Review Article

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A review of analysis of biomarkers or detection method of biomarkers in cancer

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Abstract

In the last three decades, technological advancements in health services have notably enhanced the detection and treatment of diseases, including cancer. This progress is particularly evident in the research and application of cancer biomarkers for early detection and risk assessment, aiming to lower cancer fatalities. These biomarkers represent a cost-effective alternative to traditional diagnostic methods like CT scans, though they have yet to achieve the reliability needed for clinical use. This thesis explores the development, validation, and quality control of cancer biomarkers, examining market trends in genomics, proteomics, and diagnostic technologies. The potential for biomarkers to offer less invasive and more affordable diagnostic options could lead to significant healthcare savings. Highlighting this potential, the National Cancer Institute's Early Detection Research Network has initiated a project focused on enhancing cancer cell biomarker identification, driven by individual researchers' efforts. This initiative reflects the growing emphasis on prevention over treatment in the fight against cancer.

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INTRODUCTION

In several cells, cancer can develop through a variety of routes that can run concurrently and at various speeds. Since many of these biomarkers are observable before overt cancer is clinically evident, their identification might help rationally create prevention efforts, including the development of biomarkers. These pathways incorporate genetic, molecular, and clinical processes. Biomarkers are described as changes in cellular, biochemical, molecular, or genetic processes that allow one to identify or track a normal, aberrant, or purely biologic activity. In

biological media, such as human tissues, cells, or fluids, biomarkers can be measured [1].

Biomarkers may be used to detect cancer susceptibility in individuals or to identify pathological processes prior to symptom onset. Tests for biomarkers need to be highly predictive, easily measurable, reproducible, minimally intrusive, and also well-liked by patients and doctors in order to be therapeutically valuable. The following are some potential applications for biomarkers [2]:

1. keeping an eye out for recurrence in people with existing cancer
2. Prompt identification of patients without symptoms,
3. Supporting symptomatic patients' diagnosis,
4. Monitoring those identified as having a high risk of developing cancer, as well as
5. Stand-in endpoint markers for mainstay preventive techniques like chemoprevention.

Numerous kinds of biomarkers in body fluids as well as cancer cells have been investigated, primarily in laboratory settings looking at particular observations but also in restricted clinical settings. The usefulness of a number of biomarkers, such as CD44, telomerase, transforming growth factor-α (TGF-α)3, transforming growth factor-β (TGF-β), mucin 1 (MUC1), mucin 2 (MUC2), cytokeratin 20 (CK20), and epidermal growth factor receptor erbB-2 (erbB-2) has only been slightly demonstrated [3]. Based on observational relationships, some are employed in clinical practise. The latter group includes tumour marker 125 (CA 125) and cancer antibody or prostate specific antigen (PSA). However, there hasn't been any evidence to support their use in the screening context to lower mortality. Only a few protein markers have received extensive research to now. In cancer screens, the only protein biomarker that has been demonstrated to reduce cause-specific mortality is the faecal occult blood test (FOBT). This highlights the necessity for the development of fresh and innovative protein-based markers that can be immediately and consistently detected in exfoliated cells at an early stage or in serum [4].

The majority of recent progress in both basic and applied cancer research has gone towards figuring out what mutations, translocations, and other molecular genetic anomalies people with advanced malignancies have in their DNA. This type of investigation is crucial for defining the mechanisms underlying tumour induction and for identifying people who are genetically predisposed to cancer. To be effective, early detection must, obviously, focus on the identification of lesions in time for intervention to alter the course of events. In certain specific malignancies, the presence of mutations in known oncogenes is very significant; nevertheless, in other cancers, the mutation frequency is too low to be useful in ordinary clinical practice [5]. Conversely, as they provide clear proof of aberrant gene expression at the moment of sampling in a particular patient who may not be symptomatic, RNA- and protein-based diagnostic approaches may have clear advantages over DNA-based procedures. Thus, approaches based on proteins and DNA are complimentary. Finding protein-encoding DNA sequences can lead to further research on expression in tissues or bodily fluids [6].

Methods for Cancer Detection

Cancer can be detected by a number of methods like

- Biopsy
- Radiography
- Blood and bone marrow tests
- ELISA
- Molecular biology techniques

Biopsy

Biopsy involves cutting a piece of the tissue followed by slicing and staining it. The tissue thus treated is used for histopathological studies under the microscope. The cancerous cells, if present are detected **Figure 1**.

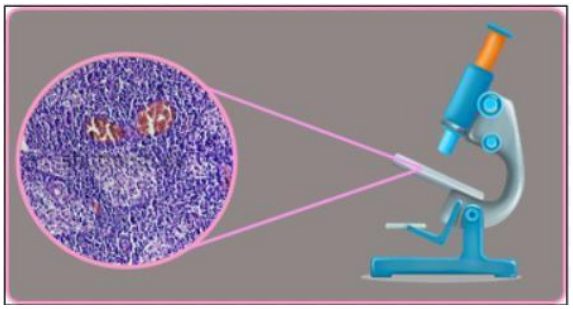

Figure 1 Cancerous cells observed under the microscope in biopsy

Radiography

Radiography makes use of radiations like X-rays in the case of computed tomography and magnetic radiations in case of MRI to detect internal cancers **Figure 2**.

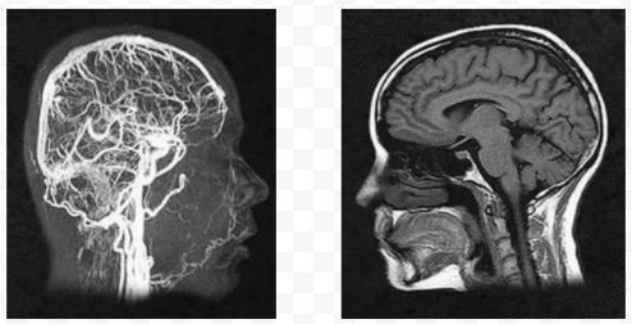

Figure 2 CT scan and MRI to detect cancer

Blood and bone marrow analysis

Blood and bone marrow analysis is done to detect leukemias [7].

ELISA

ELISA (Enzyme-Linked Immunosorbent Assay) detects the antibodies which are produced against the tumor proteins [8].

Molecular biology techniques

Molecular biology techniques can be used to detect the presence of genes that may predispose the individual to certain cancers. Example the breast cancer gene. Appropriate counselling can be given to the individual [9]. After detection or identification of these genes in any individual, they it could be suggested that they stay away from specific carcinogens to which they are prone. For example, tobacco smokes in case of lung cancer [10].

Treatment of cancer

Cancer can be treated by any of the following methods:

- Chemotherapy
- Radiotherapy
- Surgery
- Immunotherapy

Chemotherapy

Chemotherapy makes use of chemotherapeutic drugs which attack the cancer cells and make them inactive. There are few side effects associated with chemotherapy like loss of hair, discolouration of nails, weakness and nausea **Figure 3**.

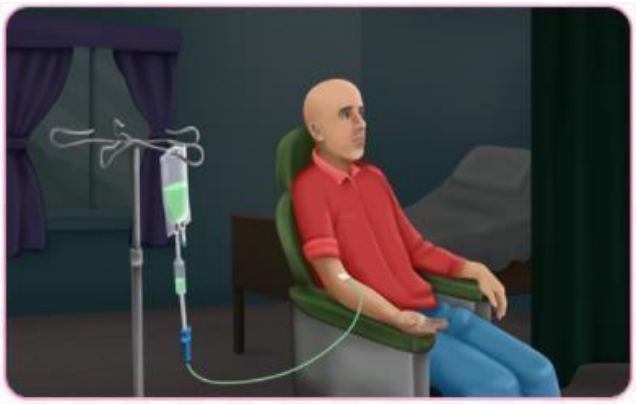

Figure 3 Patient undergoing chemotherapy

Radiotherapy

High energy radiations like gamma rays are used to kill cancerous cells.

Tumor cells are irradiated lethally by gamma radiation taking proper care of the normal tissues surrounding the tumor mass or neoplasm.

Surgery

Surgical removal of the tumor without affecting the surrounding cells **Figure 4**.

Figure 4 Surgical removal of cancer cells

Immunotherapy

Immunotherapy helps in fighting the cancer cells. Patients are given substances like α-Interferon which improves the immune response, helping in destruction of the cancerous cells [11].

Electrochemical Biosensor

Various electrochemical measurement methods

The method most frequently used to continuously measure the current produced by the oxidation or reduction of an electroactive species in a

biological reaction driven by a steady applied voltage is amperometry [12].

In a different instance, the detection of the human cervical cancer biomarker miR-21 has been reported using a selective and sensitive biosensing prototype based on a graphene nanocomposite with functionalized AuNPs.

Additionally, amperometric methods are employed to target the CTCs. For instance, the detection of prostate cancer cells in circulation with the use of gold array electrodes. Reference [13].

Typically, biosensors include [14][15]:

(A) A bioreceptor, also known as a biosensing element, is a device that the analyte has a highly specific binding affinity for.

(B) A biosurface/biointerface architecture creates an environment in which the bioreceptor can function properly.

(C) A transducer transforms the physical phenomenon or chemical response that arises from the analyte's interaction with the biological element into signals that can be read. The latter can be monitored, quantified, and processed in a repeatable manner; and

(D) a set of related electronics that includes a signal processor, amplifier, as well as interface—such as a display—that ultimately enables an easy-to-use data visualisation and assessment. An electrode is a transducer in an electrochemical biosensor.

An amperometric biosensor for the detection of cancer cells using an antipermeability glycoprotein functionalized nanoprobe has been developed; it has a Linear Range (LR) and LOD of 50 to 105 cells mL−1 and 23 ± 2 cells mL−1, respectively. The receptor is the most crucial component for the design of an electrochemical biosensor, which involves antibodies, lectins, peptides, deoxyribonucleic acid (DNA), peptide nucleic acids (PNAs), aptamers, as well as molecularly imprinted polymers (MIPs).

Label, label-free and redox species

There are numerous ways to produce an electrochemical signal. By adding an electro-active indicator or leaving it without one, it could be labelled or label-free. The majority of electrochemical measuring techniques, aside from non-faradaic EIS, call for the use of an electro-active indicator [16].

Naturally, the addition of an electro-active indicator is not required for analytes that are electrochemically active on their own. Redox ions, like ferricyanide/ferrocyanide ions (Fe (CN)63−/4−), are often dissolved in the sample solution to function as an electro-active indicator and record electrochemical biosensor output signals.

Besides quinones as well as hydroquinones (like anthraquinone), anthracyclines (like daunomycin and doxorubicin), viologens, phenothiazines (like thionine, methylene blue, and toluidine blue), and quinoxaline derivatives (like echinomycin) are other frequently utilised redox species. Metal-based redox species include oxoosmium(VI) complexes, metalloporphyrins, metalloorganics like ferrocene and its derivatives, and simple metal complexes like organic metal chelates [M(L)3]3+/2+ where M stands for Fe, Co, Os, or Ru and L for heterocyclic nitrogenous bidentate ligands like 2,2'-bipyridine (bipy) or 1,10-phenantroline (phen). Electro-active indicators also employ heavy metal ions including Pb2+, Cd2+, and Cu2+ [17].

Signal amplification

Electrochemical signal amplification is required because in the early stages of cancer, the concentration of cancer biomarkers in bodily fluids is too low [18].

Electrochemical ELISA [19][20]

This approach is among the most frequently documented techniques for identifying cancer protein biomarkers.

There are two primary signal amplification methodologies utilised because conventional ELISA is unable to reach concentration levels below nanomolar, which is insufficient to approach the clinical threshold of many protein biomarkers.

One involves using nanomaterials to change an electrode, while the other involves using nanomaterials to design additional antibody-redox-enzyme complexes. The use of nanomaterials in the creation of electrochemical biosensors was studied by Wang and Anzai. These

materials included graphene, carbon nanotubes, and metal nanoparticles.

Since they can execute high-throughput multiplexed detection assays, integrate sample preparation, and require little reagent, microfluidic chips can give electrochemical biosensors more strong performance.

Using electrochemical microfluidic devices, cancer molecular biomarkers and CTCs have been extensively identified and analysed.

Using a straightforward process centred on the use of a cutter printer for rapid prototyping, an array of eight carbon-based working electrodes (8-WE), the pseudo-reference electrode (RE), and the counter electrode (CE) were constructed to create a fully disposable microfluidic electrochemical array device (μFED) to detect the breast cancer biomarker oestrogen receptor alpha (ERα). The method by which the microfluidic device is built.

The technique's incredibly easy and affordable μFED manufacturing method would allow it to be utilised in routine public health testing, which would greatly aid in cancer diagnosis and personalised therapy. A low-cost, high-throughput electrochemical array with 32 microelectrodes that may be individually addressed was published.

By connecting eight 32-sensor immunoarrays to the miniaturized 8-port manifold, high-throughput studies were achieved, enabling 256 measurements in less than an hour. Prostate specific membrane antigen (PSA), interleukin-6 (IL-6), platelet factor-4 (PF-4), and PSA were found in serum using the prostate cancer biomarker proteins system. In clinical serum samples, Wang and colleagues developed a paper-based electrochemical aptasensor for the simultaneous detection of CEA and NSE.

The gadget has the ability to filter since it was built on four layers of chopped cellulose filter paper. Samples were introduced via the side sample inlet, passed through the microchannel, and arrived at the screen-printed three-electrode system in order for the device to function.

The sample was led by the capillary action to the two separate working electrodes on the paper within the hot wax printed channels, where it was then recognised by the appropriate DNA aptamers, enabling multiplexing analysis of the apparatus. It created an integrated microfluidic chip that uses ion concentration polarisation (ICP) to pre-concentrate methylated DNAs and electrochemical detection to identify the pre-concentrated DNAs.

The chip has two independent channels: one for preconcentration and the other for buffering, which are connected by a Nafion pattern. To facilitate the passage of pre-concentrated methylated DNA to the sensing chamber and the incubation process within the chip, four pneumatic valves were incorporated.

The three layers of the chip are the valve layer on top, the pre-concentration layer on the second layer, and the gold electrode with a Nafion pattern on the bottom.

Both the modification of electrodes and the usage of nanomaterials as signaling labels were considered. Nanomaterial-modified electrodes have the ability to immobilise a wide range of bioreceptors, including antibodies and nucleic acids, and to improve their effective surface area.

Additionally, the sandwich structure formed by the nanoparticles utilized as signaling labels has the potential to enhance cancerous output.

CONCLUSION

For nearly all cancer patients, biomarkers have a role in both diagnosis and treatment. Before receiving official clearance, newly created medications must pass rigorous testing in well-planned, randomized clinical studies and pass stringent inspections. Although biomarkers can also have a major impact on patient outcomes, sadly, they are not subject to the same regulations. Thus, it is critical that clinical, translational, and laboratory-based researchers have a thorough understanding of the issues surrounding appropriate biomarker development. This will help to ensure that clinically useful biomarkers are introduced into the clinic while preventing the introduction of biomarkers that have not undergone adequate evaluation as well as could be ineffective or even harmful to patient care.

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Conflict of Interest

The authors declare no conflict of interest, financial or otherwise.

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