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Recent advances in electrochemical biosensors for detection of oncoviruses

Goksu Ozcelikay [a], S. Irem Kaya [b], Ahmet Cetinkaya [a], Sibel A. Ozkan [a,*]

[a] Ankara University, Faculty of Pharmacy, Department of Analytical Chemistry, Ankara, Turkey
[b] University of Health Sciences, Gulhane Faculty of Pharmacy, Department of Analytical Chemistry, 06018, Ankara, Turkey

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ABSTRACT

Oncoviruses are responsible for less than half of cancers in humans. In virus-related human oncogenesis, a multi-step process leads normal cells to transform into cancerous cells in the body. Among the various oncoviruses are human papillomavirus (HPV), Epstein-Barr virus (EBV), hepatitis B virus (HBV) and hepatitis C virus (HCV), human immunodeficiency virus (HIV), human herpesvirus (HHV-8), human lymphotropic virus-1 (HTLV-1), Merkel cell polyomavirus (MCV). The Pap smear test is critical in HPV screening, but its sensitivity is relatively low in cervical lesions, and the probability of giving false results is high. In this situation, create an alternative screening method. Therefore, the applied electroanalytical measurement techniques and electrode systems are important for detecting oncoviruses using electrochemical biosensors. Electrochemical sensor strategies such as genosensors, CRISPR-based recognition assay, aptamer-based biosensors, and immunosensors are used for the detection of oncoviruses. Major viruses causing cancer and oncovirus-related cancer types and electrochemical sensor strategies are described in the review. Studies that have been published in recent years are reported in tables for explaining details. This review considered the articles published in the last 10 years. The biosensor studies for cancer-causing viruses get gradually increased.

1. Introduction

Cancer is one of the deadliest life-threatening diseases in the world. According to the World Health Organization data, approximately 18.1 million new cancer cases emerged worldwide in 2018, while 9.6 million people died from cancer.

Tumor viruses are responsible for approximately 12%–20% of cancers in humans (Liao, 2006). Tumor viruses are mainly divided into two main categories named Ribonucleic acid (RNA) and DNA viruses. Oncoviruses or tumor viruses are a general term for viruses that can cause cancer. Viral genomes contain oncogenes that can be integrated into the host genome, and the host cell then expresses these genes into oncoproteins that may initiate the carcinogenesis process in various ways. When DNA viruses naturally enter the host cell, they multiply and cause cell death. However, they cannot create viruses similar to themselves when they enter the cells they do not naturally stay in. If the conditions are right, they join the genetic structure in the nucleus of the cells and reproduce together. The cell changing this way acquires the characteristics of a tumor cell. On the other hand, oncogenic RNA viruses contain the enzyme reverse transcriptase (the enzyme that makes DNA from RNA) and thus extract the DNA sample of their RNA. Cancer-causing viruses and cancer types are given in Table 1.

Among the various cancer-causing viruses are human papillomavirus (HPV), Epstein-Barr virus (EBV), hepatitis B virus (HBV) and hepatitis C virus (HCV), human immunodeficiency virus (HIV), human herpesvirus (HHV-8), human lymphotropic virus-1 (HTLV-1), Merkel cell polyomavirus (MCV) (Mui et al., 2017). Electrochemical biosensors are analytical bio-detectors formed by combining a biological recognition surface (biosensor) that will recognize the substance to be analyzed and a system that converts this interaction into a measurable electronic signal with the physicochemical transducer. The indirect and direct measurement of the biological analyte in a biological environment was performed in the presence of a biosensor. Electrochemical biosensor strategies such as genosensors, enzyme-based biosensors, aptamer-based biosensors, and immunosensors are used for the detection of oncoviruses (Fig. 1).

2. General overview of the virus-related human oncogenesis

The factors causing cancer and their mechanisms are complex processes and are still an important topic for researchers. In this context, the prevalence of virus-related cancers in humans worldwide reaches 20%

* Corresponding author.
E-mail address: ozkan@pharmacy.ankara.edu.tr (S.A. Ozkan).

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Table 1
Cancer-causing viruses and cancer types.

Major Viruses Causing Cancer	DNA/RNA virus	Cancer Type
HPV	DNA	Cervical cancer
EBV	DNA	Burkitt lenfoma
HBV	DNA	Liver cancer
HCV	RNA	
HIV	RNA	Kaposi's sarcoma, Aggressive B-cell lymphoma, Cervical cancer
HHV-8	DNA	Kaposi sarcoma
KSHV	RNA	Castleman's disease
MCV	DNA	Skin cancer
HTLV-1	RNA	Leukemia/Lymphoma

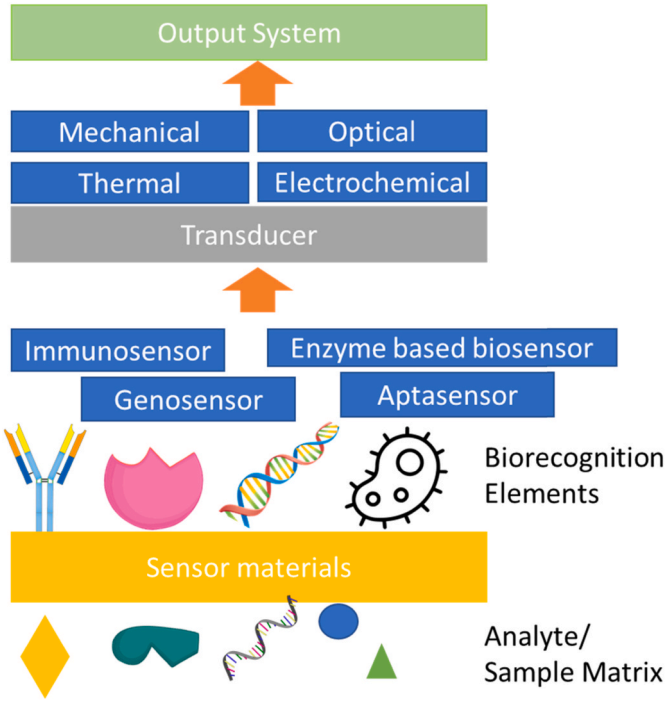


Fig. 1. The scheme of main biosensor preparation.

(Purushothaman and Chandra Verma, 2013). In virus-related human oncogenesis, there are specific mechanisms that lead a normal cell to transform into a cancer cell: The presence of chronic and long periods of persistent viral infections, oncogenic viruses that affect cell growth, apoptosis, and DNA repair processes, viruses without oncogenes that activate other oncogenes (Kumar et al., 2019; Lambert, 2009; Mesri et al., 2014; Pfister and Fleckenstein, 1999). In addition to all of these, cancer formation is also related to individual factors (additional risk factors such as immunosuppression, mutations, genetic properties, etc.) (Mesri et al., 2014; Purushothaman and Chandra Verma, 2013). Cancer-associated viruses can be DNA and RNA viruses from various families (*Retroviridae, Hepadnaviridae, Papillomaviridae,* etc.), although this will be detailed later.

2.1. - *Hepatitis C virus*

Hepatitis C virus (HCV) infection is a crucial public health problem affecting approximately 170 million people globally (Lavanchy, 2009). The main target of the HCV virus, which infects only humans and chimpanzees, is hepatocytes. However, when the studies in the literature are searched, it has been explained that the virus can also infect immunological cells (Goutagny et al., 2003). HCV, a positive-stranded RNA virus, completes its life cycle in the host cell's cytoplasm. This virus, which spreads by contact with contaminated blood, can be detected after 1–2 weeks. It causes an elevation in serum ALT levels 2–8 weeks after the onset of the immune response to the infection. If left untreated, chronic HCV infection can cause liver diseases such as fibrosis, cirrhosis, and hepatocellular carcinoma (an der Heiden and Häfner, 2011; Liang et al., 2000). It is predicted that within 20–40 years, 20–30% of patients with chronic hepatitis C may improve liver cirrhosis (Freeman et al., 2001).

2.2. - *Hepatitis B virus*

Hepatitis B virus (HBV), a double-stranded DNA virus containing reverse transcriptase, is classified with Hepadnaviridae. This virus, named after the disease it causes, hepatitis B, can cause acute and chronic infections. Typical symptoms of acute infections include yellow skin, dark urine, vomiting, and abdominal pain, while chronic diseases are usually asymptomatic until cirrhosis or liver cancer develops. In addition, HBV is a significant health problem due to the high risk of transmission. Despite an effective vaccine, it is estimated that between 250 and 300 million people are affected by hepatitis B. According to the World Health Organization (WHO) data, it is stated in the literature that 900,000 deaths each year are caused by hepatocellular carcinoma (HCC) and cirrhosis due to chronic hepatitis B. Various tests such as hepatitis B surface antibody (anti-HBs), total hepatitis B core antibody (anti-HBc), and hepatitis B surface antigen (HBsAg) are tests used to detect HBV (Khatami et al., 2021; Trépo et al., 2014).

2.3. - *Human papillomavirus*

Human papillomavirus (HPV) is one of the most common sexually transmitted infections (Harari et al., 2014). It infects the skin and mucous membranes (Satterwhite et al., 2013). While Alphapapillomavirus (Alpha-PV) type HPVs infect oral and genital mucosa surfaces, HPVs belonging to Betapapillomavirus (Beta-PV), Gammapapillomavirus (Gamma-PV), Mupapillomavirus (Mu-PV) and Nupapillomavirus (Nu-PV) types infect non-genital mucosa and skin (Bernard et al., 2010).

HPVs are classified to trigger cancerous cells according to the body area where they tend to infect. Low-risk HPVs cause genital warts, and high-risk HPVs cause cancer due to abnormal changes in cells in the genital area, such as the cervix, vulva, and anus.

More than 200 papillomavirus genotypes have been identified, and approximately 120 types have been isolated from humans (Bernard et al., 2010). In International Agency for Research on Cancer (IARC), high-risk HPV types as HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73 type and low-risk HPV types as HPV 6 and 11 are reported. Low-risk HPV types are associated with anogenital warts and lesions (Bernard et al., 2010). High-risk HPV 16 and 18 are the most common genotypes responsible for 70% of cervical cancer cases (Bernard et al., 2010). Vaccination studies for HPV 16 and 18 genotype viruses, which cause vulva, anus, oropharyngeal, and cervical cancer, have also gained momentum (Lindenbach and Rice, 2007).

The structure of the HPV genome is given in Fig. 2. While E6 and E7 in the early gene region regulate the transcription of viral genes, L1 in the late gene region encodes the major capsid protein, and L2 encodes the minor capsid protein. E3 and E8, located in the early gene region and found in some HPV types, have been discovered recently (Berg, 2010). E8 is thought to arise during the deletion of the E2 region and is responsible for receptor protein replication. HPV genotype and type number system were determined according to their biological homology between L1 protein sequences.

Cervical cancer screening programs are extremely important to reduce the incidence and death rates of this cancer. Like all over the world, Turkey is also aimed to develop cervical cancer screening programs with various methods such as Pap Smear and HPV DNA screening and to spread the screenings to the general population (Aydoğdu Tığ et al., 2019). The Pap Smear test, which is used in early diagnosis, is a

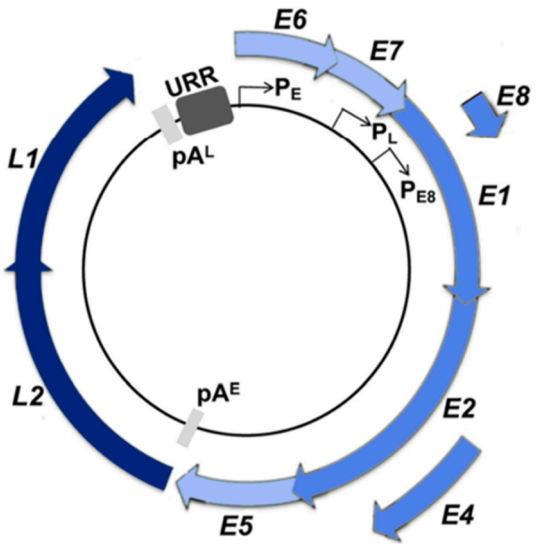


Fig. 2. HPV genome organization. It is reprinted from Ref. (Burley et al., n. d.), Springer.

test that does not harm the patient, has a low cost, and also reduces the treatment burden, morbidity, and mortality. Mayrand M.H. et al. explained the differences between PAP smear and HPV tests in terms of sensitivity and specificity (Mayrand et al., 2007). They referred that the Pap smears have relatively low sensitivity, and high specificity. However, detection of HPV DNA appears to have higher sensitivity than Pap smear. These limitations have led researchers to nucleic acid biosensors for new useable technologies.

2.4. - Epstein-Barr virus

Epstein-Barr virus (EBV), a DNA virus, belongs to the family of *Herpesviridae*. It was firstly identified in 1964 and isolated in 1969 (Manivannan et al., 2021). EBV is the first virus identified as a human oncovirus (Geris et al., 2021). The oral route is the main route for the transmission of EBV infection, and it is more common in the younger population. EBV is associated with the following tumors: Hodgkin's disease, Burkitt's lymphoma, non-Hodgkin's lymphoma, nasopharyngeal carcinoma, infectious mononucleosis, X-linked lymphoproliferative disorders (Purushothaman and Chandra Verma, 2013; Young, 2008). EBV shows its tumor induction effects on epithelial and lymphoid cells. Latent membrane protein-1 (LMP-1) is an important protein highly expressed in EBV-related cancer cells (Manivannan et al., 2021; Pfister and Fleckenstein, 1999).

2.5. - Human herpesvirus 8 (HHV-8)

Human herpesvirus 8 (HHV-8) is another DNA virus from the *Herpesviridae* family. The main transmission routes for HHV-8 infections are saliva, sexual contact, and blood. The most significant manifestation of HHV-8 infection is Kaposi's sarcoma, followed by primary effusion lymphoma and multicentric Castleman's disease. HHV-8-associated cancer cases are more common in immunocompromised patients. Latency-associated nuclear antigen (LANA) plays an active part in oncogenesis in HHV-8-related cancer development processes (Mui et al., 2019; Stanberry, 2008; Tan and Pinsky, 2017).

2.6. - Human T-cell lymphotropic virus type 1 (HTLV-1)

Human T-cell lymphotropic virus type 1 (HTLV-1) from the *Retroviridae* family is an RNA virus, and it is the first human retrovirus to be recognized as a human oncovirus. HTLV-1 can cause infective dermatitis and uveitis, and transfusion is the main transmission route for HTLV-1 infections. Adult T-cell leukemia (ATL) is also known as HTLV-1-related human cancer. In ATL cases, the Tax protein of HTLV-1, an oncoprotein, is responsible for transforming cancerous cells from infected cells. The high-level expression of tumor suppressor cell adhesion molecule 1 (CADM1) is used to diagnose ATL (Manivannan et al., 2021; Yoshida, 2008).

2.7. - Merkel cell polyomavirus (MCPyV)

Merkel cell polyomavirus (MCPyV) is a DNA virus from the *Polyamaviridae* family, and it was firstly identified in 2008. MCPyV is associated with Merkel cell carcinoma, an aggressive type of skin cancer. People with extensive sun exposure, older age, and immunocompromised patients are prone to Merkel cell carcinoma. The known transmission routes for MCPyV include respiratory, mucosal, fecal-oral, and cutaneous routes. Immunohistochemical biomarker cytokeratin-20 is used for the diagnosis of Merkel cell carcinoma (Akaike and Nghiem, 2022; Purushothaman and Chandra Verma, 2013; Yang and You, 2022).

3. Electrochemical sensor strategies for the detection of oncoviruses

Electrochemical sensor strategies are very important for the detection of oncoviruses. Recent developments in electrochemical research reveal that biosensors are easy to use, accurate, precise, and affordable for detecting tumors and viruses (de Eguilaz et al., 2020; Kaya et al., 2020; Manring et al., 2022).

Electrochemical sensors are devices containing an electrochemical transducer and provide analytical information through a biochemical receptor. Furthermore, the interaction between the analyte and the bioreceptor should be responsible for producing the measurable signal. Since these processes take place on the working electrode surface, they are also related to the concentration of analyte in solution. Also, there are electrochemical methods that do not use direct electron flow. Instead, changes in the electrode surface caused by biofunctional surfaces such as antigen-antibody and receptor-ligand are analyzed using resistance, capacitance, or impedance techniques. Also, with the development of the sensor industry, it is quite easy to convert biological interactions into simple electrical signals. These electrical properties can be realized using electroanalytical methods such as potentiometry, amperometry, voltammetry, conductivity, and impedance (Bettazzi et al., 2017).

The electrode material significantly influences the measurement, as each material has various properties such as potential range and capacitance. Apart from the traditional three-electrode electrochemical cell, there are also various modifications and miniature variations (Bettazzi et al., 2017). Among these, microfluidic cells are systems that provide simpler sampling and cleaning, as well as increased sensitivity, less reagent use, and less waste generation (Chand et al., 2013). The microbial fuel cell (MFC) can be given as an example of novel devices developed as alternatives to classical electrode systems. In this system, unlike the others, organic substrates are converted into electrical signals through microbial catabolism (Dziąbowska et al., 2018). The other three-electrode systems are lab-on-a-chip devices (LOC) that can be shrunk to a platform of a few square millimeters, have multiple functions, and produce results even in very small liquid quantities such as the picoliters level (Bettazzi et al., 2017).

Electrochemical sensor strategies such as genosensors, CRISPR-based recognition assay, aptamer-based biosensors, and immunosensors are used for the detection of oncoviruses. In this review, the articles published in the last 10 years were considered. The biosensor studies for cancer-causing viruses get gradually increased (Fig. 3).

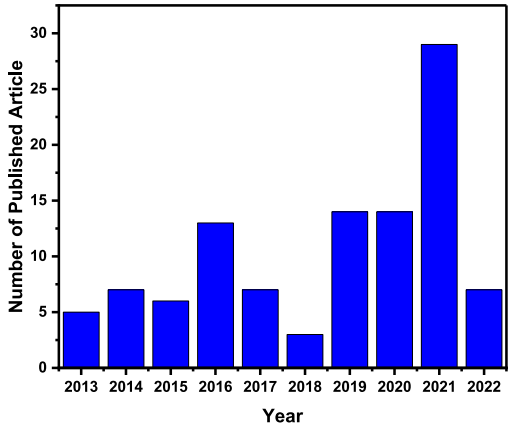


Fig. 3. The column bar graph of EC biosensors studies for cancer-causing virus according to years (Data is collected from Scopus database, 25th May 2022).

3.1. - Genosensors

Electrochemical DNA biosensors are also referred to as genosensors. It has gained a new dimension to the studies on the determination of the patient's genetic disorder or infectious diseases in a short time. The design of a cheap, fast, small-sized device that can be easily used for the early diagnosis of diseases in the clinic.

The nucleic acid analysis mainly depends on DNA hybridization in biomedical and environmental research. It is based on combining a short and single-stranded oligonucleotide probe sequence attached to the recognition surface and the synthetic target DNA sequence to form a double helix. The resulting double-stranded DNA is hybrid; this interaction is called hybridization. The interaction between the probe consisting of the oligonucleotide sequence and the target sequence is converted into an electrical signal that can be measured by the transducer system.

In the genosensor approach, DNA or RNA target is detected through the hybridization reaction between DNA or RNA and ssDNA sensing element, while in the aptasensor method, DNA or RNA aptamer, capable of binding to a target molecule with high affinity and specificity, plays the role of the receptor (Paniel et al., 2013).

Polymerase chain reaction (PCR), and other PCR-based methods are also applied for virus detection. PCR-based methods are more specific, sensitive, rapid, and accurate. The real-time PCR, multiplex PCR, and reverse transcriptase PCR (RT-PCR) were used for the detected viruses in various real samples. However, there is a limitation in terms of wrong distinguishing between viable and non-viable cells as DNA is present in both dead and alive cells(Paniel et al., 2013). Moreover, PCR requires thermal cycler which automatically adjusts temperatures for each of the steps, and it consumes longer reaction times (Bartosik et al., 2018). The sample is easy also contaminated.

Danielly S. Campos-Ferreira et al. (2013) developed an electrochemical biosensor by extracting DNA from patients with cervical cancer and studying synthetic DNA HPV 16 virus. L-cysteine was applied for electropolymerization to the gold electrode surface. The measurement is based on the methylene blue reduction DPV signal before and after hybridization between the HPV16 probe and the target DNA.A linear calibration range of 18.75 nM–250 nM was obtained, with a limit of the detection value of 18.13 nM. These results provide an alternative to existing analysis methods for detecting and diagnosing infection at an early stage by developing a new small, portable detection system for HPVs (Campos-Ferreira et al., 2013).

Martin Bartosik et al. (2016) developed an electrochemical chip in which target HPV DNA interacts with magnetic microbead-modified DNA probes. In the developed system, they followed the anti-digoxigenin-peroxidase response (Bartosik et al., 2016). Bartosik M. et al. analyzed the HPV16 and HPV18 DNA strands parallel with loop-mediated amplification (LAMP) using a magnetic bead-modified screen-printed electrode by amperometric measurement. It was applied to HPV-positive patient samples and cancer cell lines (Bartosik et al., 2018). Another researcher from Bartosik's research group immobilized biotinylated HPV16 DNA on the surface of functionalized magnetic microbeads with streptavidin. Then, after loop-mediated amplification of digoxigenin (DIG) labeled was immobilized to the surface, the antiDIG-HRP label was attached to the surface, and amperometric measurement was taken. Studies were carried out on 61 cervical tissue samples (Anton et al., 2020).

Lv et al. (2019) designed the electrode surface modified with carbodiimidazole and found the lower limit of detection of the HPV16-E7 DNA sequence to be 1 fM. To increase the sensitivity, the target HPV16-E7 DNA sequence was conjugated on a gold nanoparticle (GNP) (Lv et al., 2019). When we look at the previous studies, it was seen that no anti-DNA/RNA antibody was used, and no study on signal sensitivity was performed with an enzyme-conjugated with Horseradish peroxidase homopolymer.

Avelino K. et al. (2021) developed a nucleic acid biosensor with polypyrrole film and gold nanoparticles for HPV detection and found the calibration range to be 100 $pgmL^{-1}$- 1 $fgmL^{-1}$. LOD and LOQ values were obtained as 0.89 $pgmL^{-1}$ and 2.70 $pgmL^{-1}$ (Avelino et al., 2021). In another study by the same team, they developed a nanostructured platform based on the polyaniline matrix in the gold nanoparticle. The calibration range for HPV16 was 1 $pgmL^{-1}$-100 $pgmL^{-1}$, and the LOD value was 7.43 $pgmL^{-1}$(Avelino et al., 2020).

Campos-Ferreira S. et al. (2016), immobilized the guanine-free 23 mer HPV16 sequence cloned from the plasmid with a pencil graphite electrode to the surface. The HPV16 DNA biosensor was found in the linear range of 40–5000 $pgmL^{-1}$, and the diagnostic limit was 500 nM (Campos-Ferreira et al., 2016).

Farzin L. et al. (2020) reported that electrochemical HPV16 DNA determination was performed with the reduced graphene oxide immunosensor platform functionalized with amine-ionic liquids. The linear range was 8.5–10.7 nM, and the LOD value was 1.3 nM (Farzin et al., 2020). L. Civit et al. (2012) used an immobilization strategy consisting of a thiolated probe and a bipedal alkanethiol for the modification of the gold working electrodes. They worked with the HRP-labeled sandwich method to determine HPV16, HPV18, and HPV45. They found the working range between 0.1 and 10 nM and the LOD value to be 200 pM (Civit et al., 2012). Jimenez A.M. et al. (2016) have synthesized magnetic microbeads themselves as an alternative to commercial streptavidin-functionalized magnetic microbeads. They compared the biosensor developed with the HPV16 DNA chain analysis with the electrochemical and PCR method and found the performance of the electrochemical method to be higher (Jimenez et al., 2016).

3.2. CRISPR-based recognition assay

The clustered regularly interspaced short palindromic repeats (CRISPR)-Cas systems function in three distinct stages, namely: (1) adaptation, where new spacers are acquired from invasive elements for immunization; (2) crRNA biogenesis, where CRISPR loci are transcribed and processed into small interfering crRNAs; and (3) interference, where crRNAs guide the Cas machinery to specifically cleave homologous invasive nucleic acids(Barrangou, 2013). Cas proteins constitute a highly genetically polymorphic and functionally diverse family which is involved in the various steps of CRISPR-mediated immunity(Horvath and Barrangou, 2010).

The first CRISPR-based diagnostic method was designed in the presence of Cas9 variants that recognize double-stranded DNA (dsDNA). Many Cas9-based approaches have relied on detecting DNA, which is the

guided remodeling of cleaved proteins by catalytically inactive Cas9 partners (Zhang et al., 2017), Cas9-based extermination of PAM-containing sites(Bao et al., 2020; Pardee et al., 2016), and Cas9-induced unwinding of the non-targeted DNA strand as a targeting site for isothermal amplification. In CRISPR-based diagnostics, CRISPR-based collateral cleavage activity has been correlated with the target concentration. It can be found in the picomolar (10^{-12} M) -micromolar range (10^{-6} M). However, a lower LOD should be found and thus pre-amplification.

HPV strains cause persistent infections, such as cases of cervical cancer. An electrochemical sensor detects viral genetic material in a three-step process (Newsham and Richards-Kortum, 2021): firstly, extract viral genetic material, then amplify using loop-mediated isothermal amplification (LAMP) as an isothermal method and lastly, implement it in low-resource settings. LAMP products are correlated to a CRISPR-based recognition system. The system is activated with a target amplicon. Therefore, LAMP eliminates non-specific amplification. Methylene blue (MB) tagged oligonucleotides functionalized with Gold electrodes were used for the Cas12a enzyme deposition(Newsham and Richards-Kortum, 2021).

The genosensors and CRISPR-based recognition system were compared in terms of many aspects.

Genosensors show many advantages due to the complementarity of oligonucleotides such as sensitivity, specificity, and accurately. On the other hand, the small dimensions of the nucleic acids, large amount of sequences, and the nature of the attachment of the DNA/RNA probe make it difficult in terms of repeatability and stability(Babaei et al., 2022).

The CRISPR-based recognition system has tremendous potential to timely diagnosis of viral illness by providing a low-cost, portable equipment, and highly sensitive. It is an alternative recognition system to standard nucleic acid detection methods. Moreover, loop-mediated isothermal amplification (LAMP) was used to amplify the target DNA signal. LAMP products are added to a CRISPR-based recognition system that is activated in the presence of target amplicon, circumventing the challenge of nonspecific amplification associated with LAMP(Newsham and Richards-Kortum, 2021).

3.3. - *Aptamer-based biosensors*

Various biomaterials as selective recognition elements in biosensor development studies have been an important topic. Aptamers, in other words, synthetic antibodies, can be described as artificial single-stranded DNA or RNA oligonucleotides, and they have the advantage of in vitro selectivity (Song et al., 2008; Torres-Vázquez et al., 2022). Aptamer-based biosensors, aptasensors, have several significant advantages that enable their use in diagnostic analysis: Applicability for a wide variety of analytes (small molecules and macromolecules), high affinity and specificity properties, highly reproducible and pure in vitro synthesis process, flexible and versatile design for biosensor applications, highly selective and sensitive analysis opportunity. In vitro systematic Evaluation of Ligands by Exponential Enrichment (SELEX) process is used for the preparation of aptamers, and it can provide specific target sites. After the binding between aptamer and analyte occurs, aptamer's nucleic acid's single-stranded structure forms secondary and tertiary structures (Song et al., 2008; Torres-Vázquez et al., 2022; Wang et al., 2020).

Although aptamers are defined as synthetic antibodies and have the same function as antibodies in terms of binding to antigen, aptamers have unique advantages that make them preferred in some respects. For example; aptamers' chemical stability is higher compared to antibodies, thus this provides and advantage for the biosensor stability. Additionally, preparation of antibodies requires the use of an animal's immune system, hence it is not possible to obtain non-immunogenic target molecules. On the other hand, the SELEX process of aptamers provides a more versatile preparation approach for various targets (Song et al., 2008). However, aptasensors are still studied for further development. In this context, aptamer-based biosensors are widely utilized to determine human oncoviruses. Table 2 summarizes selected electrochemical aptamer-based biosensor applications.

Rahmati et al. (2021) (Rahmati et al., 2021) developed an electrochemical aptasensor for the detection of HCV core antigen based on N-doped carbon $NiCo_2O_4$ nanowires. Enhanced conductive and porous properties of nanowires with carbon layer provided an increased aptamer load and thus higher sensitivity for the developed aptasensor. Determination of HCV was performed in the linear range between 0.5 fg mL^{-1} and 0.12 pg mL^{-1} using the EIS method. The low LOD value and good recovery results in human blood serum samples demonstrated the accuracy, highly sensitive performance, and applicability potential for diagnostic analysis.

3.4. - *Immunosensors*

Immunosensors are bio affinity-based analytical sensing devices that use various immunochemical reactions for recognition. Antibodies have the ability to recognize antibodies, and there is a strong binding interaction between antigen and antibody; thus, it is possible to obtain enhanced sensitivity and selectivity for the detection of the target analyte. While designing an immunosensor, either antigen or antibody is immobilized on the surface (Brazaca et al., 2021; Felix and Angnes, 2018; Lu et al., 2021; Ricci et al., 2012). If it is not possible to observe the in vitro interaction between antigen and antibody, various labels (enzymes, fluorophore or chemiluminescent compounds, etc.) can be utilized (Felix and Angnes, 2018). Label-free immunosensors detect the binding between viral antigen/antibody and the biorecognition element of the sensor. On the other hand, label-based immunosensors focus on the detection of the label that indicates the antigen-antibody interaction (Brazaca et al., 2021; Felix and Angnes, 2018; Lu et al., 2021; Ricci et al., 2012). As it was mentioned above, aptasensors have some advantages over immunosensors, however, immunosensors are still highly preferred for the detection of oncoviruses as well-established and improved methods with new technologies. The use of various antibody fragments and novel nano-sized materials enable an advantageous approach in sensor applications (Arshavsky-Graham et al., 2022).

For the detection of viruses, electrochemical immunosensors are preferred as highly specific and sensitive options, and they enable low cost, faster and easier analysis without any sample preparation process compared to classic polymerase chain reaction (PCR) tests (Brazaca et al., 2021). Table 3 summarizes the selected immunosensor applications for the detection of oncoviruses.

Huang et al. (2020) developed an electrochemical immunoassay for the detection of Epstein-Barr virus capsid antigen IgA (EBVCA-IgA), a diagnostic biomarker for nasopharyngeal carcinoma using soft metal-phenolic capsule (sMPC). sMPC-based design of the probe provided ultra-high sensitivity performance with better selectivity. Along with the obtained ultralow LOD value of 0.46 fM, real sample application studies from the serum samples of nasopharyngeal carcinoma patients agreed with clinical data demonstrating the accuracy and applicability of the fabricated sensor. Additionally, the proposed immunoassay method is a simple option that has a potential application in diagnostics as a point-of-care device.

4. Conclusion and future perspectives

Today, the elucidation of cancer-related processes (prevention, diagnosis, and treatment approaches) is still an up-to-date topic for researchers in the medical, pharmaceutical, and biomedical fields. Considering the risk factors and incidence of oncoviruses, they are important in cancer research. In this context, when the studies in the literature in recent years are evaluated, it can be seen that various electrochemical sensor strategies come to the fore thanks to their advantages such as affordability, user-friendly application, high

Table 2
Selected applications of aptamer-based biosensors for detection of oncoviruses.

Target	Sensor	Method	Linear Range	LOD	Application	Recovery	Ref.
HCV core antigen	Apt/3D N–C@$NiCo_2O_4$ NWs/GCE	EIS	0.5 fg mL^{-1} – 0.12 pg mL^{-1}	0.16 fg mL^{-1}	Human blood serum	98%–103.6%	Rahmati et al. (2021)
HBsAg	GCE/rGO/Au/Apt/BSA	SWV	0.125–2.0 fg mL^{-1}	0.0014 fg mL^{-1}	Human serum	90.4%–104.15%	Mohsin et al. (2021)
Subtypes of HCV	mrGO-CuNCs/gold electrode	DPV	0.5–10 nM	405.0 pM	NA	NA	Li et al. (2020)
HCV core antigen	Apt[Anti]complex/MWCNTs-Chit/GCE	DPV	5 fg mL^{-1} – 1 pg mL^{-1}	1.67 fg mL^{-1}	Human serum	99.76%–99.89%	Ghanbari and Roushani (2018)
HPV-16 L1 protein	prGO/MoS_2-L_1	DPV	3.5–35.3 pM	1.75 pM	Human serum and saliva	95.2%–104.2%	Chekin et al. (2018)
HCV core antigen	BSA/Apt/QDs/GCE	EIS	10–70 pg mL^{-1} 70–400 pg mL^{-1}	3.3 pg mL^{-1}	Human serum	99%–103.4%	Ghanbari et al. (2017)

HCV: Hepatitis C virus, Apt/3D N–C@$NiCo_2O_4$ NWs/GCE: Aptamer loaded three dimensional N-doped carbon $NiCo_2O_4$ nanowires modified glassy carbon electrode, EIS: Electrochemical impedance spectroscopy, HBsAg: Hepatitis B surface antigen, GCE: glassy carbon electrode, rGO: reduced graphene oxide, Au: Gold nanoparticles, Apt: Aptamer, BSA: Bovine serum albumin, SWV: Square wave voltammetry, DPV: Differential pulse voltammetry, mrGO-CuNCs: magnetic reduced graphene oxide-copper nanocomposite, NA: Not available, MWCNTs-Chit: Multi-walled carbon nanotubes-chitosan nanocomposite, HPV: Human papillomavirus, prGO: porous reduced graphene oxide, MoS_2: Molybdenum sulfide.

Table 3
Selected applications of immunosensors for detection of oncoviruses.

Target	Sensor	Method	Linear Range	LOD	Application	Ref.
HBsAg	BSA/HBV mAb/poly(β-CD)/AuNPs/SPGE	Amperometry	10–200 μg mL^{-1}	0.17 μg mL^{-1}	Human serum	Teengam et al. (2021)
EBVCA-IgA	sMPC-based electrochemical immunoassay	ASV	1 fM – 1 nM	0.46 fM	Serum samples of nasopharyngeal carcinoma patients	Huang et al. (2020)
HBsAg	Au NPs/CS-Fc-AMWNTs immunosensor	Amperometry	1–250 ng mL^{-1}	0.26 ng mL^{-1}	Human serum	Chen et al. (2019)
HBsAg	GO-Fc-CS/Au NPs/GE	DPV	0.05–150 ng mL^{-1}	0.01 ng mL^{-1}	Human serum	Zhao et al. (2018)
HBsAg	Au electrode/Fe_3O_4- Ab_1/HBsAg/Ab_2-AuNPs-DNAzyme-MB	SWV	0.3–1000 pg mL^{-1}	0.19 pg mL^{-1}	Human blood serum	Alizadeh et al. (2017)
anti-HBc	HA–CNT/CGE	SWV	1–6 ng mL^{-1}	0.034 ng mL^{-1}	NA	Cabral et al. (2016)

HBsAg: Hepatitis B surface antigen, BSA: Bovine serum albumin, HBV: Hepatitis B virus, HBV mAb: Anti-HBV monoclonal antibody, β-CD: β-cyclodextrin, AuNPs: Gold nanoparticles, SPGE: Screen-printed graphene electrodes, NA: Not available, EBVCA-IgA: Epstein-Barr virus capsid antigen IgA, sMPC: Soft metal-phenolic capsule, ASV: Anodic stripping voltammetry, CS-Fc-AMWNTs: Chitosan- Ferrocene-Ammoniated multiwalled carbon nanotubes, DPV: Differential pulse voltammetry, GO-Fc-CS: graphene oxide-ferrocene-chitosan, GE: Gold electrode, SWV: Square wave voltammetry, anti-HBc: Hepatitis B core protein, HA-CNT: Hyaluronic acid–carbon nanotube hybrid, CGE: glassy carbon electrode.

sensitivity, and rapidness over other available techniques. HCV, HBV, and HPV are the mostly studied oncoviruses in the literature due to their incidence and prevalence. Also, the serious consequences they caused made them stand out for researchers. Aptamers-based sensors and immunosensors, thanks to their high selectivity, have been gaining an important place in the literature, especially for diagnostic purposes. Genosensors also appear as a method that provides more detailed information about the presence of the viral infection in the analysis. CRISPR technology, which is a relatively new approach, is preferred for oncovirus determination due to the DNA/RNA-based recognition ability and selectivity.

There are some disadvantages and challenges that need to be developed in biosensor studies. By increasing the repeatability and simplicity of the developed biosensors, integration into clinical applications should be provided. In addition, point-of-care devices should be more widespread. The immobilization issues for various materials such as biological recognition elements and nanomaterials should be overcome. In addition, many EC assays are still not compared to standard methods of detection, which is a crucial step when evaluating their performance in clinical settings. This is a situation that negatively affects the reliability of the developed sensor and needs to be worked on.

Future perspectives of electrochemical biosensors are mainly detection of sensitivity, specificity, and lowness of price. These parameters are important for high-quality sensing. The modern era needs a combination of technological and biological ways for increasingly advanced devices. Therefore, the current use and correct application of aptamers, peptides, and other biomarkers in sensor technology are crucial for accurate and rapid detection of oncoviruses. The developed biosensors will be important for the detection of oncoviruses without damaging the metabolism and physiological structure. Fast, real-time, and highly sensitive biosensing sensors must be miniaturized to be portable and easy to implement. Increasing applications of point-of-care (POC) devices and lab-on-chip (LOC) applications will be important. Moreover, the forward economic perspective of POCs and LOCs accelerates the growth of such devices. However, issues such as toxicity, reproducibility, environmental friendliness, and sustainability still remain to be addressed. While there are still some obstacles to obtaining inexpensive, eco-bio-friendly, sustainable, and reproducible POCs and LOCs, it can be hoped that they will be overcome in the near future thanks to their enormous potential. The sensor's applicability to smartphones, tablets, and portable electronic devices will also be very beneficial in terms of rapid analysis and early intervention.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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