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Colorimetric biosensors for point-of-care virus detections

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ABSTRACT

Colorimetric biosensors can be used to detect a particular analyte through color changes easily by naked eyes or simple portable optical detectors for quantitative measurement. Thus, it is highly attractive for point-of-care detections of harmful viruses to prevent potential pandemic outbreak, as antiviral medication must be administered in a timely fashion. This review paper summaries existing and emerging techniques that can be employed to detect viruses through colorimetric assay design with detailed discussion of their sensing principles, performances as well as pros and cons, with an aim to provide guideline on the selection of suitable colorimetric biosensors for detecting different species of viruses. Among the colorimetric methods for virus detections, loop-mediated isothermal amplification (LAMP) method is more favourable for its faster detection, high efficiency, cheaper cost, and more reliable with high reproducible assay results. Nanoparticle-based colorimetric biosensors, on the other hand, are most suitable to be fabricated into lateral flow or lab-on-a-chip devices, and can be coupled with LAMP or portable PCR systems for highly sensitive on-site detection of viruses, which is very critical for early diagnosis of virus infections and to prevent outbreak in a swift and controlled manner.

Contents

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1. Introduction

An infectious virus particle is made up of nucleic acid and an outer shell of proteins. Most viruses have either DNA or RNA genetic material to encode for proteins. Although a virus does not reproduce on its own, after it infects a host cell, a virus is able to direct the cell machinery to produce more viruses [1]. Viruses can be inherited through parental transmission, or spread in many ways quickly through air, water, food, saliva, blood, animal bite, or contact, etc. Over the years, mankind has been battling many different types of viruses, which is the cause of most infectious diseases for human, animals and plants, and resulting loss of finance, health, and lives. A very recent example is the outbreak of African swine fever virus (ASFV) in China, within 4 months more than 100 cases emerged, with more than 600,000 pigs culled in 22 provinces from August 2018 to December 2018 (https://www.abc.net.au/news/2018–12-18/african-swine-fever-spreads-across-china-pork-prices-to-rise/10626688). Existing testing techniques employed for detection of viruses have extremely long turnaround time ranging from 2 to 14 days, which is unable to combat for virus that spreads rapidly. The costs of existing tests are also expensive [2].

It is important to have capability to detect presence of viruses in an effective manner. Hence, the detection of viruses through colorimetric test is incredibly useful [3–6], as the human eye easily identifies a change in color to determine whether a specific virus is present, so as to prevent its spread. Meanwhile, color change is also easy to be detected using a simple camera or intensity based optical detector, with relatively simple algorithms to quantify test results in an inexpensive and instant way.

In the future, as viruses mutate into stronger forms, it is necessary for humans to be more prepared by developing sophisticated and easy-to-use detection systems to identify viruses and to keep viruses at bay. As shown in Fig. 1, this paper reviews in detail about existing colorimetric bioassays for virus detections, to compare their pros and cons for various methods on virus detections, such as loop-mediated isothermal amplification (LAMP), nanoparticles, polymerized polydiacetylene, gene expression reaction, etc., with an intention to shed a light on selection of a suitable colorimetric detection method for different types of viruses.

2. Loop-Mediated isothermal amplification (LAMP)

Loop-mediated isothermal amplification (LAMP) was developed for DNA detection by Notomi in 2000 [7]. LAMP is a simple, yet fast, selective and efficient virus detection method that amplifies DNAs using DNA polymerase, being carried out in isothermal conditions with no complex lab equipment needed [7–10]. The LAMP results are also highly repeatable and accurate [8]. LAMP is highly selective as the target DNA sequence can be recognized by six distinct sequences, then followed by another four [7]. Its high efficiency is due to the use of a single-step test tube at around 60–65 °C for approximately thirty minutes [11–14]. The single step LAMP is obtained by combining reverse transcripts of RNAs with LAMP [15]. The reaction time for LAMP is very fast at just ten minutes [11], which enables the total time required for the entire LAMP process to be from fifty [12] to sixty minutes [13].

2.1. Details of LAMP

Originally designed by Notomi (2000), four sets of primers are used to recognize six distinct sequences on the target DNA of the virus [7,16]. The four primers are two forward inner primers and two backward inner primers for first and second stages of the process respectively [12]. These primers are designed to be specific to the virus detected [15–17], such as a particular protein gene on the virus coat [18]. However, one can use five or six primers as well [14]. In the event when five primers are used, the primers consist of two inner primers, two outer ones and one loop primer [15]. Additionally, six primers are frequently used for the virus detection to be even more selective and efficient [12,14,19]. The six primers will be two inner primers, two outer primers and two loop primers [19–21]. LAMP primers can be designed by software such as Primer Explore V4 [22].

During the LAMP process, the inner primer first initiates the detection of the target DNA [7], where one particular gene of the virus is targeted by the LAMP [15]. Next, an outer primer discharges a single strand DNA (ssDNA), which is used as a template for DNA synthesis [7]. Afterwards, the second inner and outer primers prime that particular ssDNA [7]. A stem-loop DNA structure is then produced, hence yielding the original stem-loop DNA and a new stem-loop DNA, thus forming a DNA stem twice as long as

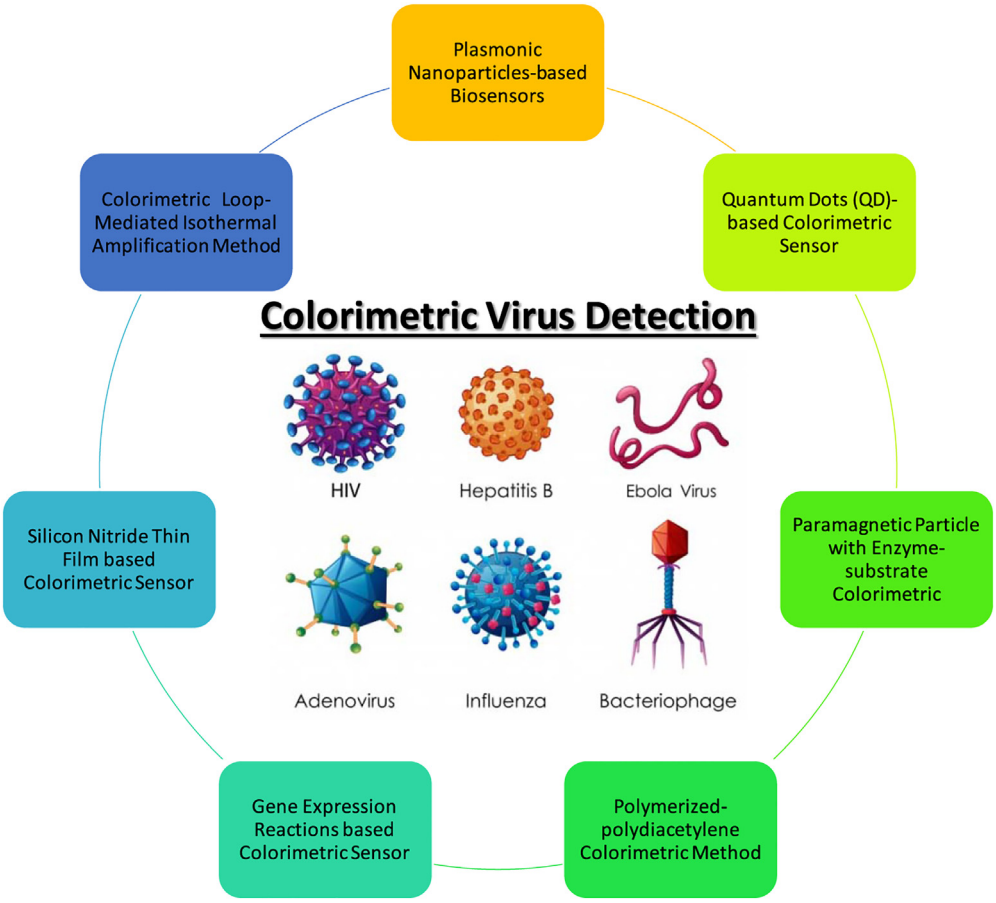

Fig. 1. Overview of existing technologies for colorimetric virus detection.

the original [7]. This is when the primers amplify the DNA [13]. This cycle continues until 10^9 stem-loop DNA have been formed, usually taking less than one hour [7]. The amplified sequence is made up of several inverted repeats and multiple loops formed by annealing between alternately inverted repeats of the original DNA strand [7]. DNAs can be amplified up to 10^{39} times [10].

2.2. Methods for measuring LAMP by color change

For naked eye to observe change of colors [13], one can use SYBR Green I, hydroxynaphthol blue (HNB) or propidium iodide. It also can be detected by color change caused by gold nanoparticles (AuNP) probes, which will be introduced in the Section 3.

SYBR Green I solution turns from orange to green [19]; HNB solution is blue for positive reactions and purple for negative reactions [14]; and propidium iodide turns pink in positive reactions or orange in negative reactions [14,23].

2.2.1. SYBR Green I and Picogreen

SYBR Green I is a DNA-intercalating [10] fluorescent dye that changes color [24] after being stained by nucleic acids [25], hence it is able to visualize the existence of viruses after LAMP occurs [11]. SYBR Green I quenches in free-state having an intrinsic intramolecular origin. The greater than 1,000-fold observed SYBR Green I fluorescence signal enhancement is caused by dampening of its intra-molecular motions when a forming complex with DNA, especially double strand DNA (dsDNA) [26]. SYBR Green I dye is tested to have the same results as electrophoresis to give good quality color change [27]. Picogreen is a tertiary amine and also has a 1000 times enhancement of fluorescence upon binding to DNA [28]. Commercial Molecular Probe Picogreen is similar to SYBR Green I and also binds to dsDNA [29–32].

2.2.2. Acridine orange

Acridine orange is a dye that improves the effect of the LAMP's visually detection of viruses, and it is most effective in infectious spleen and kidney necrosis viruses (ISKNV) in fishes [14]. A key advantage of acridine orange is that it is cheaper than other dyes such as SYBR Green I and calcein dye. It also does not require any special lighting or expensive equipment. When acridine orange is used, it turns yellow to indicate presence of virus; otherwise, it remains orange in absence of the virus that is to be detected [14].

2.2.3. Hydroxynaphthol blue (HNB)

The HNB dye is a metal ion binding indicator dye, which changes color from violet to sky blue when the reaction is positive [10]. The HNB dye can be easily employed by incorporating it into the monitor assay, and the dyes were added in the reaction mixture prior to LAMP reaction [10,33,34].

2.2.4. Propidium iodide

Propidium iodide a type of fluorescent dye that binds to DNA. When the propidium iodide was added to LAMP reaction products, without UV illumination, the negative reaction tube was deep red–orange while the positive tube showed light (almost clear) pink. This can be used to distinguish the presence of viruses in LAMP reactions. When UV illumination was shed on the tubes, only the positive one showed bright transillumination [23].

2.2.5. Change in turbidity

The presence of virus is shown by an increase in turbidity due to pyrophosphate ion attained from LAMP that causes white magnesium pyrophosphate precipitate to form in the assay [10,21,35–38]. The higher turbidity is caused by a larger amount of amplified products that leads to a larger amount of white magnesium pyrophosphate precipitate, hence forming a more cloudy solution with higher turbidity [12].

2.2.6. Agarose gel electrophoresis (AGE) with dyes

Agarose gel electrophoresis (AGE) is a color changing technique that can be used for detection of DNA or RNA, where 2% AGE is commonly used [9,10,12,36,39,40]. In order for AGE to occur, it requires UV light for transillumination and strained with ethidium bromide, but ethidium bromide is carcinogenic [9], and this result cannot be directly seen by naked eye [41]. Hence, AGE needs to be subsequently stained by dyes such as SYBR Green I for the color-change to be observed [8,41].

2.2.7. Calcein

Calcein is a type of dye that is made up of a metal ion that binds to fluorophores. It is able to cause a change in color of the fluorophore, therefore indirectly causes a color-change that in the assay [42].

2.2.8. Other methods

Other methods that can produce color changes for eye inspection include colorimetric dot-blot hybridization [43], lateral flow [44–48], electrochemical DNA chip functionalized with oligo-DNA probes [49], cationic polymer-mediated precipitation of fluorochrome-labeled oligo-DNA probe [50], alternatively binding quenching probe competition assay [51], polyacrylamide gel-based microchamber [52], and fluorescent resonance energy transfer (FRET) [53].

2.3. Limitations of LAMP

The key limitation of LAMP is that it can be too sensitive, which leads to false positive results from carry-over or cross-contamination during the entire course of experiment [54].

When LAMP amplicons were analyzed after the LAMP reaction, the products might possibly be cross contaminated resulting from cis and trans priming among the oligonucleotide primers, and cause non-specific detection of LAMP amplicons [43,55–57]. Real-time LAMP detection by turbidity, alternatively binding quenching probe competition assay and FRET will minimize such non-specific binding [53]. There is also the need to design specific primers to target specific genes in the virus, which may require some time for each set of primers for a specific virus to be designed and synthesized.

2.4. Applications of LAMP

LAMP has a large array of applications in detecting different types of viruses. The types of viruses that currently have been detected using the LAMP include but are not limited to the following:

(1) For human: severe acute respiratory syndrome coronavirus (SARS-CoV) [58,59], dengue viruses [60,61], hepatitis A viruses [12], hepatitis B viruses [7,8], hepatitis C viruses [62], human severe fever of bunya viruses with thrombocytopenia syndrome (SFTS) [63–65], influenza A H1N1 viruses infecting human [34], Zika [48], Enterovirus 71 for human hand, foot, and mouth disease (HFMD) [66], human immunodeficiency virus 1 (HIV-1) [30], Zaire ebolaviruses [67], rotaviruses in fecal samples for acute viral gastroenteritis [68].
(2) For arthropod: Chikungunya viruses [11] and arthropod-borne West Nile viruses [69].
(3) For fish and other marine animals: koi herpes viruses [19,70,71], lymphocytis disease viruses for fish [54], infectious hematopoietic necrosis viruses (IHNV) in rain-bow trout [72], viral hemorrphagic septicemia viruses [73], infectious spleen and kidney necrosis viruses (ISKNV) in fishes [14,74], cyprinid herpesvirus 2 (CyHV-2) [75,76], cyprinid herpesvirus 3 [77,78], Edwardsiella tarda in fish [79], Francisella piscicida in Atlantic cod [80], iridovirus in fish [36,81,82], white spot syndrome virus in shrimp [44,83–85], shrimp yellow head virus (YHV) [86,87], Taura syndrome virus (TSV) in shrimp [88], shrimp infectious myonecrosis virus (IMNV) [89,90], infectious hypodermal and hematopoietic necrosis virus (IHHNV) in shrimp [91,92], Penaeus monodon nucleopolyhedrovirus (PemoNPV) for shrimp [93], macrobrachium rosenbergii nodavirus (MrNV) and extra small virus (XSV) in prawn [94], acute viral necrobiotic virus in scallop [95], soft-shelled turtle iridovirus [96], abalone herpesviruses [39], mud crab dicistrovirus-1 [27], and ostreid herpesvirus 1 (OsHV-1) DNA [97].
(4) For birds and chicken: subgroup A and subgroup J of avian leukosis viruses [35,98], avian H5N1 viruses [99], infectious bursal disease viruses (IBDV) [15,100], chicken infectious anemia virus (CIAV), reticuloendotheliosis virus (REV) and Marek's disease virus (MDV) [100].
(5) For other living stock: batai virus in cattle [101], bovine parvovirus [102], capripoxvirus [10], porcine boca-like viruses [24], porcine reproductive and respiratory syndrome virus (PRRSV) [103,104], porcine hokoviruses [9], foot-and-mouth disease (FMD) virus for living stocks [29], camelpox viruses [13], duck circoviruses [105], duck hepatitis A viruses [41], and sacbrood viruses [25].
(6) For plants: potato leafroll viruses [18,106,107], tomato leaf curl New Delhi virus-[potato] [108], grapevine leafroll viruses [22], curly top virus in plants [109], and maize chlorotic mottle virus (MCMV) [110].

2.5. Benchmark of LAMPs to polymerase chain reaction (PCR)

Although PCR can be too time consuming, labour intensive, highly specific and sensitive [83] compared to LAMP for virus detection [19,111], PCR is still a common and recommended detection method for viruses [111,112], as it is a tried-and-tested detection method for viruses compared to LAMP that is relatively new. There two main types of PCR, namely conventional PCR and reverse transcript-PCR (RT-PCR). Additionally, there is also the option for real-time quantitative PCR (qPCR) and digital PCR for quantification of DNA copies, but these two types of PCR are quite expensive.

2.5.1. Conventional PCR

Conventional PCR is the original PCR method that produces copies of DNA using thermal cycling, where the assay is heated at different temperatures and at selected timings [111]. The reason for the use of thermal cycling is because heat is required to promote more effective DNA synthesis for PCR to have higher sensitivity when DNA concentration is low [19]. The PCR process is made up of two steps that are carried out in two different test tubes, where one test tube is used for amplification of the DNA and the second test tube is used for detection of the virus DNA [113].

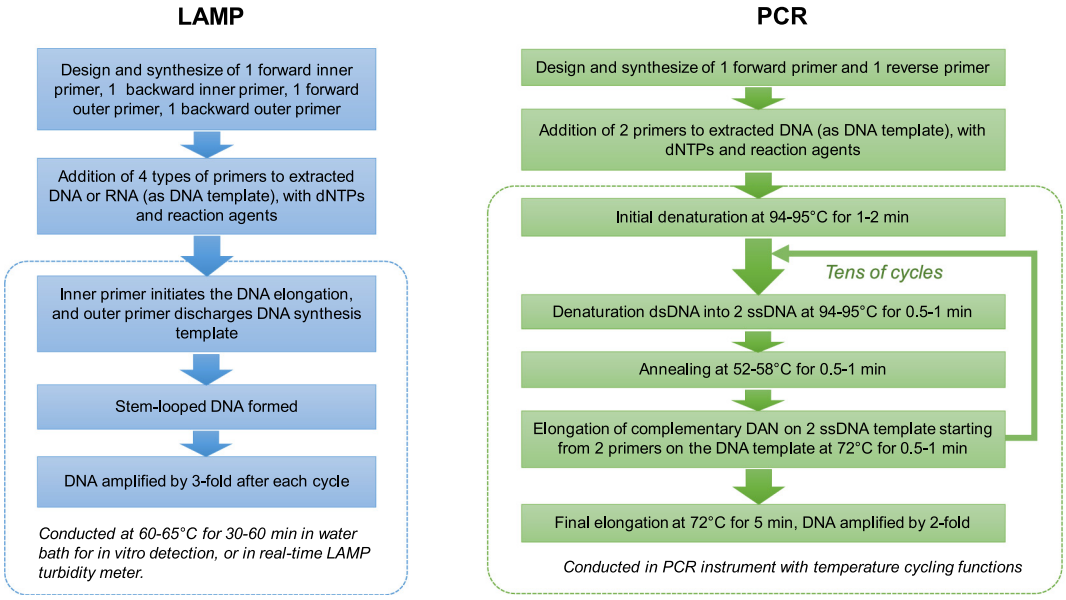

Fig. 2. Comparison of LAMP and PCR processes. Further, for real-time quantitative PCR, DNA probes with one-end of quencher and one-end of fluorescent dye are added. For RNA detection in PCR, complementary DNA of the RNA shall be synthesized. For one-step RNA-PCR reaction, enzyme will be further added in PCR reaction tube.

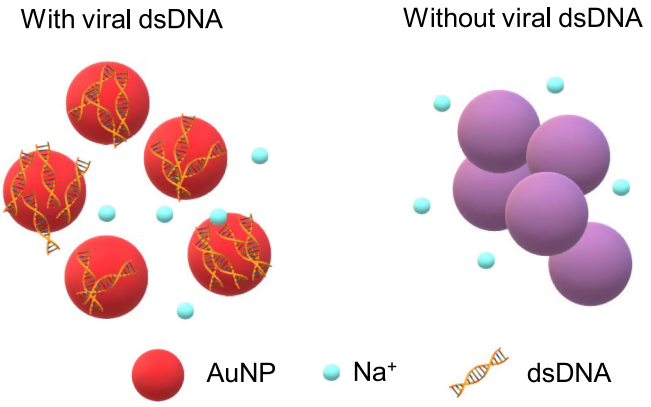

Fig. 3. Principle of gold nanoparticles to change color for detection of dsDNA with the existence of salt.

2.5.2. Reverse Transcription-PCR (RT-PCR)

RT-PCR is slightly different from conventional PCR. During RT-PCR, heat and reverse transcriptase release the viral DNA during reverse transcription. This results in a much faster amplification speed and higher sensitivity to a small amount of DNA, compared to the conventional PCR method [111]. As a result, it can be carried out on very small sample concentrations [113]. Additionally, the RT-PCR method is more straightforward for its users compared to conventional PCR, as RT-PCR is performed in a single step [111], that a single test tube is used for the entire RT-PCR process [11,111]. The PCR product is detected during the exponential period of the reaction, such that amplification and detection is able to take place in a single step, so that there is no need for two separate test tubes for amplification and detection respectively [113].

2.5.2.1. Limitations of PCR. The PCR method has its limitations. Firstly, PCR requires higher costs due to the use of expensive consumables and expensive lab equipment [54]. The expensive equipment required includes the thermal cycler, the electrophoresis tank and the UV illuminator [21]. The PCR method of detection is also complex and time consuming, requiring expensive reagents [114]. A key reason for complexity of PCR is due to the thermal cycles required for PCR to take place [54].

2.5.2.2. PCR versus LAMP. PCR and LAMP methods are of similar nature, as it involves the amplification of virus DNA, which subsequently leads to a color-change in the monitoring assay. Fig. 2 compares the process of LAMP process [7,35,36] and PCR process [41,111].

First and foremost, LAMP does not require use of such expensive consumables and expensive lab equipment that PCR requires [8], hence LAMP is more cost effective to carry out. Secondly, LAMP is applicable to RNA upon use of reverse transcription-coupled LAMP (RT-LAMP), demonstrated with detection of prostate-specific antigen mRNA in one PSA-expressing cell mixed with 1 million PSA-negative cells [7], detection of foot-and-mouth disease (FMD) virus RNA for pigs at a detection limit of 10 copies [29]. Furthermore, LAMP is more time efficient and generates faster results [19]. This is because the duration of the LAMP experiment is less than one hour, while the PCR method takes at least three hours for the results to be generated [10,11]. Lastly, the LAMP is just as sensitive, compared to quantitative real-time qPCR [9,10,54], but it is 10 [9,11,27] to 100 times more sensitive than conventional PCR [27,39,41], depending on the applications of the LAMP on different viruses. LAMP can also be used for real-time DNA quantitative analysis by measuring time-to-positive of fluorescent signals, and it shows a linear detection for HBV up to 8 orders of magnitude at a lower detection limit of 210 copies/mL [8].

3. Nanoparticles for virus detections

Recent studies have proven that nanoparticles can be used as colorimetric probes to develop versatile biosensors (also known as nanobiosensors) for virus detection [115–121]. This is largely designed based on the unique optical properties of the particular nanoparticles that can cause obvious color changes for naked eye detection or quantitative measurement by simple optical detector. As presented in Fig. 3, the major principle for plasmonic nanoparticles to change colors is based on plasmonic effect. When the gold nanoparticles (AuNPs) are protected with surround dsDNA or virus,

the nanoparticles will be dispersed in the solutions even with salt added and present as red solution due to the plasmonic absorption of the dispersed AuNPs. However, when the coating of dsDNA or virus around the AuNPs is missing, salt will cause the AuNP to aggregate and shift the absorption peak to change the solution color from red to purple.

3.1. Unmodified gold nanoparticles (AuNPs)

Unmodified AuNPs have been reported to detect RNA of hepatitis C viruses (HCV) [122], cyprinid herpesvirus-3 (CyHV-3) virus [123], bovine viral diarrhea virus (BVDV) [124,125], cucumber green mottle mosaic virus (CGMMV) [126], maize chlorotic mottle virus (MCMV) [127], and spring viraemia of carp virus (SVCV) [128]. This is because the presence of the virus RNA causes coagulation of AuNPs. Due to surface plasmon resonance effect, when the AuNPs aggregate, the solution turns from red to blue as the absorption and scattering peaks shift. In the absence of virus RNA, the single strand DNA (ssDNA) primers added into the bioassay uncoil and expose their nitrogenous bases to form attractive electrostatic forces between the bases and AuNPs [122,123]. Subsequently, the ssDNA primers attach to the AuNPs, where these primers coat the AuNPs to stabilize them, causing dispersed AuNPs remain red [122]. On the other hand, in the presence of virus RNAs, the ssDNA primer attaches to the RNA to form double strands [122]. Since there are no primers to stabilize the AuNPs, the AuNPs aggregate and the bioassay solution turns from red to blue, as the absorption and scattering peaks shift to longer wavelengths [122,123,129].

Hepatitis C virus antibody (anti-HCV) is also detected by unmodified AuNP aggregation induced by acetylcholinesterase-catalyzed hydrolysis reaction. The color of AuNP can be observed by naked eye at a detection limit of 10^{-13} g/mL anti-HCV [130]. Furthermore, unmodified AuNP was demonstrated for dengue virus detection based on peptide nucleic acid (PNA)/DNA hybridization [131]. Unmodified AuNPs undergo immediate aggregation and show purple color in the presence of neutral charge PNA due to the coating of PNA on AuNPs surface. However, complementary DNA targets will hybrid with the PNA probe and form negatively changed complexes which repulse and disperse the AuNPs to form a red color solution. The detection limit for target DNA was 0.12 μM at PNA:DNA ratio of 1:0.01 [131].

3.2. Functionalized gold nanoparticles

AuNPs are also functionalized in order to leverage color change caused by the surface plasmon resonance effect phenomenon, and then applying it to various types of viruses. Functionalized AuNPs as probes for virus detection usually lead to better virus specificity than the unmodified AuNPs.

3.2.1. Functionalized with antibody

Antibodies can be used to functionalize AuNPs for the AuNPs to be responsive to specific viruses. For instance, influenza A viruses (IAV) can be detected by aggregation of AuNPs around the IAV [132]. There is then plasmon coupling between neighbouring AuNPs to shift the peak of the adsorption spectrum to a longer wavelength, thus causing the solution to change color from red to purple. This is able to occur in the first place as antibodies (Ab) can be attached to AuNPs and the Ab has an affinity for antigens on the IAV [132].

3.2.2. Functionalized with peptide

Peptides can be functionalized onto the surface of AuNP for detecting viruses. These AuNPs are bound to cysteinylated virus-specific peptides (peptide-Cys) using the strong sulfur gold bonding [114]. In order for AuNP-peptides to detect the presence of virus, the AuNPs should surround and aggregate around the virus. The peptides used are specially designed and employed as an alternative to antibodies and they offer better affinity to the targeted virus and thus ensuring higher sensitivity [114]. In the presence of the virus, the bioassay changes color from bright red to purple, as AuNP-peptide-virus complex causes aggregation of AuNP around virus, hence the absorption and scattering peaks shift to longer wavelengths [114].

3.2.2.1. Functionalized with polyethylene glycol (PEG) and sialic acid. The AuNPs are also functionalized by coating with a layer of thiolated PEG and α2,6-thio-linked sialic acid to form glyconanoparticles, which are able to detect the difference between human and avian influenza viruses based on surface plasmonic resonance effect of the AuNPs [133]. For instance, in the presence of influenza virus, glyconanoparticles aggregates around the influenza virus to cause a shift in peak intensity from 525 nm to 536 nm, hence experiencing a small change in color [133]. The AuNPs are also able to detect viruses with only sialic acid (SA) functionalization without PEG layer. The SA layer on AuNP surface prevents AuNP aggregation in solution. In the presence of influenza B viral particles, single AuNPs can attach to hemagglutinin on viral particle surface, shortening the distance among the AuNPs and leading to a change in absorption spectra [134].

3.3. AuNP combined with LAMP

Besides on its own, AuNP can be used in conjunction with LAMP to detect viruses. In this colorimetric change virus detection method, LAMP is first used to amplify the existing DNA of the virus, such that there will be sufficient DNAs, which is followed by a possible color-change of AuNPs in salt solution [83,135]. It is reported that in the presence of white spot syndrome viruses (WSSV), the AuNPs will not aggregate in salt solution [83], because the WSSV LAMP amplified products will interact with the single strand DNA (ssDNA) probes surrounding the AuNPs and stabilize the AuNPs to prevent aggregation from occurring, causing the solution to remain red. On the other hand, in the absence of the virus, the AuNPs aggregate due to the screening effect of the salt solution, where salt is added to induce the aggregation reactions. The higher the concentration of salt added, the more intense the color change that will be observed [83,135]. Other viruses that can be detected using this method include Taura syndrome virus (TSV) [135] and high-risk human papillomarvirus (HR-HPV) [1], and caprine arthritis encephalitis virus (CAEV) [136].

Colorimetric reverse transcription (RT)-LAMP-AuNP assay is also reported for detecting shrimp yellow head virus (YHV) and shrimp infectious myonecrosis virus (IMNV) through RNA sensing [86,89]. In the presence of RT-LAMP target DNAs, the ssDNA labeled AuNP probes will still remain dispersed showing a pink color solution despite the addition of salt, while the absence of the RNA target, ssDNA-AuNPs will start to aggregate and turn into purplish solution. The assay takes about 1 h to detect YHV RNA at 1 pg of RNA detection limit [86], and 50 min to detect IMNV RNA at 10 pg detection limit [89], determined by UV–Vis spectrum of AuNP solution.

3.4. AuNP combined with ELISA

Enzyme-linked Immunoassay (ELISA) is able to detect viruses through antigen and antibody. The ELISA setup is by application of viruses to the plates, such that their antigens absorb onto the surface of the plate. This is followed by application of antibodies that have an affinity to the antigens of the virus, then enzymes are added to produce a signal, which is often in the form of a color change [137]. Compared with ELISA, nanoparticle based

colorimetric assay has less steps and is much faster in detections, and tends to be more sensitive because it is more flexible to amplify the signals.

Besides ELISA, enzymes can also be combined with metallic nanoparticles and silver solution to detect viruses through observing a color change [138]. One such example is the detection of the avian influenza virus (AIV) that carried out using an enzyme-induced metallization based on the amplification of enzymatic reaction using the optical properties of metallic NP, such as AuNPs, where enzyme-induced silver deposition occurs on the surface of the AuNPs to cause color change in the presence of AIV [139].

3.5. Lab-on-chip based on AuNP

The detection of the H1N1 virus can be conducted on a lab-on-chip and through a colorimetric immunochromatographic strip (ICS) detection and reverse transcription PCR to amplify the genes necessary for the color change to be observable by naked eye [140]. The color change involves the use of AuNPs, and streptavidin (SA)-biotin interaction, where the red color of the AuNPs determines the presence of H1N1. The color-change is due to the surface plasmon resonance effect of AuNPs.

In the presence of H1N1 virus, amplified virus DNA and biotin moieties are attached onto the AuNPs through the affinity of antibody and antigen. The bioassay then runs through the test strip and SA-biotin interaction occurs, biotin on the AuNP bonds with SA and causes the strip where SA locates to become red. When H1N1 virus is absent, the area of the strip where SA locates remains colorless. The lab-on-a-chip system developed is highly sensitive with portable microdevice to control heating and cooling of the chip with PCR amplification. Thermal cycling occurs in the microdevice, where a heater increases temperature and a fan to cool the temperature. The portable system enables on-site colorimetric pathogen identification within 2.5 h at a sensitivity of 14.1 pg RNA templates [140].

Similar lateral flow device is developed for detection of Tamiflu-resistant virus, which is based on the fact that oseltamivir hexylthiol (OHT) has higher binding affinity for Tamiflu-resistant virus than Tamiflususceptible virus [141]. AuNPs modified with OHT are used as nanoprobes for Tamiflu-resistant virus detection. In the presence of Tamiflu-resistant virus, the OHT-AuNPs will change their color from red to purple because of AuNP aggregation caused by strong interactions between OHT and neuraminidase (NA) on the surface of the Tamiflu-resistant virus. The color change allows determination of the Tamiflu-resistant virus with the naked eye at a limit of 10^4 PFU/mL, thus supporting the selection of appropriate treatments using point-of-care diagnostics [141].

3.6. Gold nanorods (Au NR)

Au NRs can be used to identify lysine amino acid of specific viruses. This detection occurs when a chain of Au NR connected to one another at their ends is formed in the presence of 11-mercaptoundecanoic acid (MUA) [142]. This is because the MUA is able to modify the ends of the Au NR by binding to the Au NR ends, such that the MUA interacts with each other to cause Au NR to be able to self-assemble by joining to other Au NR end-to-end.

There is color observed when light is incident onto the bioassay of Au NR. This is due to the longitudinal plasmon resonance absorption of the Au NR. In the presence of viral lysine, the COO^- group in MUA interacts electrostatically with the NH^{3+} group of lysine, hence there is no MUA at the Au NR ends. This results in the long chain separating to form an assay of dispersed Au NR, which leads to a shift in the absorption spectra from the initial red to blue in the presence of virus lysine. Longitudinal plasmon resonance is used instead of transverse plasmon resonance due to the difference in wavelength, as the change in wavelength in the longitudinal direction is easily observable in the visible light spectrum [142]. In this work, Eu^{3+} is added because it causes a more obvious color change to be observed compared to using other molecules or ions.

3.7. Silver nanoparticles (AgNPs)

Similar to AuNPs, silver nanoparticles (AgNPs) will also undergo color changes (yellow to orange) due to the localized surface plasmon resonance (LSPR) effect. For example, DNA-functionalized AgNPs and AuNPs are used in combination to detect the Kaposi's sarcoma-associated herpesvirus (KSHV). As both the AgNP and AuNP are simultaneously used, two independent color changes occur depending on the DNA targets [143]. Prior to the detection experiment, oligonucleotide sequences need to be fabricated based on vCyclin protein (a KSHV protein known to express itself both during the latent and lytic viral phases) found in the KSHV [143]. These oligonucleotides form oligonucleotide-NP complexes that are stable, and thus no color change is observed when there is no virus in the biosamples. However in the presence of KSHV, the oligonucleotide-NP complex cannot be formed, so the AuNPs aggregate and the biosample solution turns into a murky yellow-orange color, which is the color of AgNP solution [143].

3.8. Quantum dots (QD)

QDs nanoparticles are semiconducting materials. They are fluorescent and give off photons of a particular wavelength, and have many applications in virus detection as fluorescent labels [144–149]. However, QDs can be modified and used together with other nanostructures to detect viruses by observing for likely color change of a bioassay based on QD-Ru droplet [150]. With the formation of luminescence colorimetric droplets made up of water soluble QDs and Ru(bpy)2dppx2+ (Ru), double-stranded DNA (dsDNA) of viruses can be detected (shown in Fig. 4). Both QDs and Ru are fluorescent emitters. When there is no dsDNA, the electrostatic interaction makes Ru close to QDs and suppresses efficiently the fluorescence QDs and Ru, so the droplets appear dark green. However with the addition of dsDNA, dsDNA competes with QDs for Ru, which leads to the QD green fluorescence restored and red fluorescence emitted by Ru, causing the droplet in a mixed dark yellow color [150]. As the concentration of dsDNA present increases, greater intensity of color change is observed, as more dsDNA competes with QDs for bonding with Ru, fewer QDs are suppressed and a more intense yellow is observed [150].

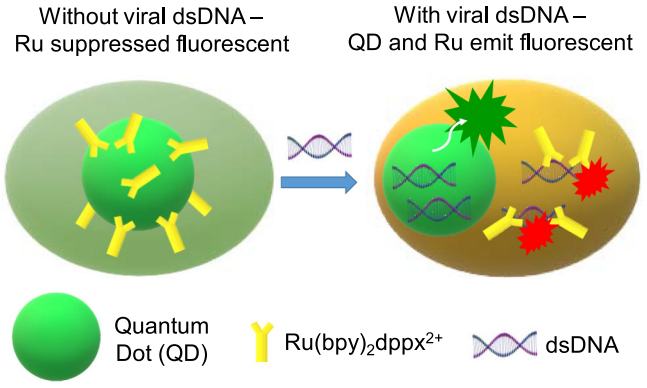

Fig. 4. Principle of Ru suppressed fluorescent emission and the dual fluorescent restoration caused color change.

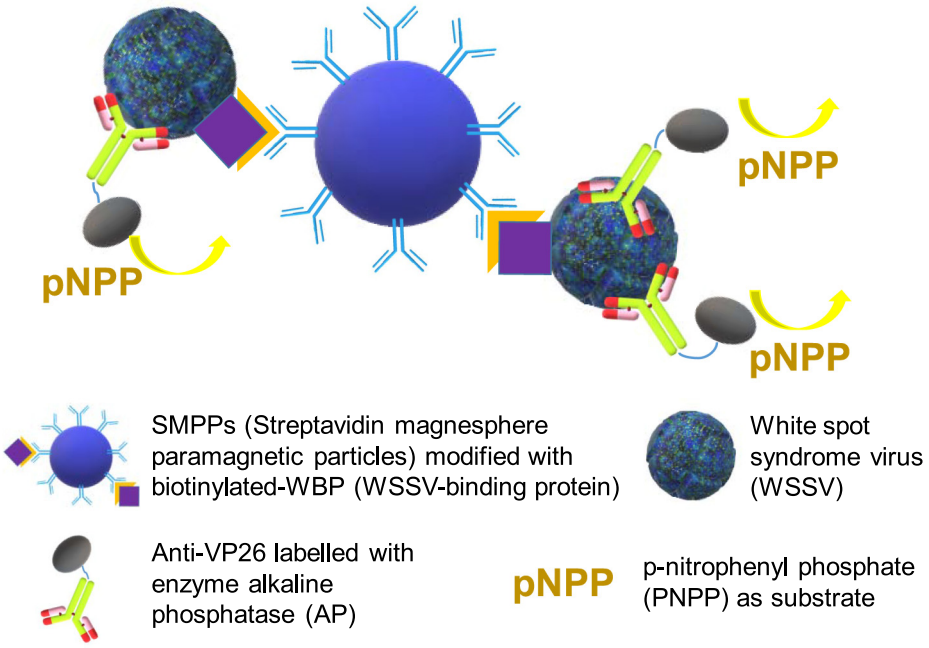

Fig. 5. Paramagnetic particle with enzyme-substrate colorimetric for white spot syndrome virus (WSSV).

3.9. Paramagnetic particles

Superparamagnetic particles can be used for color-change detection of viruses via enzyme-substrate reaction. One such example is that paramagnetic particles can be used to detect the presence of virus. White spot syndrome virus (WSSV) in shrimp is a virus that can be detected using anti-glutathione S-transferase-VP26 (anti-VP26) and WSSV-binding protein (WBP) together with modified streptavidin magnesphere paramagnetic particles (SMPPs) [151]. As illustrated in Fig. 5, biotinylated WBP is immobilized on SMPPs by biotin-streptavidin combination. WSSV will be bound to SMPPs by WSSV-WPB recognition. In each step, SMPPs can be trapped inside the test tube, for unbound molecules to be washed away. Anti- VP26 protein labelled with alkaline phosphatase (AP) are added into the buffer, for the SMPP-WBP-WSSV-Anti VP26-AP particles to be formed. When the substrate p-nitrophenyl phosphate (pNPP) is introduced, AP on the SMPPs hydrolyzes the colorless pNPP into a yellow-colored p-nitrophenol and inorganic phosphate [152]. The amount of color conversion is proportional to the amount of WSSV [151]. The sensitivity of this method was 1.6×10^4 copies per μL of WSSV [151].

4. Other colorimetric methods

4.1. Polymerized polydiacetylene

Polymers can be used for color change virus detection in the form of polymerized polydiacetylene (PDA) lipids. PDA exhibits rapid blue to red colorimetric transitions in response to a wide range of stimuli including the changes of temperature, pH, mechanical perturbations, and solvents [153]. PDA can be assembled into vesicles where the color-change is being caused by biological analytes, which change the interface of the PDA vesicles [154–157]. This causes structural perturbation of the conjugated backbone of the PDA vesicle polymers due to external stresses caused by combination of biomolecules on the surface of the vesicles.

PDA vesicles are fabricated using 10,12-pentacosadiynoic acid (PCDA) and 1,2-dimyristoyl-*sn*-glycero-3-phosphocholine (DMPC) that form a lipid solution in chloroform, which is then rotoevaporated, sonicated, cooled and stored at 4 °C for crystallization of lipid membranes, then UV irradiated at 254 nm for 5 min to attain blue PDA solution [156,158]. For example the H5N1 virus is detected with high specificity using PDA by causing the color of the assay to change from blue to red [158]. The sensitivity of the bioassay is 0.53 copy per μL, which is comparable to RT-PCR. Furthermore, the H1N1 virus can be detected, using PDA functionalized by peptide (PEP-PDA) colorimetric nanosensor, where the PDA is formed by nanoprecipitation [159]. At the same time, PEP is irradiated with 256 nm UV light, which causes the PEP to have special recognition to the H1N1 virus. This PEP is then attached onto the surface of the PDA vesicles in the presence of EDC and NHS linkers [159]. In the presence of H1N1 virus, the color of the PDA changes from blue to red due to the specific binding of H1N1 to PEP. This color change is due to higher stress, which causes a strain in the conjugated backbone of PDA vesicles to increase energy gap, then allowing for the absorption of higher energy photons, thus causing the color of the PDA vesicle solution to change from blue to red [159].

4.2. Gene expression reactions as switch on fluorescent protein expression

Cell-free gene expression reaction is an important part of synthetic biology, which can be employed for DNA and RNA detections through gene regulated fluorescent protein synthesis, with DNAs or RNAs function as a switch of fluorescent signals [160–163]. Gene networks can be designed by the components of cell extract or purified gene expression machinery, a buffer optimized for gene expression, and DNA encoded genetic network with fluorescent proteins reporters [162]. So when the targeted genes are present, the color of the solution or substrate will change. Such a detection is more likely to be qualitative, because the genes are switches for the reactions.

In 2014, Collins and his team from MIT designed a programmable paper disc employing a combination of enzymes, proteins and synthetic gene networks to change the disc color upon existence of targeted virus [164] and used the platform to detect Ebloa RNA at a low concentration of 30 nM within 90 min. As the world faces the mosquito-borne Zika viruses in 2016, there is an urgent need to quickly identify the existence of the virus in humans. The same team used similar paper discs and designed a portable and affordable Zika virus-testing platform to detect Zika virus RNA genome at sensitivity of femtomolar of Zika with around 3 h [165]. In Zika detection, some lab facilities are still necessary, the virus samples were boiled at 95 °C for 2 min to exact RNA, and the RNAs are purified by nucleic acid sequence based amplification. Although the RNA detection paper disc is a step forward to quick and cost-effective detection of RNA a bit over US$20 (the paper discs are with the colors measured by a home-made electronic optical reader at the cost of US$250), the design of such RNA gene expression reactions could be complicated. If the purification step cannot be avoided, the platform is difficult to be moved out of lab for on-site detections [165].

4.3. Metal ion solution combined with rolling circle amplification (RCA) reaction

The H5N1 virus can also be detected using HNB as a metal detector to monitor the rolling circle amplification (RCA) reaction, an amplification reaction that is similar to LAMP, through the change in magnesium ion (Mg^{2+}) concentrations in solution [166]. In the presence of the H5N1 virus, the HNB dye undergoes color change from dark blue to sky blue. This is due to HNB chelating with pyrophosphate — the byproduct from the RCA reaction in the assay, which subsequently leads to a change in Mg^{2+} metal ion concentration [166]. This detection method is similar to using HNB on LAMP product indication discussed in Section 2.

4.4. Silicon nitride thin film

A silicon nitride thin film can be used to detect viruses by observing its color change. The thin film is made up of a T-polymer (polydimethylsiloxane), which is then applied above the silicon nitride. This T-polymer has reactive amino groups, allowing capture probes or antibodies to be covalently attached to amino-functionalized T-polymer surface [167,168]. In the absence of virus, there is no color change and the thin film remains gold in color due to the destructive interference of specific wavelengths in the blue region of the visible light spectrum [167,168]. This occurs when white light is reflected from the surface, which leads to the wavelengths in the orange-red region to be highly reflective, hence forming a gold color on the unreacted surface. In the presence of the virus, specific molecular interactions, such as enzyme-catalyzed reaction (i.e., using a precipitating formulation of tetramethylbenzidine (TMB) substrate for enzyme horseradish peroxidase (HRP)), or direct conjugation of polymers or beads occurs on the surface of the thin film, leading to an increase in the mass deposited on the substrate and a purple color is observed. The increase in the deposited mass leads to the increase in path length of the light waves reflected from the surface of the thin film, causing purple light to be reflected from the thin film surface [168].

5. Conclusions

PCR may be commonly used for virus detection by observing its color change, but in the advent of the LAMP technique, it has been more extensively investigated. This is due to the capabilities of LAMP to provide efficient, effective and practical detection of various viruses. However, there are also other emerging techniques, such as the use of nanoparticles, phages, enzymes and polymers that are able to detect viruses successfully and can be employed in selected circumstances. Nanoparticle-based colorimetric assays are most suitable to be fabricated into lateral flow or lab-on-a-chip devices, and can be coupled with LAMP or portable PCR systems for highly sensitive on-site detection of viruses. Although this area of research is highly specialized, there is still much potential for the colorimetric virus detection systems to be even better than they are today, with improvements in sensitivity, portability, accuracy, ease of use, affordability, shelf life and more. It is also important that these color-changing detection techniques are easily applied to practical testing platforms or testing kits for their prolific usage beyond the lab bench for commercial purposes.

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.

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