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REVIEW

Nucleic Acids-based Functional Nanomaterials for Bioimaging

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Abstract
Nucleic acids-based functional nanomaterials in biological imaging have drawn more and more attention in recent years. The rapid development of various nanomaterials provides nucleic acids more possibility to achieve the recognition and bioimaging of different small moleculars in living cells. Coupling of nucleic acids and various nanomaterials obviously enhances the cell uptake efficiency of nucleic acids and the signal amplification strategies of nucleic acids have successfully expanded the applications of nucleic acids-based functional nanomaterials for the detection of trace small molecules in living cells, like microRNAs, proteins, and so on. This review summarizes the recent progresses of nucleic acids-based functional nanomaterials in the application of bioimaging with different amplification mechanism and the recent rapid development of stimulate-response nucleic acids-based nanomaterial for time-spatial controlled imaging of intracellular targets. The advantages of these nucleic acids-based functional nanomaterials and possibility of future development of bioimaging are discussed from the perspective of biological imaging.

Keywords Nucleic acids · Nanomaterials · Bioimaging · Signal amplification

1 Introduction

Bioimaging provides a powerful platform for the analysis and detection of pathogen, as well as the development of clinical diagnostic tools and therapeutic modalities [1–3]. One of the major challenges in pathogen bioimaging and diseases diagnosis is the lack of highly selective and ultrasensitive analytical methods for the analysis of markers of disease with low expression levels in complex biological environments. To overcome this challenge, nucleic acids were widely used in designing efficient imaging methods for analysis of the aberrant target in living cells or tissues [4–9]. For instance, nucleic acids were not only known as the carrier of genetic information [10–12], many related studies have shown that they can also be folded into different structures and different nucleic acids sequences can perform different functions, such as target recognition, treatment, and enzyme catalytic functions [13–15]. Compared with traditional chemical recognition mechanisms, nucleic acids have excellent properties such as simple synthesis, great biocompatibility and easier modification, which enable them special recognition characteristics [16, 17].

Nanomaterials have several unique characteristics, including well biocompatibility, large specific surface area, easy surface modification and good stability [18–24]. The development of functional nanomaterials provides greater flexibility for the application of nucleic acids. Unlike other biomolecules (such as proteins), nucleic acids are more stable and flexible after modification. Therefore, many nanomaterials such as gold nanoparticles (AuNPs), silica nanoparticles, quantum dots, upconversion nanoparticles (UCNPs) and magnetic nanoparticles have been combined with nucleic acids to construct various nucleic acids-functionalized nanomaterials for biological applications [16, 25–27]. Recently, the developments of isothermal amplification of nucleic acids and nanomaterials have provided new methods for bioimaging. Since the complex environment of the biological system, many smart nucleic acids nanomaterials for time-spatial accurate biological imaging have been constructed (Fig. 1).

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2 Nanomaterials as Carrier of Nucleic Acids for Bioimaging

As one of the fastest growing directions in the field of nanotechnology, nanomaterials have attracted more and more attentions of biological researchers in recent years. In the past decades, various nanomaterials with distinct properties have been synthesized such as well biocompatibility, easy to surface modification and good stability. These nanomaterials have different classifications with unique merits. For instance, AuNPs, as one of the precious metal nanoparticles [28–32], have the merits of simple to synthesize, stable, easy to modify, and unique optical or electrical properties. Semiconductor nanocrystals [33–36] have the characteristics of trapping photo-generated charge carriers at the interface and tunable emission wavelength. Magnetic nanomaterials [37–39] have superparamagnetism. UCNPs [40–43] have the merits of longer fluorescence lifetime and deeper penetration depth. Furthermore, recently, metal–organic frameworks nanomaterials [44–47] have been applied in bioimaging with excellent pH response characteristics. For instance, copper metal–organic frameworks designed by Zhang's group [48] have been applied in temporal-spatial controlled fluorescence imaging of intracellular microRNA (miRNA). Various nanomaterials with unique properties as nanocarrier of nucleic acids could efficiently transport nucleic acids into cells and have successfully expanded the applications of nucleic acids for bioimaging of trace small molecules in living cells. Understanding the interaction between various nanomaterials and small molecule [49], living cells [50], tissues [51, 52] is crucial for the applications of various nanomaterials in bioimaging and biomedicine [53].

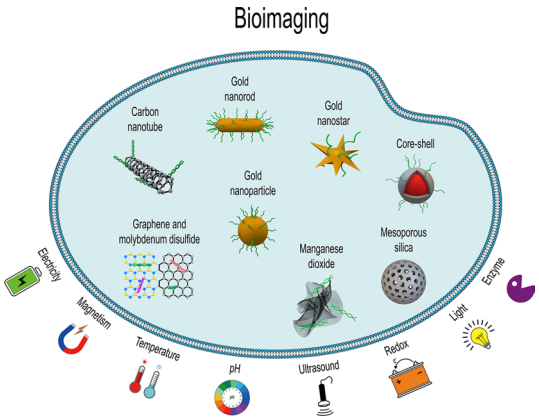

Fig. 1 Schematic illustration of various nucleic acids-based functional nanomaterials for amplified and stimulus-responsive bioimaging

3 Nucleic Acids-based Functional Nanomaterials for Bioimaging

3.1 Traditional Nucleic Acids-based Functionalized Nanomaterials for Bioimaging

The traditional nucleic acids functionalized nanomaterials applied in bioimaging are the nanoprobes obtaining one signal output after reacting with one target. These nanoprobes laid the foundation for the multifunctional design of nucleic acids-based functional nanomaterials for bioimaging. The traditional nucleic acids-based functionalized nanomaterials mainly include AuNPs-based nanoflare and nanobeacon. In 2007, Mirkin's group [54] designed a nanoflare for detecting mRNA in living cells based on strand replacement strategy by combining AuNPs with fluorophore-labeled oligonucleotides. As shown in Fig. 2a, the recognition sequence was hybridized with the reporter sequence and then connected on the surface of AuNPs. The fluorescence of the reporter sequence was quenched due to the surface plasmon resonance absorption band of AuNPs overlaps with the emission peak of the fluorophore. While meeting with target mRNA, the fluorophore-labeled reporter strand was replaced by the mRNA and thus achieved the visual detection of mRNA in the living cells. In 2010, Wright's group [55] developed molecular beacon-based nanomaterials by assembling hairpin DNA on the surface of AuNPs. The hairpin DNA in this method not only served as the recognition sequence but also as the reporter sequence. After the target mRNA hybridized with the hairpin DNA, the end sequence with the fluorophore of hairpin DNA was moved away from the AuNPs and the fluorescence was restored (Fig. 2b). This nanoprobe has the advantage of great specificity, low background, and realizes the imaging of the target in living cells. Subsequently, based on the previous works, Tang's group [56] designed a four-target nanoprobe by introducing four different harpin DNA. Based on the same working mechanism, the fluorescence of the fluorophore on the four harpin DNA was quenched by the AuNPs. Once hybridizing with their target, these four kinds of harpin DNA would be turned on and their own fluorescence was restored (Fig. 2c). These nanoflares and nanobeacons have been applied to one or more small molecule bioimaging with the advantages of simple, respond rapid and good specificity. However, the sensitivity of these methods is limited by the 1:1 format between the target identification and signal conversion.

3.2 Signal Amplified-Nucleic Acids-based Functionalized Nanomaterials for Bioimaging

Sensitive and specific imaging of intracellular small molecular such as tumor markers is important for the early diagnosis

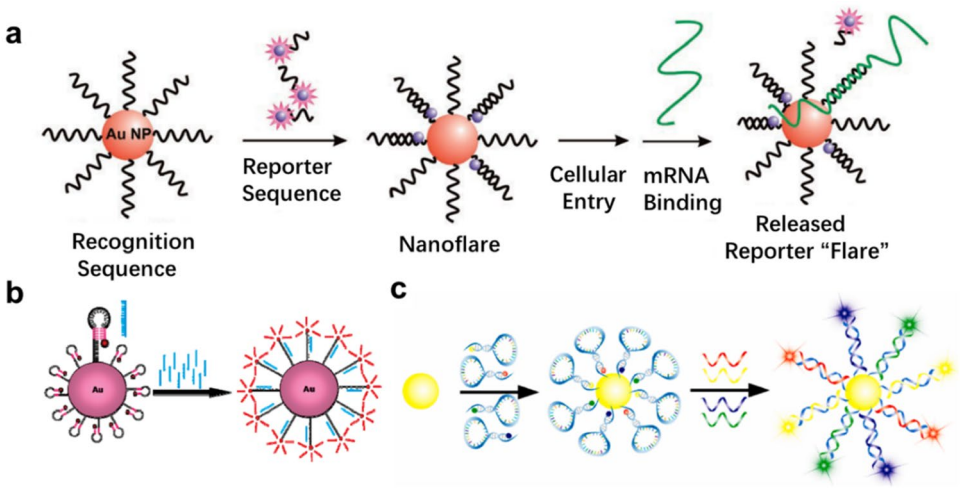

Fig. 2 **a** The detection principle of nanoflare based on strand substitution by assembling fluorophore-labeled oligonucleotides with AuNPs. Reprinted with permission from [54]. Copyright 2007 American Chemical Society. **b** The detection principle of molecular beacon-based nanomaterials by coupling hairpin DNA with AuNPs. Reprinted with permission from [55]. Copyright 2010 American Chemical Society. **c** The detection principle of the four-target nanoprobe for miRNAs imaging. Reprinted with permission from [56]. Copyright 2013 American Chemical Society

and treatment of diseases [57]. However, the detection of small molecules in organisms currently faces many challenges, such as low content and more interference [58–60]. To achieve sensitive detection of targets in living cells or tissues with low expression levels, it is necessary to design efficiently amplified nucleic acids-based nanomaterials as nanoprobes. In recent years, great progresses have been obtained in the development of amplified detection strategies for intracellular small molecular bioimaging. Taking miRNA detection as an example, miRNA signal amplification strategies mainly based on three strategies, DNA cascade reaction, Deoxyribozymes (DNAzymes) catalyst and DNA motors. The coupling of DNA amplification strategies with various nanomaterials provides new ideas for constructing new biosensing systems and made great progress in the imaging of biomarkers and disease diagnosis.

3.2.1 Amplified Bioimaging Based on DNA Cascade Reaction

The DNA cascade reaction consists of three main reactions: hybrid chain reaction (HCR), catalytic hairpin assembly (CHA), and entropy-driven DNA catalysis (EDC). Once meeting with the target sequence of nucleic acids, these reactions are initiated to undergo strand displacement reactions and further release the target into new cycle. Through these reactions, we can detect and image the marker with high sensitivity and selectivity. As any single-stranded DNA can be applied in initiating the following catalytic reactions during this process, DNA cascade reaction can be applied in the bioimaging of specific nucleic acids in living cells with low expression levels. Furthermore, the cascade reaction does not require the addition of any enzymes and there is no special temperature requirement. Therefore, nucleic acids-functionalized nanomaterials based on these cascade reactions provide a great way for the amplified imaging and detection of small molecules in living cells with low expression levels.

The two-dimensional nanomaterials like graphene oxide (GO), MoS_2, WS_2, and MnO_2 nanosheets, have the excellent properties of loading, quenching and well biocompatibility. They have drawn substantial attentions [61–67] and have been widely applied in bioanalysis with DNA cascade reactions. In 2016, Tang's group [68] designed a nucleic acids-based nanomaterial as nanoprobe to achieve the imaging of intracellular miRNA-21 (miR-21) and let-7a with signal amplificated strategy. As shown in Fig. 3a, this nanoprobe consists of GO nanosheets and four kinds of harpin DNA. These harpin DNA labelled with fluorophore were modified on the surface of GO and their fluorescence were quenched by GO. After the nanoprobe entering living cells, HCR reactions between harpin DNA 1 (H1) and harpin DNA 2 (H2) could be initiated while meeting with the target miRNA, yielding a long double strand with obviously enhanced fluorescence signals as the interaction between dsDNA and GO was very weak. Similarly, HCR reactions based on harpin DNA 3 (H3) and harpin DNA 4 (H4) were initiated by another target miRNA let-7a. Finally, this method achieved the imaging of intracellular miR-21 and let-7a with low expression levels. Jin's group [69] reported a harpin DNA-GO nanoprobe for the efficient imaging of intracellular telomerase RNA via amplified strategy (Fig. 3b). After

meeting with the telomerase RNA, one of the harpin DNA could turn on to hybridize with H2 and perform the HCR reaction. MnO_2 nanosheets have also attracted substantial attentions due to its advantage of acting as excellent carrier, quencher, and self-supplying source. In 2017, Xiang's group [70] synthesized nucleic acids-based functionalized MnO_2 nanosheets as the nanoprobe for the imaging of miR-21 in living cells. As Fig. 3c shown, after the nanoprobe entering cells, MnO_2 would be degraded to Mn^{2+} by the glutathione (GSH) and released DNA on the surface of them. The HCR initiated by the target and obtained amplified fluorescent signal outputs. Except for GO and MnO_2, Wang's group [71] designed nucleic acids functionalized MoS_2 nanosheet for the imaging of intracellular miRNA detection with CHA-amplified strategy (Fig. 3d). These nucleic acids-based functionalized nanomaterials based on two-dimensional nanomaterials have excellent property of imaging and detection of targets in living cells with low expression levels.

Combing the three-dimensional nanomaterials such as metal nanoparticles (like Au, Ag nanoparticles), UCNPs (like $NaYF_4$@$NaYF_4$:Yb, Er@$NaYF_4$), metal–organic frameworks nanomaterials with DNA cascade amplification technology to construct amplification biosensors for biomedical diagnostics also have obtained great achievement in recent years. In 2018, Wang et al. and Li et al. functionalized AuNPs with hairpins DNA and achieved the sensitive detection of miR-21 in living cells based on the CHA-amplified strategy (Fig. 4a, b) [72, 73]. In 2020, Liu's group [74] also designed a fluorescent nanoprobe based on AuNPs for in situ and dule-signal imaging of miRNA on the level of single-molecule. As shown in Fig. 4c, the capture probe H1 connected on the surface of AuNPs and the Cy5 fluorescence of H1 cannot be observed as it was quenched by

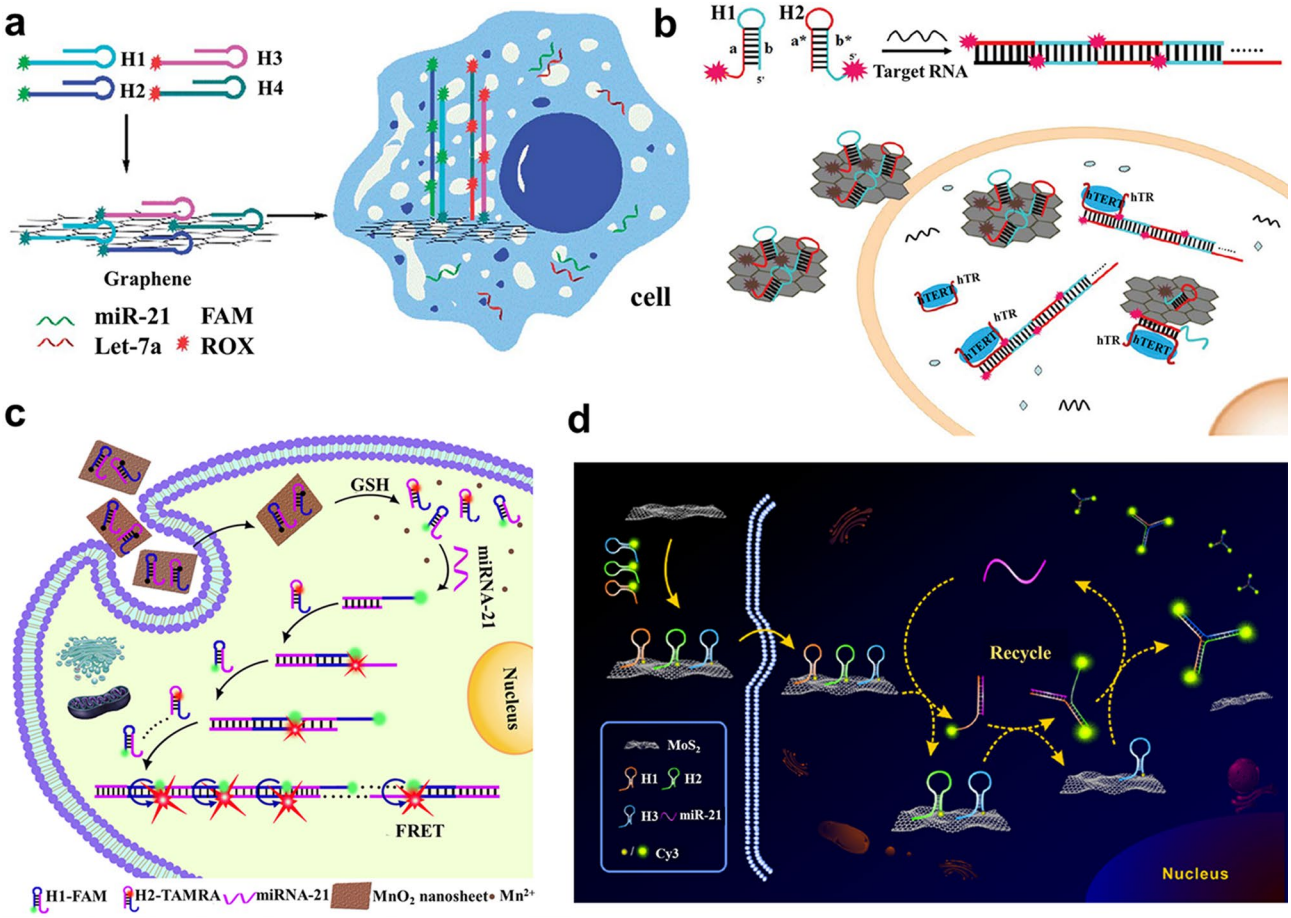

Fig. 3 **a** Design of the harpin DNA-GO nanoprobe for the imaging of intracellular miR-21 and let-7a with signal amplificated strategy (HCR). Reprinted with permission from [68]. Copyright the Royal Society of Chemistry 2016. **b** Design of the harpin DNA-GO nanoprobe for the imaging of human telomerase RNA with signal amplificated strategy (HCR). Reprinted with permission from [69]. Copyright the Royal Society of Chemistry 2016. **c** Design of the harpin DNA-MnO_2 nanoprobe for sensitive detection of miRNA-21 in Living Cells. Reprinted with permission from [70]. Copyright 2017 American Chemical Society. **d** Design of the harpin DNA-MoS_2 nanoprobe for the detection and imaging of intracellular aberrant miRNA-21 with signal amplificated strategy (CHA). Reprinted with permission from [71]. Copyright 2019 American Chemical Society

the AuNPs. After the nanoprobes entering cells, H1 reacted with the target miRNA and the opened H1 would further react with H2, followed by the performing of HCR. This strategy could detect the miRNA at femtomolar and image miRNA on single-molecule level. Based on UCNPs, Zhang et al. [75] designed a DNA-programmed UCNP-AuNPs nanoprobe for the detection of miRNA in living cells. As discussed above, the nanoprobes-based various nanomaterials and DNA cascade-amplified strategy all successfully achieved the sensitive imaging of the aberrant markers of diseases in living cells.

3.2.2 Amplified Bioimaging Based on DNAzymes catalyst

DNAzymes [76–79] are the DNA sequence can catalyze their specific substrates, and the catalytic process requires the participation of specific metal ions as cofactors [80–83]. Compared with the DNA cascade reactions, the nanoprobes based on DNAzyme catalytic activities are easier to implement integrated design. In recent years, DNAzymes with great catalytic activity such as 8–17, 10–23 DNAzyme have been widely used in the efficient detection and imaging of nucleic acids, proteins and metal ions with signal amplification [84–86]. Furthermore, as it is difficult to deliver DNAzyme and its substrate chain to living cells due to their negatively charge, people have introduced various nanomaterials as carriers for delivering DNAzyme and its substrate into living cells in recent years [87]. For example, Zhu's group [88] designed a MNAzymes nanoprobe for the logic imaging of miR-145 and miR-21 in living cells based on the mesoporous silica-coated gold nanorods (Fig. 5a). In this system, as DNAzymes were divided into two different sequences being called MNAzymes, the activity of DNAzymes was blocked. Once meeting with the miR-21, the conformation of MNAzyme motif changed and the activity of DNAzyme restored. Then, the substrates labelled with fluorophore were cleaved and moved away from the surface of mesoporous silica-coated gold nanorods, resulting in the restore of the fluorescence. Subsequently, the released strands of DNAzymes would automatically move to the adjacent substrates and carry out a catalytic loop reaction, resulting in an obvious enhanced fluorescent signal. This design of MNAzyme nanoprobe successfully realized the sensitive detection and imaging of miR-21 and miR-145 in living cells. Liu's group [89] and Xu's group [90] also reported DNAzyme amplification strategies for miRNA imaging in living cells with DNAzyme-MnO_2 nanoprobe (Fig. 5b, c). In these systems, MnO_2 nanomaterials not only served as the transporter of nucleic acids (consist of the strand of DNAzyme and its substrate), but also were reduced by intracellular GSH to Mn^{2+}, which serving as the confactors of DNAzyme catalysis. Most recently, Zhang's group [48] reported DNA@Cu-MOF nanoprobes for the amplified imaging of aberrant miRNA in living cells based on the

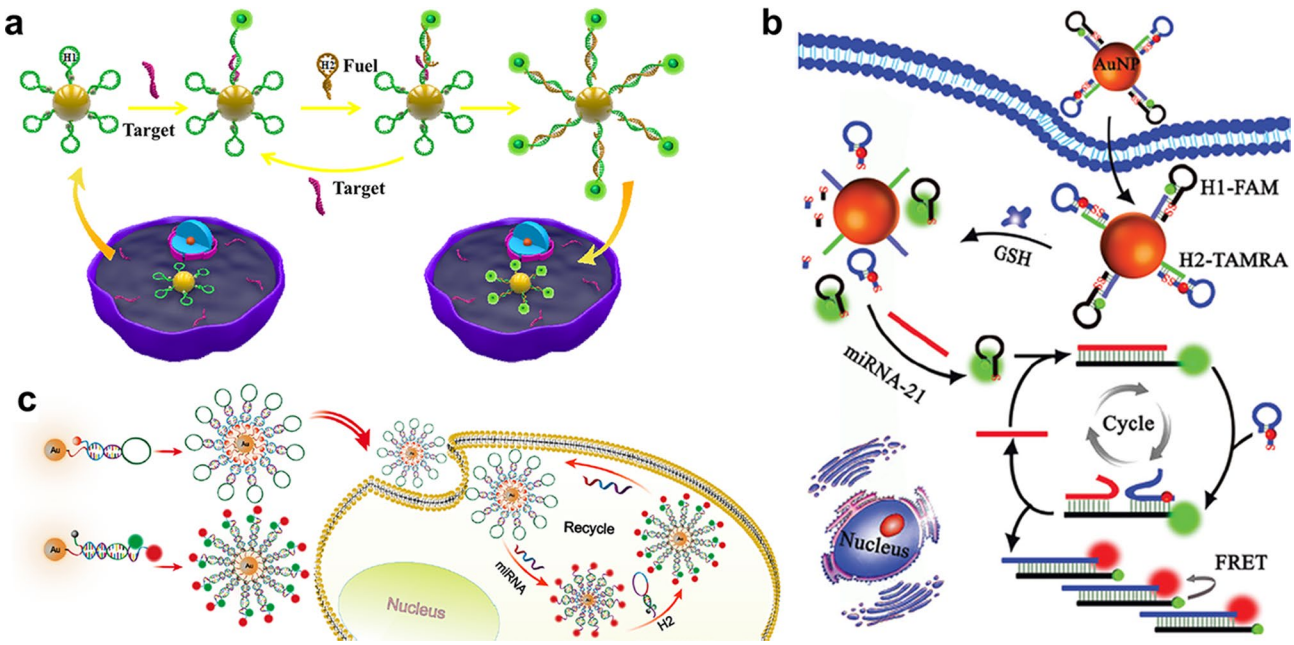

Fig. 4 **a** Design of the CHA hairpins DNA -AuNPs nanoprobe for the efficiently imaging of intracellular miR-21. Reprinted with permission from [72]. Copyright the Royal Society of Chemistry 2018. **b** Design of the bio-cleavable H1-AuNPs-H2 nanoprobes for the efficiently imaging of intracellular miR-21. Reprinted with permission from [73]. Copyright the Royal Society of Chemistry 2018. **c** Design of the fluorescent probes based on AuNPs for in situ and dule-signal imaging of miRNA on the level of single-molecule. Reprinted with permission from [74]. Copyright 2020 American Chemical Society

DNAzyme catalysis reactions. In this system, Cu-MOF was degraded into Cu^{2+} by the hypoxic after entering cells and released the harpin DNA and double strand DNA (dsDNA) on the surface of them. The dsDNA consists of the sequence of DNAzymes and the conformation of double strand, which ensures the inactive state of DNAzyme. Once meeting the target, the conformation of dsDNA was rearranged, further reaction with the harpin DNA happened and the activity of DNAzyme restored. In the presence of Cu^{2+}, the substrate strand labelled with Cy3 was released and carried out the catalytic loop reactions (Fig. 5d). These methods based on nanomaterials of MnO_2 or Cu-MOF overcame the limitation of DNAzyme that requires additional external cofactors and expanded the application of nucleic acids-based functionalized nanomaterials with DNAzyme amplification strategy.

3.2.3 Amplified Bioimaging Based on DNA Motors

As the nature protein motors own efficient and complicated working mechanism in human, in recent years, many researchers have devoted to designing synthetic DNA motors for the detection and imaging of small molecules in cells and studying the important physiological processes in organisms, like springs, walkers, and nanorobots. These synthetic DNA motors have excellent biocompatibility and the merits of high sensitivity and selectivity for imaging and detection of intracellular small molecule in living cells [91–99]. DNA motor usually consists of motors, fuels and tracks and the higher local concentration of tracks ensures the in-situ signal amplification. Briefly, initiated by the target, the locked walking ligands would return to be free and start working along the tracks. To improve the endocytosis efficiency of the DNA motors and the local concentration of the tracks to obtain a more sensitive detection and imaging effect, many methods have been developed by assembling the DNA motors on multifunctional nanomaterials.

The participation of various nanomaterial plays a great role in the designing of DNA motors with excellent biocompatibility and high sensitivity for the detection and imaging of intracellular small molecules in living cells [100–107]. In 2017, Peng et al. [104] designed a DNA motor based on AuNPs and DNAzyme for the amplified imaging of miRNA in living cells. As the results shown in Fig. 6a, once meeting with the miRNA, the walking strands of the DNA motors would restore its free state. As the end of walking strands was designed as the DNAzyme, it would hybridize with the substrate chain on the tracks. In the presence of cofactors, the substrate chains were cleaved to release the fragment containing the fluorophore. The distribution of tracks ensured more signal output while meeting the aberrant miRNA in

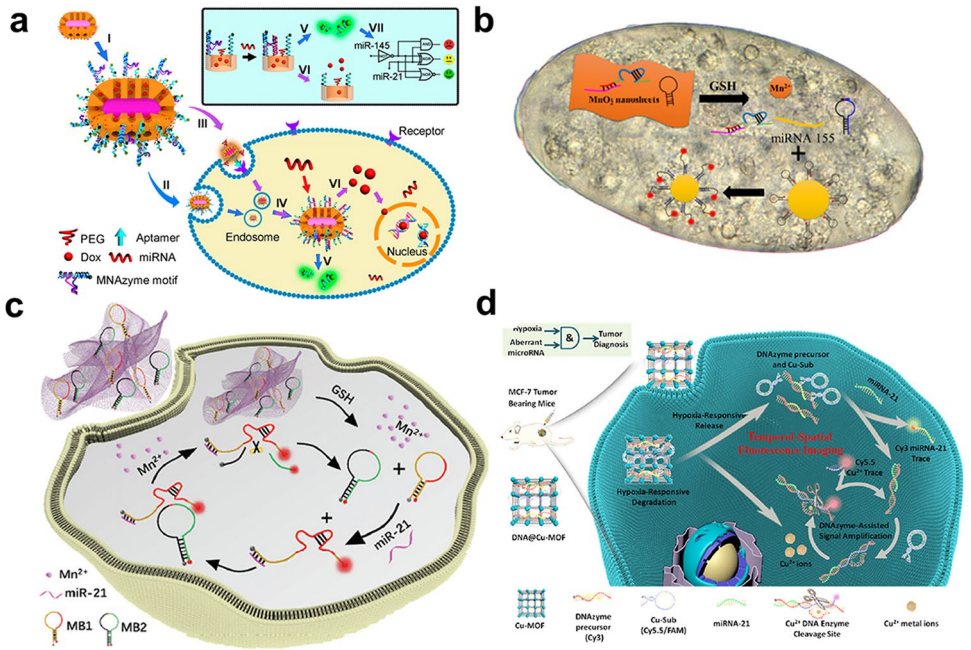

Fig. 5 **a** Application of the MNAzymes nanoprobe for the logic imaging of miR-145 and miR-21 in living cells based on the mesoporous silica-coated gold nanorods. Reprinted with permission from [88]. Copyright 2015 American Chemical Society. **b** Application of DNAzyme amplification strategies for miR-155 imaging in living cells with DNAzyme-MnO_2 nanoprobe. Reprinted with permission from [89]. Copyright 2018 American Chemical Society. **c** Application of the target-triggered DNAzyme-MnO_2 nanoprobe for miR-155 imaging in living cells by DNAzyme amplification strategies. Reprinted with permission from [90]. Copyright the Royal Society of Chemistry 2019. **d** Application of a DNA@Cu-MOF nanoprobes for the amplified imaging of aberrant miRNA in living cells based on the DNAzyme catalysis reactions. Reprinted with permission from [48]. Copyright 2020 American Chemical Society

living cells. Furthermore, Zhou's group [108] reported another DNA motor for the sensitive imaging of intracellular miR-21 by assembling two DNA harpin (H1 consist of the sequence of DNAzyme, H2 consists of the sequence of substrate) on the surface of AuNPs (Fig. 6b). Soon after, Ye's group [106] designed a simpler DNA motor based on EDC strategy for the imaging of intracellular miRNA without the participation of the cofactors. As shown in Fig. 6c, in the presence of miRNA, the walking strand connected with the signal DNA on the surface of AuNPs, and then autonomously and progressively walked along the tracks by EDC, followed by an obviously enhanced signal output. Compared to the DNAzyme motors, this nanomachine avoided the background produced by the non-specific cleavage of DNAzyme and realized the sensitive imaging of intracellular miRNA. To avoid adding metal ions as cofactors in the application of DNAzyme motors, Kong's group [109] designed a self-powered DNAzyme motor-MnO_2 nanosystem for miRNA imaging. The target-induced mechanism of this motor is strands displacement reaction and this strategy can be applied in the detection of miRNA or other nucleic acids sequences. Just recently, Xu's group [110] designed a binding-induced DNA motor-MnO_2 nanosystem for miRNA imaging. Different from the previous methods, this method can be applied in the detection and imaging of any biomolecule in living cells by changing the two ligand molecules including proteins, thrombin and streptavidin (Fig. 6d).

4 Stimulus-Responsive Nucleic Acids-based Functionalized Nanomaterials for Bioimaging

Despite great gains on the constructing of nucleic acids-based nanomaterials for imaging of small molecule in living cells with low expression levels, there are still challenges for bioimaging of small molecules in complex biological systems due to the disadvantages of low bioavailability, poor targeting specificity, and generation of false positive signals. Facing with these problems, many stimulus–response nucleic acids nanomaterials have been constructed for time-spatial accurate biological detection and imaging [111–115]. These methods have attracted widespread attention and have become one of the powerful tools in the field of nanomedicine diagnosis and treatment. The working mechanism of the stimulus-responsive nucleic acids nanomaterials is mainly through the intelligent design of nucleic acids or nanomaterials to realize biological detection at a specific site and time under stimulus. The forms of stimulation mainly include internal stimulation (pH, redox potential, biomolecules) and external stimulation (light, temperature, magnetism).

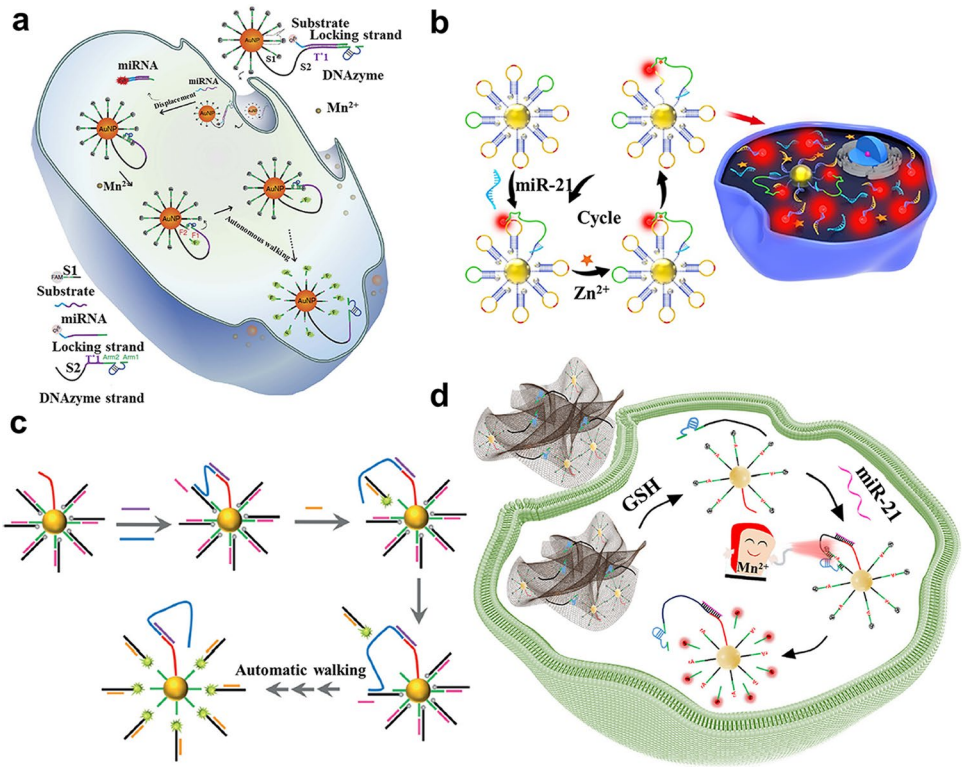

Fig. 6 **a** Scheme of the DNA motor based on AuNPs and DNAzyme for the amplified imaging of miRNA in living cells. Reprinted with permission from [104]. Copyright 2017 Nature Publishing Group. **b** Scheme of the harpin DNA-AuNPs nanomachine for the amplified imaging of intracellular miRNA. Reprinted with permission from [108]. Copyright 2017 American Chemical Society. **c** Scheme of a simpler DNA motor based on EDC strategy for miRNAs analysis. Reprinted with permission from [106]. Copyright 2017 Wiley–VCH Verlag GmbH &Co. KGaA, Weinheim. **d** Scheme of the binding-induced DNA motor-MnO_2 nanosystem for miRNA imaging. Reprinted with permission from [110]. Copyright 2020 American Chemical Society

4.1 Endogenous Stimulus-Responsive Nucleic Acids-based Functionalized Nanomaterials

Tumor tissue maintains a microenvironment conducive to tumor cell survival and development. The intracellular environment and extracellular microenvironment of tumor tissues and normal tissues are different. For example, compared with normal tissue, the pH in the lysosomes of cancer cells is lower than that in normal cells [116, 117]. Furthermore, tumor tissue has a hypoxic, reductive and acidic microenvironment, and the intracellular reactive oxygen species (ROS) and GSH in tumor tissues are overexpressed [118]. In recent years, endogenous stimulus-responsive nucleic acids nanomaterials have been well applied in bioimaging of small molecules imaging in living cells or tissues in the special location. For example, Wang's group [119] designed the DNA-honeycomb MnO_2 nanosponge for the efficient imaging of miRNA in living cells based on CHA-HCR-DNAzyme-amplified strategy. After this nanosysterm entering cells, the honeycomb MnO_2 nanosponge was reduced to Mn^{2+} by endogenous GSH and released the DNA strands for CHA-HCR-DNAzyme amplification reaction. This nanoprobe kept the DNAzyme away from the nonspecific degradation before being delivered into living cells and the CHA-HCR-DNAzyme-amplified strategy largely improved the sensitivity of miRNA detection (Fig. 7a). Li's group [120] constructed a DNA nanoprobe driven by an acidic pH for specific ATP imaging in the extracellular environment of tumors. As shown in Fig. 7b, this nanoprobe was designed by connecting the ATP aptamers with a pH (low) insertion peptide. Only in the acidic pH of the extracellular environment of tumors, pH (low) insertion peptide could insert into the cell membrane and realized the accurate imaging of extracellular ATP of tumor. This nanoprobe achieved the imaging of ATP in the environment of the extracellular environment of tumors in vivo. After that, Xu's group [121] proposed a smart acid-responsive DNAzymes nanoprobe for imaging of Zn^{2+}, Pb^{2+} in living cells by assembling the pH sensitive DNA sequences and metal-assisted DNAzymes on the surface of AuNPs. After this nanodevice entering cells, the locked DNAzyme could be activated by the acidic environment in the lysosomes (pH 4.5–5.0) and realized the imaging of dual metal ions in living cells. Therefore, the exogenous stimuli existing inside the microenvironment of cells or tissues was successfully applied in the small molecule imaging in cells or tissues at our desire site.

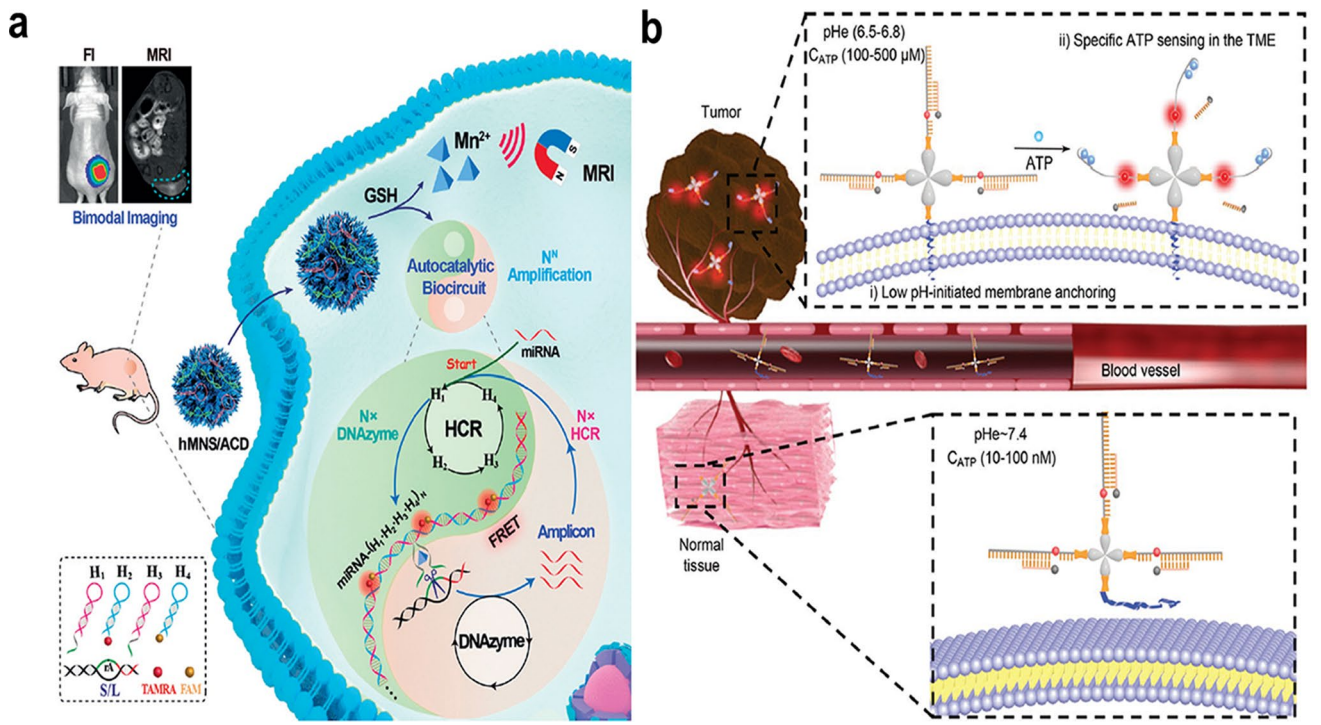

Fig. 7 **a** The scheme of the nanoprobe based on honeycomb MnO_2 nanosponge for the efficiently imaging of miRNA in living cells with CHA-HCR-DNAzyme-amplified strategy. Reprinted with permission from [119]. Copyright 2020 Wiley–VCH Verlag GmbH &Co. KGaA, Weinheim. **b** The scheme of a DNA nanoprobe driven by an acidic pH for ATP imaging in the extracellular environment of tumors. Reprinted with permission from [120]. Copyright 2019 Wiley–VCH Verlag GmbH &Co. KGaA, Weinheim

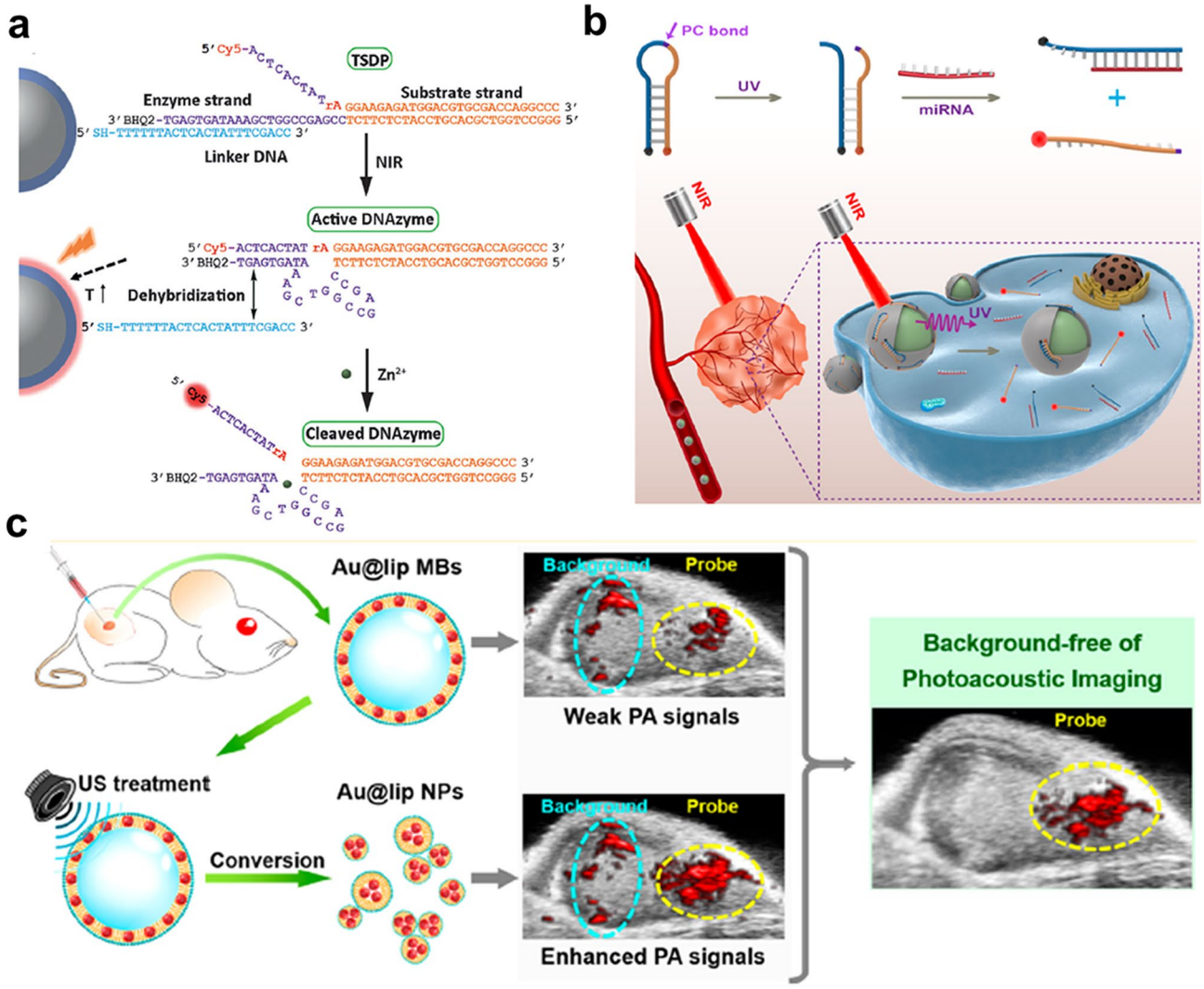

Fig. 8 **a** Scheme of the NIR light activated nanoprobe of TSDP-AuNS for intracellular Zn^{2+} imaging. Reprinted with permission from [126]. Copyright 2019 Wiley–VCH Verlag GmbH &Co. KGaA, Weinheim. **b** Scheme of the NIR light activated nanodevice for the time-controlled imaging of intracellular miRNA based on UCNPs. Reprinted with permission from [127]. Copyright 2019 American Chemical Society. **c** Scheme of the ultrasound responsive method for photoacoustic imaging by a microbubbles containing AuNPs. Reprinted with permission from [130]. Copyright 2019 American Chemical Society

4.2 Exogenous Stimulus-Responsive Nucleic Acids-based Functionalized Nanomaterials

Unlike the exogenous stimuli existing inside the microenvironment of cells or tissues, exogenous stimuli can be applied in the small molecule imaging in cells or tissues at our desire time [122–125]. Near-infrared (NIR) light as an excellent stimulus has drawn more and more attentions for the designing of stimulus-responsive methods for the imaging of biomolecular due to its less toxic and deeper penetration depth. For instance, as shown in Fig. 8a, Wang et al. [126] designed a NIR light controlled imaging strategy by the nanoprobes of DNAzyme-gold nanoshells (AuNS). The conformation of the three-stranded DNAzyme precursor (TSDP) ensured the DNAzyme to be inactive. Under NIR light irradiation, as the local temperature increases, the dsDNA consisted of the DNAzyme strand and its substrate strand was released from the surface of AuNS. The fluorescence of Cy5 on the strand of DNAzyme was quenched by the quencher on the substrate strand. Once meeting with the Zn^{2+}, the strand of substrate would be cleaved and restore its fluorescence. This method overcame the limitation of DNAzyme, susceptibility to metal-dependent cleavage during delivery into living cells and realized the NIR light controlled detecting of metal ions in biological systems. Li's group [127] designed a NIR light activated nanodevice for the time-controlled imaging of intracellular miRNA based on UCNPs. In this system, the harpin DNA contained an ultraviolet (UV)

light photocleavable bond. Under NIR light irradiation, the UCNP transformed the NIR light to UV light, followed by the conformation change of the harpin DNA which hybridized with intracellular miRNA. This method realized the time-controlled miRNA imaging in living cells (Fig. 8b). Furthermore, his group also constructed a series of NIR light activated nanodevices and successfully realized in-situ sensitive detection of important biomolecules and monitoring of intracellular pH fluctuations [128, 129]. Furthermore, recently, Liu's group [130] reported an ultrasound responsive method for photoacoustic imaging by microbubbles containing AuNPs (Fig. 8c). As discussed above, stimulus–response nanodevices can cleverly inhibit the activity of the detection system before delivering into our desire site and restore its activity by many stimulus tools.

5 Conclusions and Perspectives

In summary, the development of nucleic acids-based functional nanomaterials has made a great sense for bioimaging. Various amplified or stimulus-responsive nucleic acids-based functional nanomaterials have been designed for the imaging of small molecules in living cells or tissues. Owing to the development of amplified nucleic acids-based functionalized nanomaterials based on various excellent nucleic acids-amplified strategy like DNA cascade reactions, DNAzymes catalyst and DNA motors for signal amplification, intracellular small molecules in living cells with low expression levels can be detected and imaged, which facilitated the develop of the diagnosis of disease. Particularly, stimulus-responsive nucleic acids-based nanomaterials have shown excellent advantages for time-spatial controlled detection and imaging of targets in living cells and tissues and presented great promise for imaging of genes or other small molecules in subcellular domain, like cell nucleic, mitochondria. Furthermore, two or more stimulus-responsive systems with dule/multiple kinds of amplification strategy have great promise for more accurate disease diagnosis and treatment. The results of nucleic acids-based functional nanomaterials provide excellent platforms for the disease diagnosis and treatment and this emerging field still shows a bright prospect in the future.

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