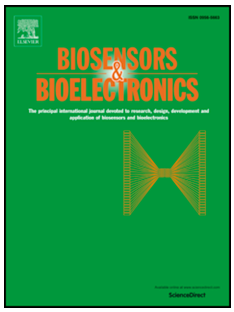

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Recent progress and prospects of alkaline phosphatase biosensor based on fluorescence strategy

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Abstract

Alkaline phosphatase (ALP) is a membrane-bound enzyme widely present in biological tissues and is extensively used as a biomarker in clinical diagnosis because abnormal ALP levels in organisms are often closely related to many diseases. In order to meet the urgent needs of human health and the development of precision medicine, the classic method of detecting ALP seems to be unable to meet a “tailor-made” treatment plan for patients. In order to get the best therapeutic effect and the lowest side effects, the researchers have made considerable efforts and established numerous strategies for detecting ALP. In this review, we focus on the current development and basic principles of fluorescence strategy to detect ALP, and compare the advantages and disadvantages of detecting ALP based on different fluorescent detection modes. In addition, to more intuitively understand the performance of different materials for detecting ALP, a table is presented. Finally, the future trends and prospective in this field will be discussed, it could be speculated that invent and design the detection mechanism based on the relationship between the new material and ALP is the key to effective detection of ALP, and process data with a computer analog digital platform will be a welcome and obsessive technology. It is hoped that some insights and inspiration for future research work will be provided.

***Keywords**:* Alkaline phosphatase; Fluorescence biosensor; Turn-off; Turn-on; Ratiometric

1. Introduction

Alkaline phosphatase (ALP) is a zinc-containing dimeric metalloprotein with a molecular weight typically between 70,000 and 180,000 Da. Enzymes from mammalian sources usually contain carbohydrates. The amino acid composition seems to be typical of many other enzymes found. In current studies on ALP, the ALP active site includes a serine residue and its surrounding amino acid sequence similar to a serine residue (McComb et al. 2013). The average serum ALP range of normal adults varies from 40 to 150 U/L (Song et al. 2014a). ALP levels are often associated with certain diseases in the organism. For example, elevated levels of ALP in serum are often related with biliary obstruction (Center et al. 1992), leukemia response (Raskin and Valenciano 2000), lymphoma (Wiedemann et al. 2005), osteoblastic bone tumors (Fuller et al. 2001; SATO et al. 2002), osteomalacia (Kaneko et al. 2008; Webster 2010), and diabetes (Jin et al. 2019). At the same time, some metabolic disorders, including blood system diseases such as Wilson's disease and leukemia, are usually associated with decreased levels of ALP in serum (Giannini et al. 2005) (Brichacek and Brown 2019). Interestingly, endotoxemia is common in infants with infant cardiopulmonary bypass. Natural ALP activity and endotoxemia is inversely related, and the addition of exogenous ALP in ex vivo reduces endotoxin activity assay (Davidson et al. 2019). In addition, low levels of ALP activity are associated with necrotizing enterocolitis in preterm infants (Yang et al. 2019). Therefore, ALP levels in human serum were commonly used to diagnose pathological or physiological processes involving the hepatobiliary system, bone or placenta. In addition, ALP could be measured in saliva, urine, cerebrospinal fluid, leukocytes, and

synovial fluid to express physiological or pathological processes in the organism, although the use of this measurement in clinical medicine was not as clear as serum alkaline phosphatase (Bodansky and Jaffe 1934; Fishman and Ghosh 1967; Gutman 1959; Highman et al. 1968; Kaplan 1972; Kay 1932; King 1953; Posen et al. 1977; William 1942).

To date, a variety of methods for detecting ALP, including fluorometry (Liu et al. 2017b) (Chen et al. 2019; Gwynne et al. 2019; Jung et al. 2019), capillary electrophoresis method (Craig et al. 1996; Murakami et al. 2001; Whisnant and Gilman 2002; Whisnant et al. 2000), electrochemical method (Gyurcsányi et al. 2002; Ino et al. 2012; Ma et al. 2016b; Peng et al. 2015; Shen et al. 2016; Wu et al. 2016) (Zhang et al. 2019b), chromatography (Takuya et al. 2006), colorimetry (Hu et al. 2017b; Huang et al. 2019; Jiao et al. 2014; Song et al. 2018a; Wang et al. 2018a), surface enhanced Raman scattering method (Ingram et al. 2009; Ruan et al. 2006; Sun et al. 2019), chemiluminescence method (ALBILLOS et al. 2011; Bronstein et al. 1989; Fisher et al. 1995; Park et al. 2011; Ximenes et al. 1999), and isotope labeling method (Fernley and Bisaz 1968) have been developed. Generally speaking, the above methods were sufficient to play a potential role in traditional or classical clinical trials, such as indicating the presence of disease and guiding the treatment of later disease. However, due to the intricate systems of organisms, tandem reactions often occur between diseases or cause other diseases. Therefore, developing a method with higher precision and sensitivity to locate the presence of ALP in different body fluids or cells has extremely important practical significance for its application at the single cell level. It is worth mentioning that the fluorescence analysis method has

attracted much attention from researchers and was used to detect ALP because of its simplicity, convenience, rapidity and high sensitivity (Han et al. 2017; Han et al. 2019b; Han et al. 2018; Zhang et al. 2019a; Zhang et al. 2018a).

Tang et al. reviewed strategies based on colorimetry (Hu et al. 2017a; Hu et al. 2016a), fluorometry, chemiluminescence method, electrochemical method, Surface-enhanced Raman scattering method, photoelectrochemical method, electrophoresis method and others for detecting ALP (Tang et al. 2019). Here, based on recent studies, we focus on recent advances about the detection of ALP by fluorescence methods. It is hoped that some insights will be provided for the development of new idealized detection strategies to meet the actual needs of accurately diagnosing diseases associated with ALP levels.

2. The progress of the fluorescence strategy for detecting ALP

The currently established fluorescence methods for detecting ALP based on the changes in fluorescence intensity caused by ALP were mainly classified into the following categories: “turn-off”, “turn-on”, and ratiometric strategies. Among them, the “turn-off” mode was the most widely used strategy. The “turn-on” strategy was very popular among researchers because of its high sensitivity and the ability to avoid false positive signals. Ratiometric strategies typically avoided interference from probe concentrations or drift from the source or detector. Therefore, the development of the above strategies in ALP detection have been reviewed and summarized in detail.

2.1 Fluorescence "turn-off" detection strategy

The general concept of fluorescence quenching includes any effect that could reduce the intensity of fluorescence. The narrow concept refers only to physical or chemical processes that occur due to a decrease in fluorescence intensity between fluorescent molecule and solvent or solute molecule. The fluorescent "turn-off" mode is a detection strategy based on whether the fluorescent signal is quenched or attenuated (Lakowicz 2013). A substance that interacts with a luminescent molecule to cause a decrease in fluorescence intensity is a quencher. The quenching process could be divided into two types: dynamic and static quenching. Dynamic quenching is the interaction between the quencher and the excited state of the luminescent substance. In this process, the excited state of the luminescent substance passes through the collision with the quencher molecule in the form of energy conversion or charge transfer, resulting in losing its excitation energy and return to the ground state. Static quenching is the interaction between the quencher and the ground state molecules of the luminescent substance. During this process, a complexation reaction occurs between the quencher and the ground state molecules of the luminescent substance. The resulting complex does not illuminate in the actually detected spectral region (Nagarkar et al. 2013; Sohn et al. 2003). In addition, the decrease in fluorescence intensity is also related to the following factors. The first is the inner filter effect. When the concentration of the solution is too high, the impurities in the solution increase the absorption of the incident light, thereby reducing the intensity of the excitation light. At the same time, after the incident light is strongly absorbed by the luminescent material in the front part of the solution pool, the incident light

received by the luminescent substance in the rear part of the solution pool is weakened, so that the light intensity is lowered, and the detection window of the instrument is usually aligned with the solution pool. In the central region, the fluorescence intensity detected was significantly reduced. Secondly, when the molecules are aggregated at a high concentration, aggregation may occur between the luminescent molecules to form a ground state or an excited state of the polymer, resulting in a change in the fluorescence spectrum and/or a decrease in the fluorescence intensity. Finally, the fluorescence self-absorption phenomenon may occur when the absorption spectrum of the luminescent substance overlaps with the emission spectrum, and the emitted light may be partially reabsorbed, resulting in a decrease in luminescence intensity. When the concentration of the solution increases, the self-absorption phenomenon is exacerbated (Lakowicz 2013).

2.1.1 Detection strategies based on carbon nanomaterials

Fluorescent carbon nanomaterials have attracted widespread attention due to their unique chemical/physical properties such as good water solubility, low toxicity, biocompatibility, and photochemical stability. Therefore, carbon nanomaterials are expected to replace the traditional semiconductor quantum dots, becoming a class of fluorescent sensors that are widely used (Baptista et al. 2015; Duan et al. 2015; Strauss et al. 2014; Wu et al. 2015). Li et al. prepared fluorescent carbon dots (CDs) with quantum yield up to 49% by one-step method and used it for the detection of ALP based on the mechanism of inner filter effect (Fig. 1A). This method displayed significant advantages in facilitating the analysis of ALP compared to other assays for detecting ALP. Specifically, when p-nitrophenylphosphate (PNPP) was added to

fluorescent CDs, it was hydrolyzed into p-nitrophenol (PNP) by the subsequently introduced ALP. The absorption spectra of PNP and the fluorescence excitation spectra of CDs showed complementary overlap, resulting in a significant fluorescence weakened of CDs. This proposed detection strategy simplified the steps of detecting ALP and provided a new insight into the development of simple and sensitive detection of other biomolecules, the limit of detection (LOD) was 0.001 U/L (Li et al. 2016). Similarly, a series of fluorescent probes based on carbon nanomaterials were used to detect ALP (Hu et al. 2017c; Kang et al. 2015; Kim et al. 2018; Mao et al. 2017). Cu^{2+} was used as a common intermediate for the detection of ALP. For example, when Cu^{2+} and pyrophosphate (ppi) were added to the fluorescent graphene quantum dots (GQDs), the original fluorescence of GQDs was maintained after Cu^{2+} and ppi were coordinated. However, when ALP was introduced, ppi was hydrolyzed to phosphate (pi) and the released Cu^{2+} will bind with GQDs, causing the fluorescence of GQDs to be quenched, the LOD of this method was 0.017 nM (Zhu et al. 2015). Ppi as the substrate of enzymatic hydrolysis was widely used to detect ALP in fluorescent system. Qian et al. also added Cu^{2+} to the system in which carbon quantum dots (CQDs) and ppi served as fluorescent indicators and enzyme substrates, respectively. Cu^{2+} could interact with carboxyl groups on the surface of CQDs and further trigger CQDs aggregate, resulting in the fluorescence of CQDs to be quenched. In the presence of ALP, ppi was hydrolyzed to pi. The interaction between Cu^{2+} and pi was stronger than with the carboxyl group, so that the fluorescence of CQDs was restored and the LOD of this method for ALP sensing was 1.1 U/L. This proposed method broadened the field of view of carbon nanomaterials for detecting

ALP (Qian et al. 2015b). Heavy metal-free graphtic C_3N_4 (g-C_3N_4) nanosheets typically exhibited low toxicity, strong fluorescence, and good biocompatibility. Therefore, it could be applied to biological sample detection and biological imaging. The novel high quantum yield g-C_3N_4 nanosheets were synthesized and used for highly sensitive, label-free detection of ALP for the first time (Fig. 1B). The biosensor provided a convenient, fast, low-toxic, highly sensitive detection platform for ALP-based clinical diagnostic and biomedical applications with a LOD of 0.08 U/L (Xiang et al. 2016). Analogously, β-cyclodextrin-modified CQDs and boron nitride quantum dots (QDs) were also used to detect ALP (Han et al. 2019c; Tang et al. 2016). Compared to the intermediate Cu^{2+}, Fe^{3+} showed relatively low toxicity. Using Fe^{3+} as an intermediate for detecting ALP was a more beneficial strategy for organisms (Fig. 1C) (Niu et al. 2018).

2.1.2 Detection strategies based on polymer materials

Compared with fluorescent dyes, water-soluble conjugated polyelectrolytes (CPs) exhibited excellent signal amplification and fluorescence quenching properties due to their conjugated polymer backbone. In addition, the excellent optical and electrical properties of CPs made it an effective platform for detecting environmental molecules and biomolecules. Liu et al. developed a system for the detection of ALP based on carboxylate-substituted poly (phenylene ethynylene) polymer ($PPECO_2$)-Cu^{2+}-ppi. The sensitive detection of ALP was achieved by the interaction of the negatively charged $PPECO_2^-$ and Cu^{2+}, which provided an amplified fluorescence quenching effect. The proposed method displayed a LOD of ~5.0 nM (Liu and Schanze 2008). Li et al. also established a simple, sensitive, label-free

method for detecting ALP. The addition of Cu^{2+} to fluorescent conjugated polymer ($PPESO_3$) could lead to fluorescence quenching. When triphosadenine (ATP) and ALP were added separately, the fluorescence was sequentially recovered and quenched owning to ATP could be hydrolyzed by ALP. Subsequently, the released Cu^{2+} was again combined with $PPESO_3$, and ALP and ATP were detected based on changed in the fluorescence signals, respectively (Fig. 2A). The LOD of this method for ALP sensing was 0.01 U/mL (Li et al. 2014b). Similarly, they used phenyl phosphate, which could be hydrolyzed to phenol by ALP, as a substrate. $PPESO_3$ was added subsequently to the system of horse radish peroxidase and H_2O_2 to detect ALP with high selectivity and sensitivity (with a LOD of 0.5 U/L). This method provided an effective platform for detecting ALP in human serum samples (Li et al. 2014a). In addition, the cerium coordination polymer nanoparticles-based fluorescent platform could also achieve sensitive and selective detection of ALP with a LOD of 0.09 U/L (Chen et al. 2018a).

2.1.3 Detection strategies based on noble metal nanomaterials

Compared with fluorescent dye molecules, the advantages of metal nanoclusters depended on their simple preparation methods, good biocompatibility and excellent fluorescence properties (Shang et al. 2011; Tao et al. 2015). Thus, metal nanoclusters have obtained a great attention and widely used in the field of biosensing and bioimaging. Chen et al. synthesized cysteine-directed fluorescent gold nanoclusters (AuNCs) and established a fluorescence method for the specific detection of ALP and ppi based on the different competition between ppi and cysteine for coordination of Cu^{2+} (Fig. 2B). Accordingly, coordination of Cu^{2+} with cysteine on AuNCs caused the

fluorescence of AuNCs to be quenched. When ppi was added to the Cu^{2+}-quenched AuNCs, the interaction between Cu^{2+} and ppi restored the fluorescence of AuNCs. However, the introduction of ALP caused ppi to be hydrolyzed, and Cu^{2+} was then combined with AuNCs to quench its fluorescence again. The LOD of this method to detect ALP was 0.1 U/L (Chen et al. 2014). Similarly, the strategy of ALP detecting based on 3-aminophenylboronic acid functionalized gold nanoclusters (APBA-AuNCs) established by Su's group has been applied to the detection of enzyme activity in real samples and obtained satisfactory results, indicating that the biosensor has good application prospects in the detection of enzyme activity. The LOD of this method for detecting ALP was 0.005 U/L (Liu et al. 2019). Similar to AuNCs, silver nanoclusters (AgNCs) combined with different functional substances could also be another nanoscale materials that could effectively detect ALP, and it usually showed considerable detection performance (the LOD was 0.005 U/mL) (Fig. 2C) (Ma et al. 2016a). In addition, other nanomaterials based on nanoscale gold and silver, such as gold nanoparticles (AgNPs), gold nano-cubes and silver nanoparticles (AgNPs) could be combined with other functional substances to achieve the specificity and sensitivity detection of ALP (Lu et al. 2018; Sharma et al. 2018; Xu et al. 2018; Zhang et al. 2016). Unfortunately, metal-based nanomaterials usually exhibited drawbacks such as cumbersome processes and high toxicity, but were still widely used in the detection of ALP.

2.1.4 Detection strategies based on semiconductor quantum dots (QDs)

Compared with carbon nanomaterials, semiconductor QDs are insufficient due to their high toxicity and metal cost. But they still attracted widespread attention for

sensing and bioimaging due to its unique photophysical properties, such as narrow emission bands, large Stokes shift, high fluorescence quantum yield and anti-photobleaching (Liu et al. 2011; Sharma et al. 2012; Willner and Willner 2010; Zhang et al. 2012). Jia et al. reported a strategy for detecting ALP based on β-cyclodextrin-functionalized CdTe QDs (β-CD/QDs). The design idea stemmed from the fact that the enzyme substrate and product display different quenching effects on β-CD/QDs. In detail, when PNPP was introduced into β-CD/QDs, which still maintained highly fluorescence. However, in the presence of ALP, the PNP formed by hydrolysis of PNPP and entered the cavity of β-CD, causing the fluorescence of β-CD/QDs to be quenched (Fig. 2D). The LOD of the proposed method was 10 mU/mL. This method provided a new detection strategy for designing a sensing system based on host-guest recognition (Jia et al. 2010). Freeman et al. established a fluorescence method based on CdSe/ZnS QDs for the detection of ALP, which allowed multiplexed assay of enzymes (Freeman et al. 2010). Subsequently, tryptophan-functionalized $CuInS_2$ QDs and CdS QDs prepared by Su et al., CdTe/CdS QDs sythesized by Tang et al. were also used for the detection of ALP (Liang et al. 2018; Liu et al. 2014; Ren et al. 2014). In addition, Zhong et al. added ALP to the system of water-soluble fluorescent disulfide quantum dots (MoS_2 QDs) and PNPP, resulting in spectral overlap between the UV-vis absorption spectra of PNP generated by the hydrolysis of PNPP and fluorescence excitation spectra of MoS_2 QDs. An ALP detection method based on IFE mechanism was established with a LOD of 0.1 U/L. This method has been successfully used for the detection of ALP in serum samples as well as cell imaging (Zhong et al. 2018).

2.1.5 Detection strategies based on metal-containing 2D nanomaterials

As emerging 2D nanomaterials, manganese dioxide (MnO_2) and cobalt oxyhydroxide (CoOOH) nanosheets has been applied in many fields due on its could be used as oxidant (Liu et al. 2016). The above oxidized nanosheets could be reduced to Mn^{2+} and Co^{2+} by a specific reducing agent. Typically, nanosheets exhibited excellent adsorption capacity and broad UV absorption (200-600 nm). These properties made nanosheets an effective candidate for fluorescence quenchers and energy receptors (Liu et al. 2017c; Liu et al. 2018; Zhang et al. 2017). In addition, when the structure of the nanosheets was destroyed by the reducing agent, the fluorescence will be restored again. Therefore, Liu et al. and Na et al. developed a method for detecting ALP based on CoOOH and MnO_2, respectively (Fig. 3A). The LOD of the above method was 0.36 μM and 0.045 U/L, respectively (Liu et al. 2018; Na et al. 2018). These new strategies provided a convenient, sensitive and efficient platform for detecting ALP.

2.1.6 Detection strategies based on organic molecules

In recent years, although some inorganic nanomaterials have been discovered in fluorescent analysis, the research history of organic fluorescent molecules was the longest. The synthesis of organic molecules account for a very important position and its application was the most extensive and diverse. Aggregation induced fluorescence emission (AIE) refers to a phenomenon in which the potential fluorescent substance exhibit fluorescence emission when it is aggregated, and the fluorescence quenching will occur when it is in the de-aggregated state. Chen et al. grafted glucosamine hydrochloride onto tetraphenylethylene (GH-TPE) to obtain a fluorescent probe with

AIE properties, which de-aggregated with the enzyme substrate in the presence of ALP, resulting in fluorescence quenching (Fig. 3B). Excellent detection results indicated that fluorescent probes with AIE properties have potential applications in biomacromolecules detection and inhibitors screening (Chen et al. 2010). Zhu et al. used fluorescent 8-quinolyl phosphate as a substrate and ALP-hydrolyzed non-fluorescent 2-hydroxyquinoline as a signal detection molecule for the ALP sensing. It was a simple and clinically useful analytical method with a LOD was 0.229 U/L (Zhu and Jiang 2007). In addition, the use of terbium guanosine monophosphate (Tb-GMP) chelate with long-term emission lifetime was also a good strategy for detecting ALP in biological systems and clinical samples with a LOD of 0.001 U/L (Ma et al. 2014). Using sol-gel transformation was another design idea to detect ALP. In the presence of ALP, the sol fluorescence probe FmocK(FITC)FFYp (P1) (where FITC was fluorescein) was transformed into hydrogelator Fmoc-k (FITC)FFY, which further self-assembled into a non-fluorescent gel (Fig. 3C). The LOD of the proposed method for ALP sensing was 0.06 U/mL. This approach provided a new option for the quantitative determination of ALP in cells in real time (Dong et al. 2015). Another method for real-time detection of ALP was based on fluorescent $Cu(BCDS)_2^{2-}$ (BCDS=bathocuproine Disulfonate) probe. The substrate ascorbic acid 2-phosphate (AA2P) was hydrolyzed by ALP to ascorbic acid (AA), which enabled $Cu(BCDS)_2^{2-}$ to be reduced to a non-fluorescent substance. The LOD of the proposed method for ALP sensing was 0.27 mU/mL (Mei et al. 2018). Interestingly, for the first time, Pandith et al. achieved the detection of ppi and endogenous ALP by hydrazone-based detection system and obtained satisfactory

results. The LOD of the proposed method for ALP sensing was 0.012 U/mL (Pandith et al. 2019). With the continuous development of synthesis and application technology, the research on organic fluorescent molecules will continue to deepen, and its applications in biological and chemical analysis will become more and more extensive.

2.2 Fluorescent "turn-on" detection strategy

The fluorescence turn-on detection strategy is expressed as: when an analyte is added to a substance with weak fluorescence signal or potential fluorescence performance, the fluorescence of the substance is enhanced or the fluorescence signal appeared. The analytes are further detected based on the altered value of the fluorescent signal. Compared with the fluorescent "turn-off" detection mode, fluorescent "turn-on" detection mode was favored by researchers because it could effectively avoid false positive signals from background fluorescence of sample and biological matrix, self-quenching, solvent quenching, and so on. In this regard, the fluorescent "turn-on" detection mode has undoubtedly become a new star in the fields of analytical chemistry, biochemistry and medicinal chemistry. In particular, a wide variety of fluorescent systems for detecting ALP, such as carbon nanomaterials, polymeric materials, metallic nanomaterials, organic molecules and other fluorescent probes, have been widely developed and applied.

2.2.1 Detection strategies based on carbon nanomaterials

In recent years, carbon nanomaterials have become a rising star in biosensing and bioimaging. Qian et al. employed solvothermal methods to prepare carbon

quantum dots (CQDs) that emitted green fluorescence and apply them for the detection of ALP (Fig. 4A). This strategy was not only a reliable, convenient, and highly sensitive method (with a LOD of 1.4 U/L), but also a method for recyclable detection of ALP, since the product $CePO_4$ was a precipitate that could be easily removed from the detection system (Qian et al. 2015a). Hydrolysis of AA2P by ALP to produce AA, which could induce changed in the fluorescence signal of the detection system, was an effective and convenient detection method for ALP by directly introducing an enzyme substrate (Huang et al. 2016; Liu et al. 2017d; Qu et al. 2017; Song et al. 2018b).

2.2.2 Detection strategies based on polymer materials

Near-infrared fluorescent polymer nanoparticles (CyOH@Tb-GMP) emitting at 718 nm were constructed and used for the detection of endogenous ALP. Compared with ordinary near-infrared fluorescent dyes, this material exhibited better photobleaching resistance and has been used for ALP sensing in cells, tissues and mice, and has obtained satisfactory results (with a LOD of 0.0033 U/mL) (Ou-Yang et al. 2018). In addition, methods for detecting ALP using ATP as an enzyme substrate have also been reported successively. The ALP probes based on tetracationic perylene and cationic water-soluble poly (diethynylfluorene-co-diethynylcarbazole-codiethynyl- benzothiadiazole) constructed by Chen et al. and Zeng et al. showed good results (Chen et al. 2013; Zeng et al. 2012). Similarly, Xiao et al. synthesized fluorescent polydopamine nanoparticles (F-PDA) capable of undergoing fluorescence resonance energy transfer (FRET) with MnO_2 nanosheets, and the FRET mechanism was perfectly used for the detection of ALP. Accordingly,

AA2P was hydrolyzed to AA by the subsequently added ALP in the system of F-PDA-MnO_2 nanosheets, and AA further reduced MnO_2 nanosheets to Mn^{2+}, resulting in recovery of fluorescence of F-PDA (Fig. 4B). This method displayed a LOD of 0.34 mU/mL (Xiao et al. 2018).

2.2.3 Detection strategies based on noble metal nanoclusters

Fluorescent noble metal nanoclusters (NCs), a nanomaterial composed of a small number of metal atoms with large Stokes shifts and a simple preparation method (Chen et al. 2015; Choi et al. 2012; Lu and Chen 2012). Therefore, they were widely used in the detection of biomolecules, especially in ALP. Liu et al. established an experiment to assay ALP using PNPP as a substrate. The fluorescence of AuNCs was quenched or weakened when PNPP was introduced into AuNCs because of the absorption spectrum of PNPP and the excitation spectrum of AuNCs displayed a good largely overlap. In the presence of ALP, PNPP was hydrolyzed to PNP, which was significantly different from the absorption spectrum of PNPP, resulting in the fluorescence of AuNCs was restored. The LOD of this method was 0.002 U/L, and potential applications were obtained in real samples (Liu et al. 2017b). Similarly, the products obtained by ALP hydrolyzed pyridoxal phosphate and AA2P could be reacted with AuNCs to achieve selective detection of ALP (Halawa et al. 2017; Han et al. 2019a; Hu et al. 2016b). CuNCs, as another nanomaterials, which used AA2P as a substrate to detect ALP have also received extensive attention from researchers (Wang et al. 2018b; Zhang et al. 2017). In addition, noble metal-based fluorescent indicators such as AgNCs, CuNPs, and AuNPs could also achieve satisfactory results

when detecting ALP (Li et al. 2017a; Lim et al. 2015; Ma et al. 2018; Zhang et al. 2013).

2.2.4 Detection strategies based on organic molecules

Compared with other probes, organic molecular probes were the most widely used in the detection of ALP because of their clear and obvious detection mechanisms. At this point, fluorescent probe molecules with different emission wavelengths have been widely studied and synthesized by researchers. In particular, near-infrared (NIR) fluorescent probes have been popular among researchers for their unique advantages. Tan et al. synthesized a NIR probe based on a derivative of 3-diha-1H-xanthene- 6-ol (DHXP) for ALP activity detecting in cells and mice. The as-prepared NIR DHXP displayed excellent biocompatibility and rapid cell-internalization ability (Fig. 5A), which expected to become a useful tool for biomedical research (Tan et al. 2017). Similarly, the Li et al. prepared CyP probe molecules to detect endogenous ALP activity. This probe has been successfully applied to the analysis of ALP in cells, tissues and mice with good results (with a LOD of 0.003 U/mL) (Fig. 5B) (Li et al. 2017b). In addition, Gao et al. and Liu et al. established a fluorescence method based on small organic molecules to analyze ALP activity. The LOD was 0.28 U/L and 0.31 U/L, respectively (Gao et al. 2018; Liu et al. 2017a). Compared with NIR probes, organic molecules with shorter wavelengths were still widely used in the detection of ALP activity, although they exhibited weak tissue penetration ability and could not avoid the background fluorescence interference of biological matrix. Liang et al. synthesized two phosphate-modified tetraphenylethylene probes with AIE characteristics, which was hydrolyzed by ALP into a polymer with fluorescence

signal enhancement with a LOD of 0.2 U/L (Liang et al. 2013). Similarly, the AIE probe designed by Zhang et al. achieved detection of ALP and screening of its inhibitors (Zhang et al. 2018b). Zhang group designed a probe for detecting ALP by introducing a self-immolative linker between a phosphate moiety and resorufin, the obtained probe exhibited excellent biocompatibility, cell internalization and optimistic application prospect, with a LOD of 1.09 U/L for ALP sensing (Zhang et al. 2015). In addition, some method for detecting ALP based on organic molecule has also been proposed (Cao et al. 2016; Fenoll et al. 2002; Gu et al. 2013; Hu et al. 2015; Hussain Sarpara et al. 1999; Jia et al. 2015; Johnson 1969; Kim et al. 2011; Park and Kim 2013; Rietz and Guilbault 1975; ROCCO 1990; Sasamoto et al. 1995; Wang et al. 2014a; Wang et al. 2014b; Zhu et al. 2006).

In addition, as a complementary for fluorescent “turn-on” detection strategy, “in situ” fluorescence enhancement reaction could effectively avoid time-consuming and tedious steps such as synthesis, post-modification and purification of fluorescent materials. Therefore, the “in situ” fluorescence system for the detection of target analytes has been favored by researchers in recent years. Schrenkhammer et al. used phenol produced by ALP hydrolysis of phenyl phosphate to enhance the fluorescence of europium(III)-tetracycline 3:1 complex (Eu_3TC), thereby selectively detecting ALP with a LOD of 4 μmol/L (Schrenkhammer et al. 2008). Malashikhina et al. and Chen et al. also used PNP produced by ALP hydrolysis of PNPP to enhance the fluorescence of CdS QDs and Ce^{3+}-calcein to the immunoassay of ALP, the LOD of 0.5 mU/mL and 0.023 mU/mL was achieved by the above method, respectively (Chen et al. 2018b; Malashikhina et al. 2013). Sun group used ALP catalytic

hydrolysis of substrate AA2P to generate AA, which could react with APTMS (3-aminopropyl-trimethoxysilane) via “in situ”, and the generated fluorescent SiNPs were immune-analyzed for ALP with a LOD of 0.2 mU/mL. This method also realized the naked eye detection of AFP (Alpha-fetoprotein) (Sun et al. 2016). Similarly, they also used a similar principle to establish a series of “in situ” fluorescent immunoassays for detecting ALP (Sun et al. 2018; Zhao et al. 2019a; Zhao et al. 2019b).

2.3. Ratiometric fluorescence strategies

Unlike ordinary fluorescence strategies, such as “turn-off” and “turn-on”, ratiometric fluorescent probes use two fluorescence intensities as output signals, and the ratio of these two fluorescence intensities was more conducive to avoid interference from factors such as autofluorescence, probe concentration, and emission intensity.

2.3.1. Organic molecule based ratiometric fluorescence strategies

Introducing phosphate group into molecules was one of the most common strategies for ALP detecting. Hou et al. coupled phosphate group and amine-*N*-oxide group to 1,8-naphthalimide derivative and it could been dephosphorylated by the ALP, leading to changed in its photophysical properties. In addition, the introduction of amine-*N*-oxide group could enhance the solubility and biocompatibility of the probe. Therefore, the ratiometric detection of ALP in aqeous and cells was realized, the LOD was 0.38 U/L (Hou et al. 2015). Lu et al. designed a dicyano-based compound containing phosphate groups with strong intramolecular charge transfer (ICT)

character that could be converted into a compound containing phenolic hydroxyl by introducing ALP. In the presence of ALP, the fluorescence emission peak moved from 550 nm to 650 nm. Colorimetric and fluorescent dual-mode detection of ALP was achieved based on changed in the ratiometric signals, the LOD of fluorescent mode was 3.8 U/L, respectively (Lu et al. 2016). In addition, Zhao et al. prepared a fluorescent probe based on electrospun fibrous strips, which achieved a ratiometric fluorescence detection of ALP in serum samples, and the results were consistent with the enzyme-linked immunosorbent assay. The LOD of this method for ALP sensing was 100 mU/mL (Zhao et al. 2017).

Excited intramolecular proton transfer (ESIPT) was a photochemical process that occurred when a molecule containing a hydrogen bond was in an excited singlet state (Zhao et al. 2012). The ESIPT process tended to change the conjugated system of the fluorophore, causing the emission to move toward the long wavelength (Fan et al. 2016; Song et al. 2014b). Song et al. synthesized phosphorylated chalcone, which displayed good water solubility and emitted greenish-yellow fluorescence. When ALP was added, the enzymatic product formed by dephosphorylation of the chalcone molecule, making the enzyme product emitted deep red fluorescence due to the spontaneous aggregation of the product and the ESIPT process, which involving the transformation from enol form to ketone form (Fig. 6). Meanwhile, they utilized the excellent biocompatibility of phosphorylated chalcone to map the endogenous ALP in living cells. The LOD of this method was 0.15 mU/mL (Song et al. 2014b). Subsequently, Fan et al. also designed a ratiometric fluorescent probe that detected the ALP based on the ESIPT process. In the presence of ALP, the

2-(benzimidazol-2-yl) phenyl phosphoric acid molecule with a fluorescence emission peak at 363 nm was converted to 2-(2'-hydroxyphenyl) benzimidazole, and a new fluorescence emission peaks appeared at around 430 nm. Based on this phenomenon, a LOD of 0.0013 U/mL was achieved by this method (Fan et al. 2016).

Two-photon fluorophore could be excited by two low-energy photons, which could avoid the disadvantages of shallow tissue penetration, autofluorescence of cells and tissues, and photobleaching caused by one-photon excitation. Therefore, two-photon fluorophore exhibited excellent performance in cell and tissue imaging (Zhou et al. 2016). Zhou et al. first prepared a naphthalene-based compound showing ICT properties for detecting ALP. In the absence of ALP, the ICT process of probe molecules with a wavelength of 428 nm was inhibited. When ALP was introduced, the phosphate group in the naphthalene-based compound was released, and the formed compound having a phenolic hydroxyl structure could undergo an ICT process. In addition, the phenolic hydroxyl compound exhibited a distinct emission peak around 508 nm. Thus, a two-photon fluorescent probe for detecting ALP in living cells was presented. The linearity of the method ranged from 20 to 180 U/L with the LOD of 2.3 U/L (Zhou et al. 2016).

Detection of ALP using a complex formed by the electrostatic interaction of a charged polymer electrolyte with a molecule bearing a phosphate group was an effective strategy. Zheng et al. modified betaine onto positively charged polyethylenimine and then introduced pyrene derivative containing phosphate group. The resulting polymer showed a fluorescence emission peak at 488 nm. In the presence of ALP, the phosphoric acid group was cleaved, resulting in a new

fluorescence emission peak at 378 nm. The ratio fluorescence strategy could effectively detect ALP in biological fluid such as serum, with a LOD of 0.1 U/mL (Zheng et al. 2014). Deng et al. prepared ratiometric fluorescent responsive infinite coordination polymer (ICP) nanoparticles for detecting ALP. The network polymer consists of Tb^{3+} coordinated guanine monophosphate (GMP) and coumarin. The coumarin was released from the ICP network polymer when the ALP was added, and the fluorescence emission peak will move from 552 nm to 450 nm. Thus, sensitive detected of ALP and screened of inhibitors could be achieved by measuring the ratio of fluorescence intensity at 552 nm to that at 450 nm, with a LOD of 0.010 U/mL (Deng et al. 2015). Sun et al. designed a ratiometric detection strategy for Cu^{2+} and ALP activity based on semiconducting polymer dots assembled with rhodamine B hydrazide. This method displayed a linearity ranged from 0.005 to 15 U/L with a detection limit of 0.0018 U/L (Sun et al. 2017).

3. Conclusion and prospective

In this paper, we reviewed the fluorescence detection strategies, including fluorescence “turn-off”, “turn-on”, and ratiometric strategies, and compared their working principles, advantages and disadvantages. From the table 1 of the comparison of the detection performance, it could be found that most of the fluorescent materials usually used Cu^{2+}, AA2P, PNPP, etc. as intermediates for the detection of ALP, and the use of these intermediates tended to complicate the process of detecting ALP. In addition, probes based on organic molecules and ratiometric probes could avoid the use of the above intermediates, which is a very efficient method for ALP sensing. Unfortunately, the preparation of organic molecules and

ratiometric probes was complex, limiting their widespread application. In addition, with the rapid development of biomedicine, accurate diagnosis of diseases associated with ALP levels is an urgent need for human health. By reviewing the methods used for ALP sensing, it could be found that the accuracy and rapid detection of ALP is highly dependent on the discovery and application of new materials. Therefore, inventing and designing the detection mechanism based on the relationship between the new materials and ALP is the key to effective detection of ALP. In addition, to obtain a superior detection performance, processing data with a computer analog digital platform will be a welcome and obsessive technology. In summary, based on the continuous progress of detection methods for ALP, we believe that the fluorometry will bring a bright future for the development of life sciences and biomedicine.

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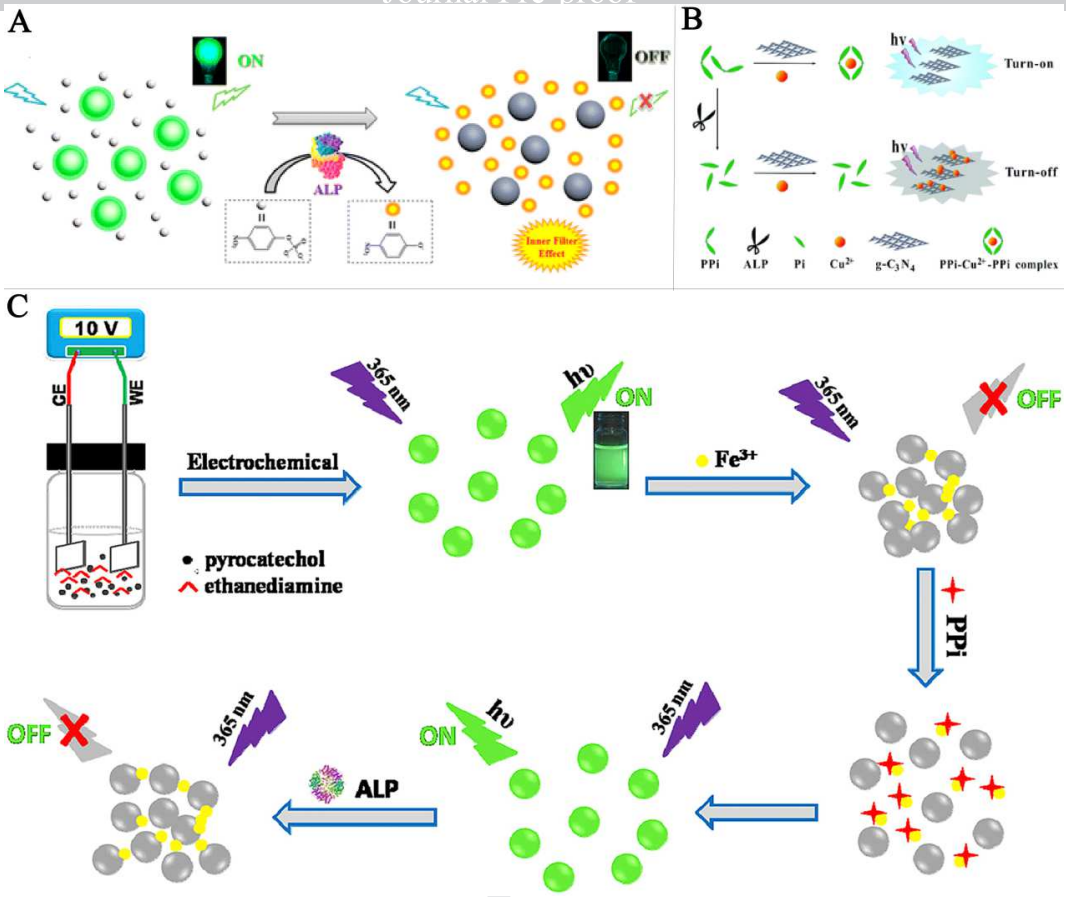

Fig. 1. The strategy of (A) fluorescent CDs (Li et al. 2016) (Copyright 2016, American Chemical Society); (B) Cu^{2+}-modulated g-C_3N_4 nanosheets (Xiang et al. 2016) (Copyright 2016, Royal Society of Chemistry); (C) and Fe^{3+}-modulated N-doped CQDs (Niu et al. 2018) for ALP sensing (Copyright 2018, Elsevier).

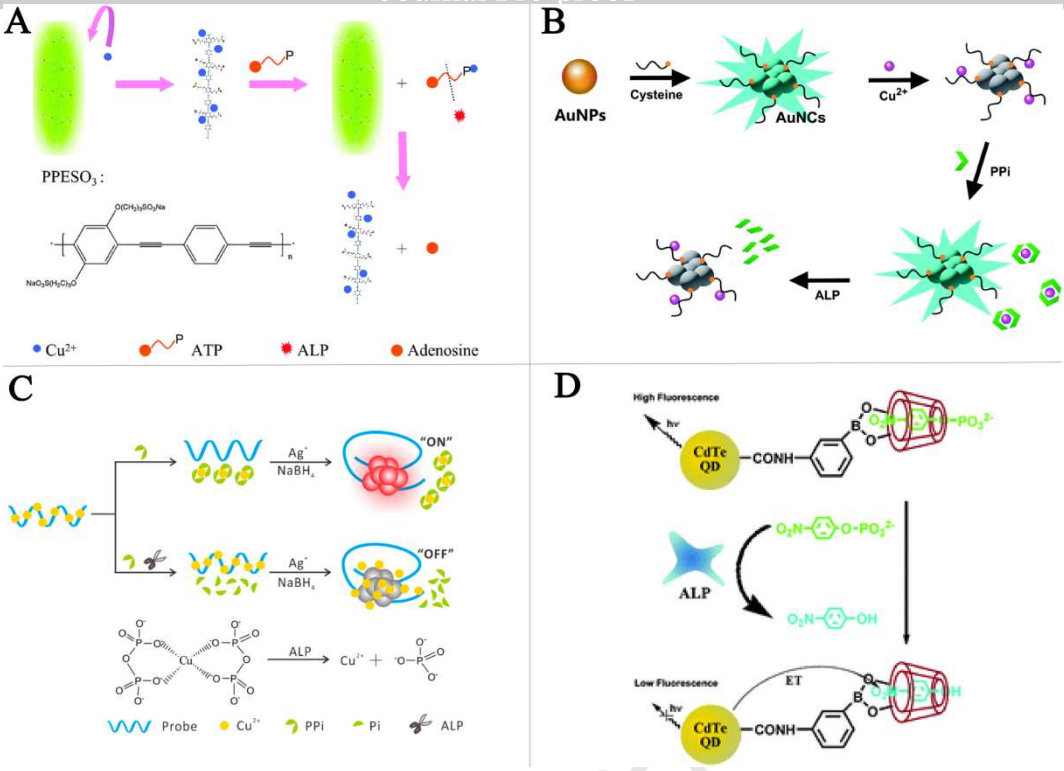

Fig. 2. Schematic diagram of (A) $PPESO_3$ (Li et al. 2014b) (Copyright 2014, Royal Society of Chemistry); (B) AuNCs (Chen et al. 2014) (Copyright 2014, Royal Society of Chemistry); (C) AgNCs (Ma et al. 2016a) (Copyright 2016, American Chemical Society) and (D) β-CD/QDs (Jia et al. 2010) probe for ALP detecting (Copyright 2010, Royal Society of Chemistry).

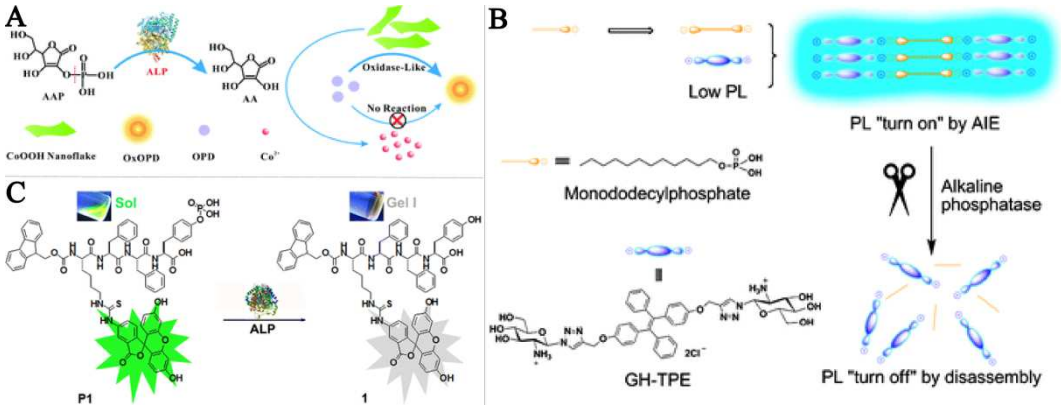

Fig. 3. (A) Fluorescence and colorimetric dual mode detection of ALP activity by CoOOH nanosheets (Liu et al., 2018) (Copyright 2018, Royal Society of Chemistry); (B) Schematic diagram of detecting ALP with GH-TPE fluorescent probe (Chen et al. 2010) (Copyright 2010, Royal Society of Chemistry); (C) Fluorescent FmocK(FITC)FFYp (P1) “turn-off” for detecting ALP (Dong et al. 2015) (Copyright 2015, American Chemical Society).

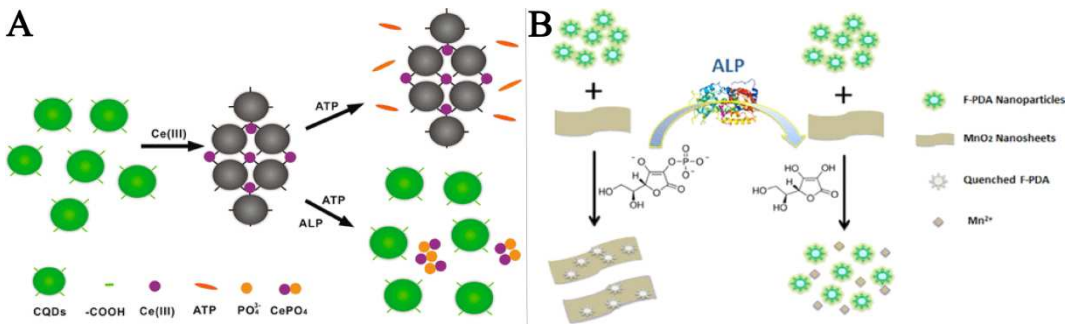

Fig. 4. Schematic diagram of (A) Ce^{3+}-modulated probe (Qian et al. 2015a) (Copyright 2015, American Chemical Society); (B) F-PDA-MnO_2 nanosheets (Xiao et al. 2018) for the detection of ALP (Copyright 2018, American Chemical Society).

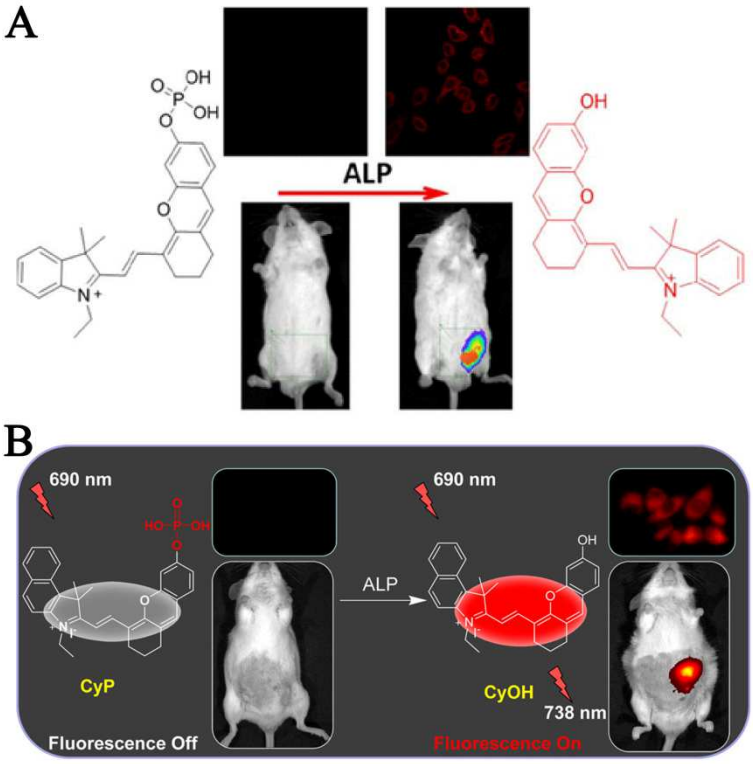

Fig. 5. Schematic diagram of (A) DHXP (Tan et al. 2017) and (B) CyP (Li et al. 2017b) in detecting endogenous ALP in vivo. (Copyright 2017, American Chemical Society)

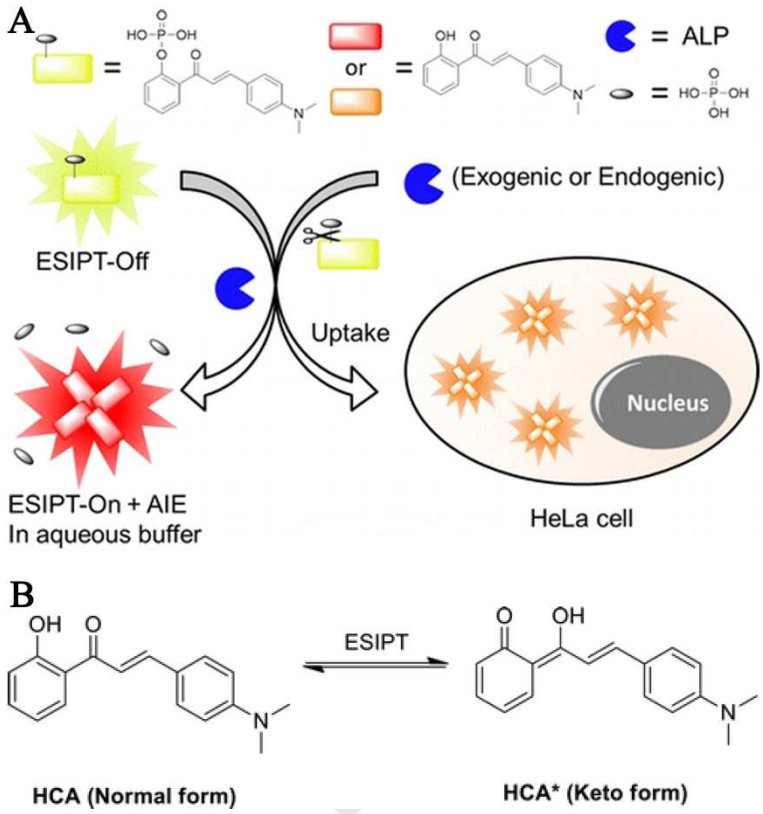

Fig. 6. (A) Schematic of the detection of ALP by phosphorylated chalcone. (B) ESIPT process of HCA (Song et al. 2014b). (Copyright 2014, American Chemical Society)

Table 1. Comparison of detection performance of different methods.

Detection mode	Material	Linearity range	LOD	Intermedium	Ref.
turn-off	CDs	0.01—25 U/L	0.001 U/L	PNPP	(Li et al. 2016)
	CDs	2.5—40 U/L	1.0 U/L	Cu^{2+}, PPi	(Kang et al. 2015)
	carbon-based fluorescent probe	0.5—10 nM	0.25 nM	Cu^{2+}, PPi	(Kim et al. 2018)
	N-CDs	2.5—45 U/L	0.4 U/L	Cu^{2+}, PPi	(Hu et al. 2017c)
	β-CD-N/B-C-dots	0.003—5.5 U/L	0.3 mU/L	PNPP	(Mao et al. 2017)
	GQDs	0—2.5 nM 5—10 nM	0.017 nM	Cu^{2+}, PPi	(Zhu et al. 2015)
	GQDs	16.7—782.6 U/L	1.1 U/L	Cu^{2+}, PPi	(Qian et al. 2015b)
	g-C_3N_4	0.1—1000 U/L	0.08 U/L	Cu^{2+}, PPi	(Xiang et al. 2016)
	β-CD-CQDs	3.4—100.0 U/L	0.9 U/L	PNPP	(Tang et al. 2016)
	BNQDs	2—200 U/L	0.8 U/L	Fe^{3+}, ppi	(Han et al. 2019c)
	N-CQDs	5—360 U/L	1.1 U/L	Fe^{3+}, ppi	(Niu et al. 2018)
	$PPECO_2^-$	0—300 nM	~5.0 nM	Cu^{2+}, PPi	(Liu and Schanze 2008)
	$PPESO_3$	0.5—15 μM	0.1 μM	Cu^{2+}, ATP	(Li et al. 2014b)
	$PPESO_3$	0—30 U/L	0.5 U/L	phenyl phosphate	(Li et al. 2014a)
	cerium coordination polymer nanoparticles	0.1—10U/L	0.09 U/L	/	(Chen et al. 2018a)
	AuNCs	0.1—10 U/L	0.1 U/L	Cu^{2+}, ppi	(Chen et al. 2014)
	APBA-AuNCs	0.02—2.0 U/L	0.005 U/L	PNPP	(Liu et al. 2019)
	DNA/AgNCs	0.03—0.24 U/mL	0.005 U/mL	Cu^{2+}, ppi	(Ma et al. 2016a)
	Au-NPs@GMP-Tb	0.001—0.4 U/mL	0.0004 U/mL	GMP	(Zhang et al. 2016)
	AuNPs	0.2—100 U/L	60 mU/L	ppi, $CePO_4$:Tb	(Xu et al. 2018)
	protein stabilized gold nanocubes	0.0312—1 U/L	1.616 U/L	PNPP	(Sharma et al. 2018)
	GQDs/AgNPs hybrid	0.05—2.5 U/L	0.02 U/L	AA2P	(Lu et al. 2018)
	β-CD-functionalized CdTe QDs	0—800 U/L	10 U/L	PNPP	(Jia et al. 2010)
	CdTe/CdS QDs	3—1000 U/L	3 U/L	PNPP	(Ren et al. 2014)
	$CuInS_2$ QDs	8.4—168 mU/L	3.6 mU/L	Cu^{2+}, PPi	(Liu et al. 2014)
	AuNC@vancomycin	0—58 μM	3.3 μM	Fe^{2+}/H_2O_2	(Liang et al. 2018)
	MoS_2 QDs	0—5 U/L	0.1 U/L	PNPP	(Zhong et al. 2018)
	CoOOH	0.5—60 μM	0.36 μM	AA2P	(Liu et al. 2018; Na

					et al. 2018)
	MnO_2	0.13—10 U/L	0.045 U/L	amifostine	(Na et al. 2018)
	/	1.0—16.0 U/L	0.229 U/L	8-HQ	(Zhu and Jiang 2007)
	Tb-GMP chelate	0.001—200 U/L	0.001 U/L	/	(Ma et al. 2014)
	FmocK(FITC)FFYp (P1)	0—2.8 U/mL	0.006 U/mL	/	(Dong et al. 2015)
	$Cu(BCDS)_2^{2-}$	0—220 U/L	0.27 U/L	AA2P	(Mei et al. 2018)
	hydrazone-based FLRHYDDFP probe	0.05—1.05 U/mL	0.012 U/mL	Cu^{2+}	(Pandith et al. 2019)
turn-on	CQDs	4.6—383.3 U/L	1.4 U/L	Ce^{3+}, ATP	(Qian et al. 2015a)
	CQDs	1.0—90 U/L	0.45 U/L	AA2P	(Huang et al. 2016)
	CDs-MnO_2	1—100 U/L	0.4 U/L	AA2P	(Qu et al. 2017)
	N-GQDs	0.1—5 U/L	0.07 U/L	AA2P	(Liu et al. 2017d)
	CDs	5—200 U/L	0.8 U/L	AA2P	(Song et al. 2018b)
	CyOH@Tb-GMP	0.01—2.5 U/mL	0.0033 U/mL	/	(Ou-Yang et al. 2018)
	poly (diethynylfluorene-co-diethynylcarbazole-codiethynyl- benzothiadiazole)	0—1.20 unit/mL	/	ATP	(Zeng et al. 2012)
	F-PDA	1—80 U/L	0.34 U/L	AA2P	(Xiao et al. 2018)
	AuNCs	0.02—50 U/L	0.002 U/L	PNPP	(Liu et al. 2017b)
	BSA-AuNCs	1.0—200.0 U/L	0.05 U/L	pyridoxal phosphate	(Halawa et al. 2017)
	AuNCs	0.01—450 U/L	0.002 U/L	AA2P	(Hu et al. 2016b)
	PAH-AuNCs	0.5—100 U/L	0.2 U/L	AA2P	(Han et al. 2019a)
	PEI capped CuNCs	1—50 U/L	0.27 U/L	AA2P	(Zhang et al. 2017)
	CuNC-CoOOH aggregates	0.5—150 U/L	0.1 U/L	AA2P	(Wang et al. 2018b)
	DNA-AgNCs	1—800 U/L	1 U/L	G-rich DNA	(Ma et al. 2018)
	CuNPs	0.06—600 U/L	0.035 U/L	ppi	(Li et al. 2017a)
	dsDNA-templated CuNPs	0.1—2.5 nM	~0.1 nM	PPi, Cu^{2+}	(Zhang et al. 2013)
	DHXP	0—0.1 U/mL	0.07 U/L	/	(Tan et al. 2017)
	CyP	0.01—2.0 U/mL	0.003 U/mL	/	(Li et al. 2017b)
	NALP	1 U/L—30 U/L	0.28 U/L	/	(Liu et al. 2017a)
	QcyP	0—400 U/L	1.0 U/L	/	(Gao et al. 2018)
	phosphate-modified tetraphenylethylene probe	3—526 U/L	0.2 U/L	/	(Liang et al. 2013)

	TPEQN-P	0—30 U/L	0.0077 U/L	/	(Zhang et al. 2018b)
	4-methylumbelliferone phosphate	63—633 U/L	/	/	(Rietz and Guilbault 1975)
	benrothiazole derivatives	0—20 pmol	/	/	(Sasamoto et al. 1995)
	/	80—630 nM	/	trifluoromethyl-β-umbelliferone phosphate	(Hussain Sarpara et al. 1999)
	2-carboxy-1-naphthyl phosphate	0.01—1.6 1.6—4.8 U/L	7.44 mU/L	/	(Zhu et al. 2006)
	tetraphenylethylene molecules	/	18 U/L	/	(Gu et al. 2013)
	fluorescein derivatives	0.0175—0.3 U/mL	0.0175 U/mL	/	(Wang et al. 2014b)
	resorufin	0—6 U/L	0.12 U/L	AA2P	(Wang et al. 2014a)
	flavone-based fluorescent probe	/	0.032 U/L	/	(Hu et al. 2015)
	Eu_3TC	2.5—17.5μmol/L	4 μmol/L	phenyl phosphate	(Schrenkhammer et al. 2008)
	/	0—50 mU/mL	0.5 mU/mL	PNPP	(Malashikhina et al. 2013)
	/	1.0—4.0 ng/mL	0.041 ng/mL	PNPP	(Chen et al. 2018b)
	/	0—150 μg/L	5 μg/L	AA2P	(Sun et al. 2016)
	/	0.01—10 U/L	0.01 U/L	4-aminophenyl phosphate	(Sun et al. 2018)
	/	0.1—30 U/L	0.06 U/L	AA2P	(Zhao et al. 2019a)
	/	0.02—2 U/L	0.0023 U/L	hydroxyphenyl phosphate	(Zhao et al. 2019b)
Ratio-metric	1,8-naphthalimide derivative	0.5—5 U/L	0.38 U/L	/	(Hou et al. 2015)
	dicyano-based compound	50—200 U/L	3.8 U/L	/	(Lu et al. 2016)
	electrospun fibrous strips	0—100 U/L	5 U/L	/	(Zhao et al. 2017)
	phosphorylated chalcone	0—150 U/L	0.15 U/L	/	(Song et al. 2014b)
	2-(benzimidazol-2-yl) phenyl phosphoric acid	0.01—0.5 U/mL	0.0013 U/mL	/	(Fan et al. 2016)

naphthalene-based compound	20—180 U/L	2.3 U/L	/	(Zhou et al. 2016)
pyrene derivative	/	0.1 U/mL	/	(Zheng et al. 2014)
Tb^{3+} coordinated guanine monophosphate (GMP) and coumarin	0.025—0.2 U/mL	0.010 U/mL	/	(Deng et al. 2015)
Pdots@RB-hy	0.005—15 U/L	0.0018 U/L	/	(Sun et al. 2017)

1

Highlights

- The fluorescence turn-off, turn-on, ratiometric mode for sensing ALP was reviewed
- The detection principles of those modes were discussed based on different probes
- The advantages and drawbacks of those detection modes were discussed
- A prospect for the detection of ALP activity was proposed

Declaration of interests

☒ 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.

☐ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: