing the development of various diseases. Caspase 3, also known as CPP32, is a cysteine protease that plays a key role in the execution phase of apoptosis. Graphene oxide-peptide nanohybrid is an effective tool for detecting caspase 3 activation in living cells. Yu and his colleagues identified its (Caspase 3) activation in living cells using graphene oxide- peptide nanohybrid as an intracellular protease nanosensor(54). In that study, the peptide probe was attached to GO using the hydroxy succinimide (EDC-NHS) coupling method, and the resulting nanohybrid was stable and soluble in water and cell growth medium. The intracellular protease nanosensor was able to detect caspase 3 activation with a detection limit of 0.4 in HeLa cells, and it showed great potential for detecting apoptosis in other cell types as well. This study demonstrated the potential of GO-based nanohybrids as tools for detecting cellular processes and diseases (15).

In addition, GO-based fluorescent dye-containing probes have been developed to detect specific DNA sequences. They identified three nucleotide sequences related to AIDS (HIV), smallpox (VV), and Ebola (EV) viruses using Alex Fluor 488, ROX, and Cy5 organic dyes, respectively (35, 55).

In addition to apoptosis and DNA detection, graphene oxide has been utilized in various medical and biological applications. For example, graphene oxide nanosheets have been shown to be capable of loading and releasing various drugs, including anticancer drugs and antibiotics, in a controlled manner. GO-based biosensors have also been developed for the detection of various biomolecules, such as glucose, cholesterol, and enzymes. In tissue engineering, GO has been incorporated into scaffolds for cell growth and differentiation, as well as for wound healing applications. Overall, the versatile properties of GO have led to its potential use in various medical and biological applications, with ongoing research and development in these fields.

Drug delivery:

GO has been used as a drug delivery platform due to its large surface area, biocompatibility, and ability to bind to various biomolecules. It can be functionalized with various therapeutic agents, such as anticancer drugs and genes, and delivered to the target site in the body.

Biosensors:

GO-based biosensors have been developed for the detection of various biomolecules, including cancer biomarkers. The large surface area and high sensitivity of GO make it an ideal material for biosensing applications.

Imaging:

GO has been used as a contrast agent in imaging techniques such as magnetic resonance imaging (MRI) and computed tomography (CT) due to its high biocompatibility and ability to enhance image contrast.

Cancer therapy:

GO has shown promise in cancer therapy due to its ability to selectively target cancer cells and induce cell death through photothermal therapy, photodynamic therapy, and drug delivery.

Tissue engineering:

GO has been used as a scaffold material in tissue engineering due to its ability to support cell growth and proliferation. It has been used in the regeneration of various tissues, including bone, cartilage, and nerve tissue.

Overall, the unique properties of graphene oxide have led to its application in various biomedical fields, including drug delivery, biosensing, imaging, cancer therapy, and tissue engineering.

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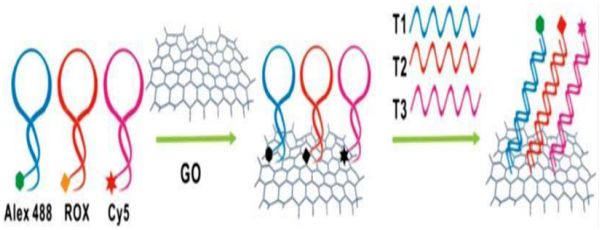

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Figure 4. GO-based fluorescent dye-containing probes to detect specific DNA sequences.

The use of GO in identifying DNA and protein biomolecules is a promising application in the field of diagnostics. The process involves adsorbing single-stranded DNA probes with organic dyes on the surface of GO, and then adding complementary DNA of each probe to hybridize with the target DNAs and separate them from the GO surface. The fluorescence intensity of the organic dyes decreases during the first step and increases during the second step, allowing for the detection of the target biomolecules with high sensitivity and selectivity.

Lu and his colleagues have successfully identified DNA and protein biomolecules using this method, including a DNA probe related to the AIDS virus and a human thrombin aptamer labeled with the fluorescent dye FAM. The process involved adsorbing the probe onto the GO surface, which caused a decrease in fluorescence emission, followed by hybridization with the target DNA and separation from the GO surface, resulting in an increase in fluorescence emission(56, 57).

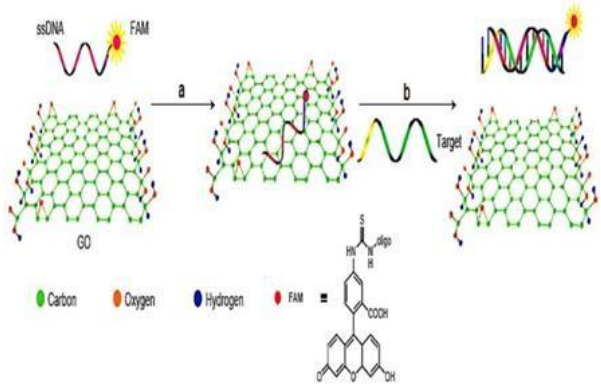

Figure 5. Structure of How to identify DNA using GO.

The method described in Figure 4 involves the use of single-stranded DNA probes or aptamers labeled with fluorescent dyes (like FAM, Alex 488, ROX,…) that are attached to the GO sheets through non-covalent interactions, resulting in a decrease in fluorescence intensity. The addition of the target biomolecule (DNA or protein) causes hybridization or binding to the probe or aptamer, resulting in the separation of the biomolecule (for example a double stranded DNA) from the GO surface and an increase in fluorescence emission (Figure 5).

For protein detection like thrombin, an aptamer labeled with FAM was adsorbed onto the GO surface, causing a sharp decrease in fluorescence emission. The binding of the thrombin protein as a target molecule to the aptamer resulted in separation from the GO surface and an increase in fluorescence emission. The aptamer is highly specific in binding to thrombin, and the detection limit for this method is around 2 nM, indicating high sensitivity and selectivity.This process has the potential to revolutionize the field of medical diagnostics by enabling the accurate and efficient detection of diseases and biomarkers

Conclusion

The biosensor based on graphene oxide-DNA appears to be a promising approach for detecting lung cancer. Graphene oxide is a two-dimensional material that has attracted considerable attention in biosensing applications due to its large surface area, unique electronic and mechanical properties, and high chemical stability. The use of DNA as a probe offers high specificity and selectivity for target detection. This approach has several advantages, including the use of a non-invasive method for detecting lung cancer and the potential for early detection. The use of graphene oxide-DNA biosensors is also cost-effective, fast, and easy to implement. However, further studies are required to validate the accuracy and reliability of this biosensor for lung cancer detection.

Acknowledgments

Conflict of Interest

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Authors' Contributions

Statement of Ethics

Funding

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