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BIOSENSORS FOR CANCER DETECTION APPLICATIONS

Abstract

Cancer is one of the most deadly diseases, and current detection options are ineffective. Recently, a large amount of research has been conducted for the development of biosensors able to detect cancer biomarkers. Many biosensors have been created for cancer detecting purposes. I examined literature reviews outlining current biosensing methods. These reviews provided an overview of the sensing techniques that are currently in existence as well as evaluations of their effectiveness. I also read experimental reports that outline the construction of biosensors fabricated in laboratories and the results of their testings. These papers help to showcase the feasibility and effectiveness that a biosensor has when detecting cancer. In this paper I discuss signal transduction systems, piezoelectric sensors, carbon nanotubes, quantum dots, and raman signals for use as cancer biosensors. Since cancer is such a deadly disease, an accurate biosensor is needed that can detect cancer earlier than current methods. In this paper I will provide an overview of each method along with an evaluation to determine what cancer detecting system is the best.

Overview of Biosensors for Cancer Detection Applications

Doctors and researchers agree that current cancer detection techniques are ineffective. Cancer is most commonly detected by ultrasound, MRI, or biopsy, but a group of British and Turkish researchers state that these current methods rely on the physical properties, or appearance, of the tumor, rendering them ineffective (Altintas, Uludag, Gurbuz, & Tothill, 2011). Cancer is caused by an accumulation of genetic mutations and therefore needs to be caught early before the disease progresses. Since early detection increases the chances that treatment will be effective, a new method of cancer diagnosis is desperately needed. Many researchers believe that cancer biomarkers, small abnormalities in the body's chemical or genetic composition can be detected in the very early stages of cancer, aiding in early diagnosis. A group of Indian researchers led by Jayanthi (2017) explain that these mutations or abnormalities "can act as nucleic acid-based biomarkers in diagnosis" (Jayanthi, Das, & Saxena, 2017). By looking for small abnormalities, cancer can be detected before the tumor has time to grow. A group of Russian researchers agree that by monitoring these biomarkers, abnormal amounts can be detected, aiding in early detection and effective treatment (Ranjan, Esimbekova, & Kratasyuk, 2017). These researchers believe that biomarkers have great potential to help revolutionize cancer detection. A group of professors at ETH Zurich believe that nanotechnology is a promising solution for sensing diseases [such as cancer] and managing health problems (Grieshaber, MacKenzie, Voros, & Reimhult, 2008). I also believe that these biomarkers have the potential to aid in early cancer diagnosis. Many different methods of detection have been developed. In this paper I will investigate the current sensing methods that exist for the detection of cancer biomarkers, and I will evaluate them on a variety of criteria, such as accuracy, feasibility and safety.

Signal - Transduction Systems

Many devicesfor detecting cancer biomarkers include a biorecognition element within a biosensor system. There are many different ways that a detection system can be configured to work properly. A team of international researchers led by Thevenot (2001) explained that in a system of this nature, the biorecognition molecules interact with a target, which is then converted into a measurable signal by the transducer (Thevenot, Toth, Durst, & Wilson, 2001). Essentially these biorecognition elements, usually an enzyme or antibody, are immobilized on a transducer surface and then interact with a target, the biomarker, to produce a signal that can be interpreted. There are a variety of changes that can be detected, which show the presence of the biomarker. A group of researchers clarify Thevenot's statement, explaining that

> ...the BRE [biorecognition element] often employs antibody, enzyme, short DNA strand or aptamer against specific cancer biomarker in close association to a physical transducer (electrochemical, optical and piezoelectric) which amplifies the signal response manifold after which the data is digitized to give results in form of display readout. (Ranjan et al., 2017)

One such sensor was created using an immobilized peptide, which then interacts with hydrogen peroxide (H_2O_2), a biomarker for breast cancer. This sensor was able to detect much smaller amounts of hydrogen peroxide than sensors that have been engineered previously, with a detection limit of .03 μ□ (Zhao, Yan, Zhu, Li, & Li, 2012). This means that the sensor could detect the presence of the biomarker even when it was only present with a concentration of .03 μ□. A sensor with this degree of accuracy is very important since extremely small concentrations can be detected, allowing for much earlier detection of cancer. While Ranjan Esimbekova and

Kratasyuk acknowledge the potential for BREs, they state that they are unable to last for long periods of time, and are not quick nor easy to assemble (Ranjan et al., 2017). While these are obvious flaws in this form of detection, these signal transduction systems can utilize a variety of compounds or materials for BREs, which makes them especially versatile.

Quantum Dots

Another way to detect cancer biomarkers is through the use of quantum dots. Quantum dots are nanoparticles that manipulate electrons while being resistant to photobleaching[1]. In addition, they are easy to excite but only emit in small ranges, making them accurate and sensitive (Wagner, Li, Li, Li, & Le, 2010). When a quantum dot is excited, internal electrons transform to higher levels. When they go back to lower levels, a photon is emitted, which causes a glow (Wang, Peng, Chen, & Li, 2015). Many scientists believe in the potential of quantum dots. A team of researchers led by Hossain (2017) argue for the great potential of these quantum dots because of the many unique characteristics that they posses, including optical and electrical characteristics (Hossain et al., 2017). Zhou, Liu, and Zhang also cite the optical and electrical properties that make quantum dots a topic of interest along with their stability and size control **(**Zhou, Lui, & Zhang, 2015). While most scientists do agree about the potential for quantum dots, several have health concerns. A team of researchers at the University of Alberta believe that despite the potential that quantum dots offer, they pose too great of a health hazard due to their toxic effects (Wagner et al., 2010). Unless quantum dots can be redesigned to be less toxic they are not a plausible option for cancer detection. A group of doctors in China share these fears about the toxicity of quantum dots. They have many concerns including toxicity, poor biocompatibility, and the lack of accurate analytic systems (Wang et al., 2015). Quantum dots

[1] Loss of colour by a pigment (such as chlorophyll or rhodopsin) when illuminated.

biggest advantage is that they are easily excited, which means that the sensor will react to the biomarker even in extremely small amounts. However, the concerns regarding toxicity make this type of sensor implausible. A device that tests for the presence of cancer should not pose additional health risks to the user.

Capillary Array Electrophoresis and Raman Signals

Another possibility for early cancer detection is the use of capillary array electrophoresis. DNA methylation is an indicator of cancerous cells. The use of capillary array electrophoresis as a way to detect DNA methylation is an important topic in cancer research (Wang et al., 2011). One method is surface enhanced Raman spectroscopy (SERS). A study performed by Wang's team (2011) was able to effectively detect mucin protein, a pancreatic cancer biomarker, using SERS technology when other detection techniques failed (Wang et al., 2011). Hu and Zhang were able to design a SERS chip that can detect methylated DNA in very small amounts, even if only 1% of the DNA is methylated (Hu & Zhang, 2012). They believe that this provides endless possibilities for the future and this can be expanded (Hu & Zhang, 2012). However, Ranjan et al. disagrees that this is effective for the detection of cancer since it takes too long and can affect the sample. In addition, interference can make it difficult to identify the signals (Ranjan et al., 2017). A team of researchers from Bangladesh and Australia led by Hossain (2017) believe that there are many challenges for this type of sensor, including building a device that functions without human assistance and ensuring accuracy. While they have doubts, they do believe that more research needs to be done (Hossain et al., 2017). DNA methylation is one of the most well known markers of cancer, since it is a direct effect of the genetic mutations. However, DNA methylation also occurs in cases other than cancer. Basing a cancer biosensor off of the levels of DNA methylation can be problematic because it could result in false positives. While this does have the potential to be very effective and detect cancer earlier than most of the other sensors discussed, at its current stage, this type of sensor is not feasible.

Carbon Nanotubes and Graphene

Many researchers believe that carbon nanotubes (CNTs) coupled with graphene have the greatest potential for biomarker recognition. These are the most common materials used in antibiotic detecting biosensors (Lan, Yao, Ping, & Ying, 2017). These materials are so interesting and promising because of the astounding properties that they possess. Kumar and Rao (2017) discuss these interesting properties in their paper. They state that CNTs can behave as semiconductors or metals depending on the situation;, they also have quasi-one dimensional structures, high chemical stability, are strong, and have a large surface to volume ratio (Kumar & Rao, 2017). Their strength and large surface area make them attractive candidates for sensors. A different researcher, Zhu, agrees by saying the special features of CNTs, namely "...their nano dimensions and graphitic surface chemistry, make them extremely attractive for new types of electrochemical, electric, and optical biosensors" (Zhu, 2017). Current CNT research is investigating the electrochemical detection of compounds such as glucose, immunoglobulin and a prostate antigen, a cancer biomarker (Kumar & Rao, 2017). This shows the versatility that CNTs can provide, since they are able to detect a wide variety of molecules. One sensor has been created by a group of Indian researchers that can detect lung cancer within an accuracy range of 5 fg mL^{-1} to 50 ng mL^{-1} (Singh, Choudhary, Kaur, Singh, & Arora, 2016). Zhu believes that CNTs have potential, however, he acknowledges that their largest problem is the high surface energy of CNTs, which makes it more difficult to handle CNTs in a controlled way (Zhu, 2017).

Piezoelectric Sensors

On the other hand, Kumar and Rao (2017) note that nano-transducers make the recognition process more seamless. Instead of separate transducers and bioreceptors, a nano-transducer is able to integrate both of these properties into one processing system. These sensors also have high sensitivity and quick response times (Kumar & Rao, 2017). While this seems like a siginificant difference, this PZ sensor is still very effective, but their uncontrollable nature needs to be addressed if they are going to become a feasible option for cancer detection. A piezoelectric (PZ) sensor interprets small changes in the mass, frequency or other measurable properties of the biorecognition element, often through the binding of molecules to antibodies. Most piezoelectric sensors utilize the signal transduction system explained above. A group of Chinese researchers created a PZ sensor in which an antibody is immobilized on the sensor and then interacts with molecules in the body. When binding occurs, the frequency changes depending on the mass of the antibody(Yang, Huang, Sun, & Xu, 2016). This frequency change points to the presence of the specific molecule being tested for. In a study conducted by these same researchers, a PZ sensor was created to detect cervical cancer; it had a fairly quick analysis time and was able to effectively detect the biomarker in ranges of 50 to 1200 ng mL^{-1} (Yang et al., 2016). Several different groups of researchers believe that this type of sensor is a good option for cancer detection and have created sensors that utilize piezoelectric crystals. A group of Chinese researchers created a sensor that aids in the detection of ovarian cancer. Interaction of the cancer antigen with the cancer cells created a mass change which led to a change in frequency from 1080 Hz to 282 Hz (Chen, Huang, Chen, & Shi, 2013). This change in frequency indicates that a cancer biomarker is present. Both groups of researchers were able to demonstrate the potential for PZ biosensors through their respective studies. Fracchiolla, Artuso, and

Cortelezzi believe that biosensors based on the recognition of antigens and antibodies have many advantages compared to other methods, including cheaper and faster production in addition to being more flexible (Fracchiolla, Artuso, & Cortelezzi, 2013). The CNTs and graphene sensors discussed are less effective than the PZ sensors. A PZ sensor is able to detect the marker at 100 million times lower concentrations. Piezoelectric sensors are dependent on a change in the sensor that can then communicate the presence of the biomarker. PZ sensors are stable and are able to detect minute concentrations of the biomarker, which makes them a reliable option for effective cancer detection.

Conclusion

Many different biosensors have been created and tested for cancer detection. Since there are many different forms of cancer and each form is going to have a different biomarker, versatility is the most important aspect of a biosensor. While all of the sensors discussed are effective in detecting cancer biomarkers, I believe that versatility and safety are the most important criterion for a sensor. For that reason, I propose that a piezoelectric sensor is the best option. A sensor of this type is cheap and easy to produce while also being able to detect a biomarker in very small concentrations. In addition, it is an application of signal transduction systems, making it very versatile, since a variety of compounds or molecules can be utilized as the biorecognition elements. Sensors of this type are safe since most utilize biological compounds or molecules as the biorecognition element. While sensors of this type are in existence, more research needs to be done to create more PZ sensors for other types of cancer.

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