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Redox-Mediated Quantum Dots as Fluorescence Probe and Their Biological Application

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Abstract

Semiconductor quantum dots (QDs) as a new class of fluorescent labels have become valuable fluorescent platforms for biological applications due to their unique optical properties. In addition to their well-known size-dependent emission spectra, QDs are extremely sensitive to the presence of additional charges either on their surfaces or in the surrounding environment, which leads to a variety of optical properties and electronic consequences. By using thiols as bridges between QDs and redox-active ligands, the fluorescence effects of functionalized QD conjugates were investigated because QDs are prone to exchange electrons or energy with the attached ligands upon excitation, resulting in their fluorescence change. The recovery/enhancement or quenching of the QD conjugate fluorescence could be reversibly tuned with the transformation with the redox state of surface ligands. Moreover, quenching of the QD emission is highly dependent on the relative position of the oxidation levels of QDs and the redox-active ligand used. Importantly, the utility of these systems could enhance the compatibility of functionalized QDs in biological systems and can be used for monitoring the fluorescence change to trace in vitro and intracellular target analyte sensing. We believe that redox-mediated quantum dots as fluorescence probe are a significant step forward toward biosensing.

Keywords: quantum dots, redox-mediation, charge transfer, fluorescence, biosensor

1. Introduction

Semiconductor quantum dots (QDs) or nanocrystals with sizes smaller than the so-called Bohr exciton radius (a few nanometers), resulting in an effect called quantum confinement due to the appearance of discrete energy states in both the conduction and valence bands [1, 2]. Optoelectronics of colloidal QDs offer a compelling combination of solution processing and fluorescence tunability through quantum size effects [3, 4]. They, however, are affected by a variety of parameters including defects in the nanocrystal structure and the surface or with the

surrounding medium [5]. QDs, in particular, have a large-area solution processing on their surfaces and are always capped with functional ligands, which provide surface passivation and promote compatibility with the surrounding medium [6, 7]. These ligands along with the surrounding matrix alter the overall optical and electronic properties of QDs as a result of efficient elimination of the surface native defects, often attributed to the saturation of dangling bonds, improved passivation, and higher packing densities [8–10]. So far, the processibility of colloidal QDs is also exploited in a diversity of applications by fine-tuning their surface ligand characteristics of the semiconductor nanoparticles [11–14]. For example, a water-soluble surface ligand is required for biological sensors [15], an electron conductive layer is important for photoelectric devices [16], and a polymerizable surface is needed to make fluorescence polymer composites [17]. Unlike most organic dyes, QDs are also highly sensitive to charge transfer, thus altering their fluorescence properties [18, 19]. Notably, coupling redox-active ligands to the QDs surface can promote transfer of external electrons (and holes) to QD [18, 19]. Due to an efficient Auger recombination, the presence of additional charges can lead to quenching of the QD fluorescence [20]. The quenching degree of QD fluorescence depends on the location of the added charge, with a complete quenching observed for charges existing in the QD core, due to the strong spatial overlap between charge(s) and exciton, whereas partial quenching is observed for charge(s) locating on the QD surface (due to weaker overlap with the exciton) [19, 20]. When electron transfer between QDs and the molecules bound to their surface occurs, the nanocrystal and its attached ligand molecule exist in highly reactive charged forms long enough to interact with the surrounding environment. The redox-active moiety-functionalized QDs may promote the transfer of external electrons and holes to either the QDs core conduction band or the QDs surface states [21]. Therefore, controlling charge transfer of redox-active surface ligands across functionalized QD conjugates has been attracting increasing interests for advanced diagnostics and in vivo imaging as well as ultrasensitive biosensing [22, 23]. Redox-active compounds including metal complexes, ions, and dyes have already been investigated for use in photo-induced electron-transfer QD sensing. Since the development of high-performance QDs and the advent of excellent coupling techniques to modify them with biological systems [23–25], there has been a urgent need to exploit the interactions of QDs with the redox-active ligand for sensing [26, 27]. A few preliminary researches have reported the redox-active ligand-functionalized QDs and their use to monitor specific biological events. Biofunctional QDs enjoy increasing interest in basic and applied science because of the many possible applications of these structures to fields including proteomics, microarray technology, and biosensors. It is expected that these redox-active ligand-functionalized nanocrystal will be able to perform specific functions, such as biorecognition in the context of an electrical measurement, better than either purely organic or inorganic systems.

2. Quinone/hydroquinone as redox-active surface ligands of QDs

Quinone/hydroquinone is ubiquitous in nature and constitutes an important class of naturally occurring redox molecules [28]. It is well-known that quinone/hydroquinone fulfills a universal and possibly unique function in electron transfer and energy conserving system [29]. Especially, a number of quinones/hydroquinones have the critical biological functions involving

brain activity and neurotransmission (i.e., dopamine), blood clotting (i.e., vitamin K), protein post-translational modification (i.e., topaquinone), cellular signaling molecule metabolism (i.e., estrogens and catecholamines), and antioxidant metabolism (i.e., ubiquinone and tocopherol congeners) [30–32]. Redox moiety was introduced into the surface ligands to achieve the redox-switchable fluorescence properties that could be useful for signal multiplexing, since QDs are highly sensitive to the electron-transfer processes. Recently, the research of functionalized QDs fabrication of redox quinone/hydroquinone on the surface of nanocrystals enjoys increasing interest and performs the specific functions, such as biosensing, ultrasensitive detection, and biomimetic research.

3. Ubiquinone-quantum dot bioconjugates and their application

In particular, ubiquinones [coenzyme Q, (CoQ)] are composed of the redox-active ubiquinonyl ring with a tail of isoprenoid units in different homolog forms occurring in nature, which are the only lipid-soluble antioxidant and plays a very important role in the cell membrane physiology [33]. CoQ acts as a mobile electron carrier in the energy-transducing membranes of mitochondria, which can be reduced by NAD(P)H-dependent enzymes. The reduced form CoQH₂ is a potent radical scavenger and antioxidant that protects membranes and lipoproteins from peroxidations as a potent radical scavenger [34, 35]. The redox state can be determined not only by the extent of oxidation (oxidative stress), but also by that of reduction (enzymatic reaction). As well-known, fluorescence enhancement/quenching in QDs can be switched by electrochemically modulating electron transfer between attached molecules and QDs (**Figure 1**) [36]. For this purpose, three CoQ disulfide derivatives ([CoQC_nS]₂) possessing the basic ubiquinone structure of 2,3-dimethoxy-5-methyl-1,4-benzoquinone with different mercaptoalkyl side chain lengths at the 6-position (n = 1, 5, and 10) (**Figure 2**, left). The emission of functionalized QDs can be reversibly tuned in two directions, enhancement or

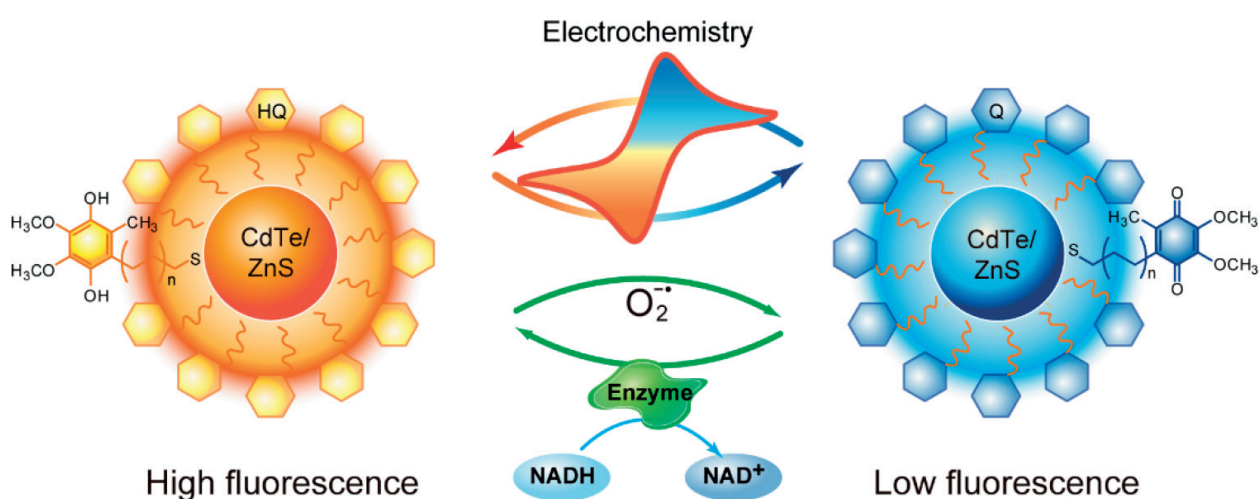


Figure 1. Schematic of fluorescence enhancement/quenching characteristics of CoQH₂ and CoQ-functionalized CdTe/ZnS QDs. Adapted with permission from [36]. Copyright 2011 Wiley-VCH Verlag GmbH & Co. KGaA.

quenching, depending on the different redox state of substrates bound to the surface of the QDs (**Figure 2**, right). Following photoexcitation of functionalized QD bioconjugates, the conductive band electron of QDs is transported to the lowest unoccupied molecular orbital of the oxidized ubiquinone acceptor and the electron is then went back to the valence band of QDs via nonradiative pathways. Thus, ubiquinones play the surface trap states acting as nonradiative de-excitation paths for photo-induced electron carriers, resulting in fluorescence quenching. It is worth noting that reduced ubiquinol ligands on the surface of QDs yield an obvious fluorescence enhancement. In this case, the photo-excited CoQH₂-QD bioconjugates decay to the ground state because the ubiquinols serve as poor electron donors. This switching results in recovering a high fluorescence compared to bare QDs. Furthermore, the reduced ubiquinols provide an efficient passivation of the surface trap states to overcome the potential surface defects, leading to a significantly enhanced fluorescence in CoQH₂-QD bioconjugates. According to energy band, bandgap of surface-capping ligand ubiquinol is larger than that of CdSe/ZnS QDs and hole trapping is also negligible. Upon photoexcitation, the resulting electrons and holes are confined in the surface regions of the ubiquinol-functionalized QDs, thus increasing the fluorescence. In addition, the fluorescence efficiency and stability of CoQH₂-QD bioconjugates against photo-oxidation has shown significant improvement due to the antioxidation effect of ubiquinol. Therefore, there is the remarkable fluorescence difference between CoQ and CoQH₂-capped QDs. Notably, the capping layer of reduced ubiquinol ligands enhances the QDs' fluorescence intensity significantly, while a modification using the oxidized ubiquinone ligands presents efficient quenching on fluorescence intensity of QDs under the identical conditions (**Figure 2**, right). We show fluorescence quenching efficiency to be dependent on alkyl chain spacer length of surface ligands, as more pronounced quenching was observed for C₂ spacer-modified QDs. Surface-attached CdTe/ZnS QDs exploiting coenzyme Q derivatives CoQ and CoQH₂ can be chemically attached to the surface of the QDs in an effort to mimic the electron transfer in the part of mitochondrial respiratory chain. Our system is extremely sensitive to NADH and superoxide radical (O₂^{•-}) species, and mimics a biological electron-transfer system in the part of the mitochondrial respiratory chain. In addition, *in situ* fluorescence spectra-electrochemical results further validate that the reduced state of ubiquinols significantly increase the fluorescence of QD bioconjugates, while the oxidized state of the ubiquinones decrease the fluorescence at varying degrees.

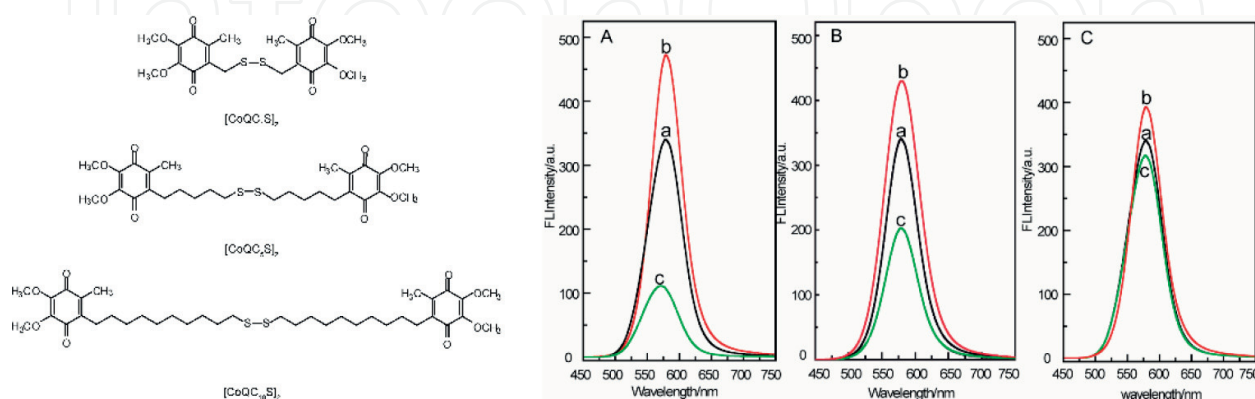


Figure 2. (Left) Chemical structures of synthesized [CoQC_nS]₂, $n = 1, 5, 10$. (Right) Fluorescence spectra of functionalized QDs. (a) CdTe/ZnS QDs, (b) [CoQH₂C_nS]₂, and (c) [CoQC_nS]₂-functionalized CdTe/ZnS QDs. A: $n = 1$, B: $n = 5$, C: $n = 10$. Adapted with permission from [36]. Copyright 2011 Wiley-VCH Verlag GmbH & Co. KGaA.

To further enhance the compatibility of ubiquinone-QD bioconjugates in biological system, the ligands Q₂NS, Q₅NS, and Q₁₀NS were designed and synthesized by a facile click reaction between ubiquinone with terminal alkynes and alkylazide-disulfides via copper(I) tris (benzyltriazolylmethyl) amine catalyzed 1,2,3-triazole formation [37] (**Figure 3a**). In this system, the quinoid moiety in the Q_nNS surface ligands was introduced to achieve the redox-switchable fluorescence properties for signal multiplexing. The 1,2,3-triazole groups can enhance the compatibility of Q_nNS-QDs in biological system because of the similarity with histidine. Three alkyl spacers (C₂, C₅, C₁₀) confer various electron-transfer abilities either the core or the surface of QDs. As a final point, the disulfide group facilitates modification of Q_nNS ligand to the surface of QDs. Using the Q_nNS-QD bioconjugates, enhancement or quenching of the fluorescence of QD bioconjugates can also be switched by modulating the redox state of surface-capping ubiquinone ligands (**Figure 3b**) [38].

Interestingly, the emission of QD bioconjugates was enhanced when the surface-attached ubiquinone layer was reduced to ubiquinol in the presence of NADH and complex I in an effort to mimic the initial stages of mitochondrial respiration. The fluorescence intensity of ubiquinol-QDs was decreased gradually when the O₂^{•−} was added. As the concentration of O₂^{•−} is higher, the luminescence of the QDs is quenched to a higher extent, consistent with the formation of a higher coverage of the oxidized ubiquinone-modified QDs. Moreover, these systems provide the general framework for the creation of probes to monitor the reactive oxygen species in living cells according to their redox state, suggesting that this principle can be generalized to many different biological systems and applications. To demonstrate 1,2,3-triazole groups incorporated into the ubiquinone ligands can enhance the compatibility of QD bioconjugates in biological systems, we investigated a time-dependent fluorescence process using ubiquinone-assembled QDs with or without 1,2,3-triazole groups. A significant increase in the incubation time was observed for the same enhancement of fluorescence compared to the triazole-linked ubiquinone-QDs in the presence of NADH and complex I (**Figure 3**). This is because that the triazole groups behave similarly to histidine ligands and can be used to cap enzymes through proteins- or peptide-affinity coordination of triazole residues, leading to the triazole ubiquinone ligands efficiently improving binding affinity with complex I. The ubiquinone-QD bioconjugate system could be used for monitoring in vitro and intracellular complex I levels by the fluorescence changes of QD. Epidemiological researches show that the activity of complex I of Parkinson patients is impaired. Therefore, this system can be employed as a potent fluorescence probe for early stage Parkinson disease diagnosis and progression monitoring by observing complex I levels in human neuroblastoma SH-SY5Y cells.

Another novel strategy that uses QDs functionalized with quinonyl ligands was developed [39]. A novel biosensor based on “switch-on” photoluminogenic strategy employing of quinonyl glycosides functionalized QDs for the ingenious and biospecific imaging of human hepatoma Hep-G2 cells that express transmembrane glycoprotein receptors (**Figure 4**). The closely coupled quinonyl glycoside ligands are envisioned to have dual functions: the quinone part acts as a quencher of QDs and the glycoside part as a ligand for targeting a specific receptor. Moreover, self-assembly of quinonyl glycosides to QDs through a sulfide bond may produce QD bioconjugates that expose the glycosides in a clustering manner, enhancing their binding avidity with the target receptors. We observed that the quenched fluorescence

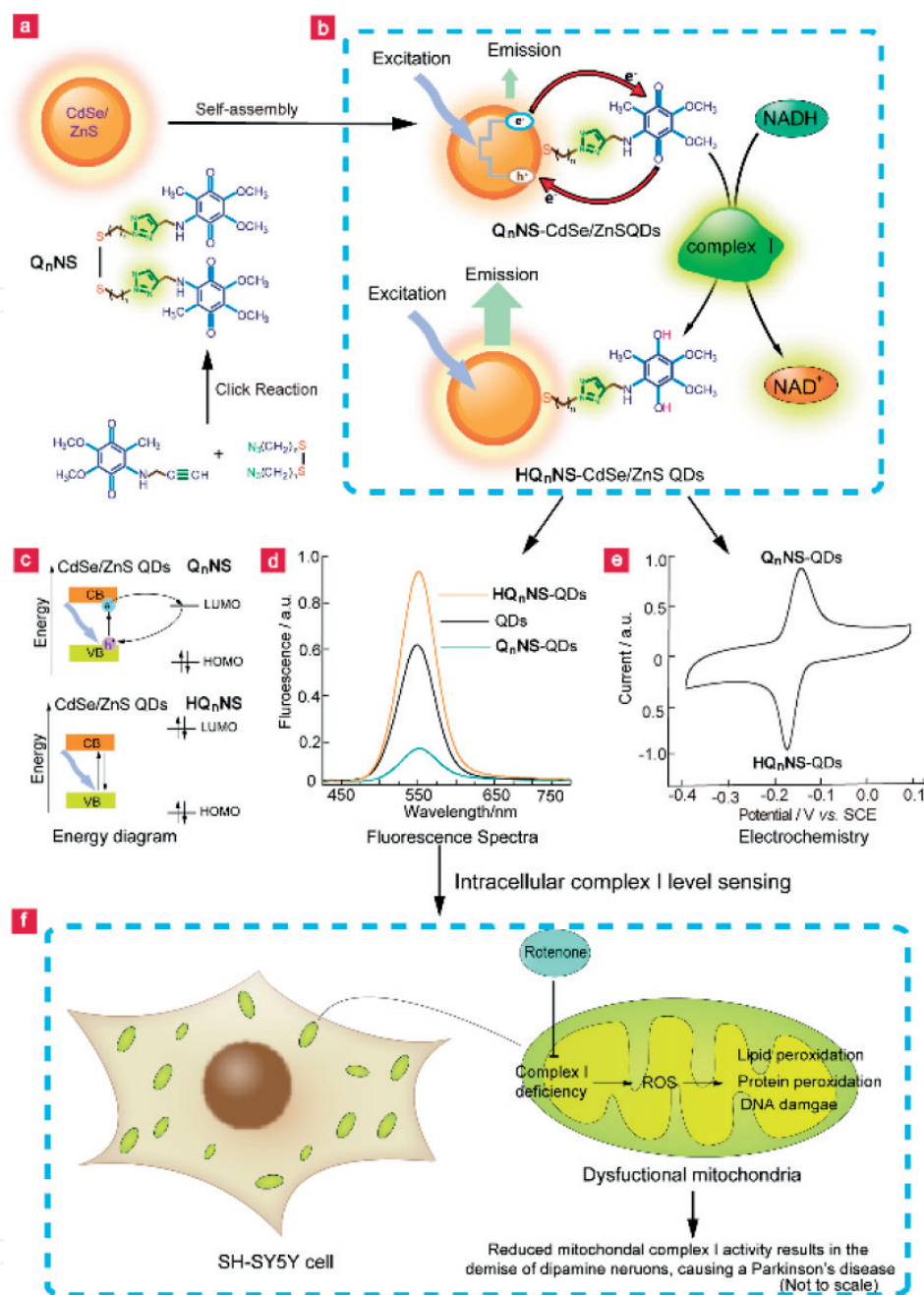


Figure 3. Schematic of ubiquinone-CdSe/ZnS QDs as redox fluorescence biosensor for Parkinson's disease diagnosis. (a) ubiquinone-terminated disulphides (Q_nNS) synthesis and self-assembly of Q_nNS on to CdSe/ZnS QDs. (b) Conceptual visualisation of Q_nNS -QDs as complex I sensor *in vitro*. Under oxidized state (Q_nNS), ubiquinone functions as a favorable electron acceptor, this results in effective QDs' fluorescence quenching. Addition of complex I to Q_nNS -QDs solution in the presence of NADH, ubiquinone coupled electron transfer and proton translocation from NADH, producing reduced ubiquinol (HQ_nNS) form on the surface of QDs to mimic the initial stages of the respiratory chain. Ubiquinol when in close proximity to the QDs produces fluorescence enhancement. (c) Energetic diagram of the QDs bioconjugates and possible electron transfer processes: electron transfer from the QDs CB to Q_nNS LUMO, followed by the back QDs VB. HQ_nNS only weakly accepts/donates electrons or energy and the excited QDs can return radiatively to the ground state. Under these conditions, the presence of HQ_nNS results in a significant fluorescence enhancement. (d) Fluorescence spectra of ubiquinone/ubiquinol- functionalised CdSe/ZnS QDs. e, Cyclic voltammetry of Q_nNS -CdSe/ZnS QDs. (f) Visualisation of Q_nNS -CdSe/ZnS QDs as an intracellular complex I sensor. The mitochondrial-specific neurotoxin, rotenone, inhibits complex I and leads to Parkinson's-like pathogenesis. Parkinson's disease is characterized by impaired activity of complex I in the electron-transfer chain of mitochondria. Adapted with permission from [38]. Copyright 2013 Nature Publishing Group.

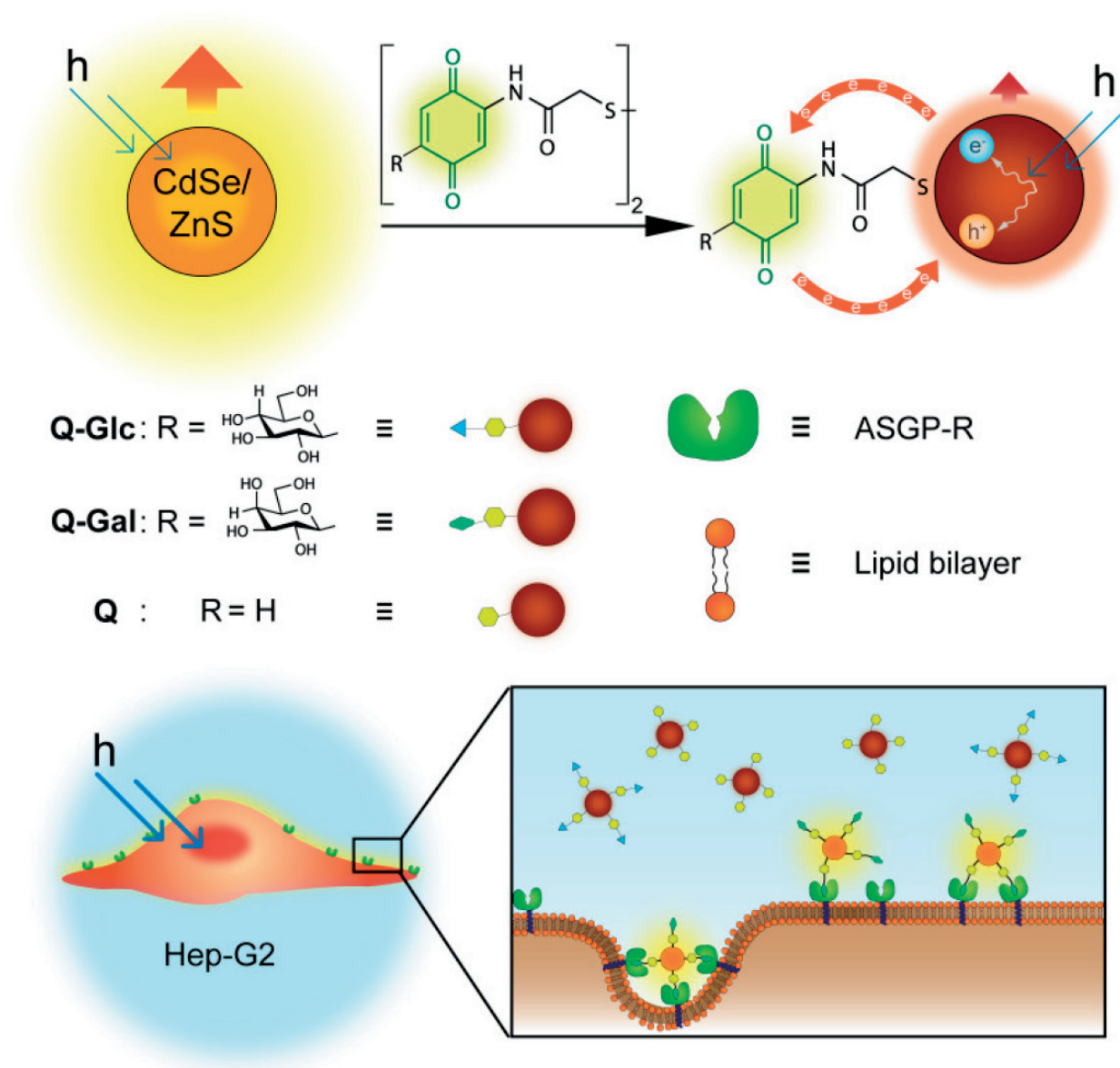


Figure 4. Schematic diagram of quinonyl glycosides functionalized QDs as a novel “switch-on” fluorescence probe for specific targeting and imaging transmembrane glycoprotein receptors of human hepatoma Hep-G2 cancer cells [Q-Glc: quinonyl glucoside disulfide; Q-Gal: quinonyl galactoside disulfide; Q: quinonyl disulfide]. Adapted from [39]. Copyright 2014 American Chemical Society.

of the functionalized QDs (by quinone) could be recovered by a lectin that selectively binds to the quinonyl glycosides clustering the QDs, but showed insignificant fluctuations toward a panel of nonselective lectins. We further determined that QDs coated with quinonyl galactosides could optically image transmembrane glycoprotein receptors of a hepatoma cell line in a target-specific manner (which they showed much weakened imaging ability toward cells with a reduced receptor level). This unique system, by taking advantage of the effective quenching ability of benzoquinone for QDs and natural ligand-receptor pairing on the cell surface (that recovers the signal), paves the way for the development of highly specific and low-background techniques for bioimaging of cancer cells as well as probing of unknown cell-surface receptors.

4. Dopamine-functionalized quantum dots and their application

Dopamine (DA) is an essential neurotransmitter in central nervous system and facilitates various functions in brain. DA-induced neurotoxicity has long been known to be triggered by the oxidation of DA and may play a role in pathological processes associated with neurodegeneration. Under oxidative stress, DA could readily oxidize to produce DA quinone catalyzed by tyrosinase in the presence of O_2 and contribute to the nucleophilic addition with sulfhydryl groups on free cysteine (Cys), glutathione, or Cys residue contained in protein [40, 41]. The interaction between DA quinone and Cys residue yields the formation of 5-Cys-DA in vitro and in vivo. As well-known, Cys residue is particularly critical for maintaining dynamic redox balance of cell and physiological function, which is directly correlated with the level of cellular stress. However, DA inactivation modification between Cys residue and DA quinone may disturb mitochondrial function, scavenge the thiol protein, inhibit protein function, and possibly lead to cell death [42]. Moreover, this modification decreases in the endogenous level of Cys residues, which is often found at the active site of functional proteins. Recent studies suggest that disturbance of Cys residue homeostasis may either lead to or result from oxidative stress in cell, contributing to mitochondrial dysfunction occurs early, and acts causally in neurodegenerative pathogenesis [43]. Therefore, it is of considerable significance to investigate the nature of this interaction process in physiology and pathology.

Due to the superior optical and photophysical properties of QDs, biorecognition or biocatalytic reactions have been followed by fluorescence resonance energy transfer or electron-transfer processes stimulated by redox-active biomolecule-functionalized QDs [44–50]. The DA-functionalized QDs were prepared through the following steps: (1) 596-nm-emitting thiohydracrylic acid capped CdTe/ZnS QDs and a redox-active DA thiol derivative (DAs) as surface-capping ligand were designed and synthesized; (2) the ligand molecule DAs was self-assembled onto the surface of QDs [51]. About 24 DAs molecules per QD were chosen as the optimal ratio from the spectra according to the QDs self-assembled with increasing ratio of DAs. DAs quinone on the surface of QD bioconjugates are generated in the enzymatic oxidation of DAs by tyrosinase/ O_2 , resulting in the fluorescence quenching (**Figure 5**). With adding a three-fold maximum tyrosinase/ O_2 , the fluorescence intensity of DAs-functionalized QDs was obviously quenched as expected. However, even much more excess tyrosinase/ O_2 did not greatly affect the fluorescence of bare CdTe/ZnS QDs ($\leq 10\%$ quenching). After DAs-QDs catalyzed by tyrosinase/ O_2 , the resulting product DAs quinone acting as an excellent electron acceptor is efficient for hole trapping of QDs and induces the fluorescence quenching. Fluorescence intensity of DAs quinone-QD bioconjugates recovered gradually upon addition of increasing amounts of Cys. Approximately 96% of the fluorescence was recovered after addition of Cys. It is worth noting that the 5-Cys-DAs containing catechol moiety on the functionalized QDs significantly recovered fluorescence. Here, the photo-excited-functionalized QD bioconjugates decay radiatively to the ground state of QDs because the 5-Cys-DAs ligands could function as poor electron acceptors. This in turn results in a fluorescence recovery due to the transformation from DAs quinone to DAs on the surface of functionalized QDs, blocking the electron transfer from QDs to benzoquinone. Only the presence of Cys residues (Cys or GSH) could induce rapid fluorescence recovery of the DAs quinone-functionalized QDs, confirming the specific coupling of Cys and DAs quinone in this system. In this study, photophysical properties of QDs

were used to monitor the redox process of DAs and the formation of 5-Cys-DAs by mimicking the interaction process that DA oxidizes to form DA quinone, which binds covalently to nucleophilic sulfhydryl groups on Cys residues. The enzymatic process catalyzes the transformation of ligand structure between DA quinone and catechol, leading to the fluorescence change of functionalized QD bioconjugates (**Figure 5**). Several lines of evidence suggest that disturbance of Cys residue

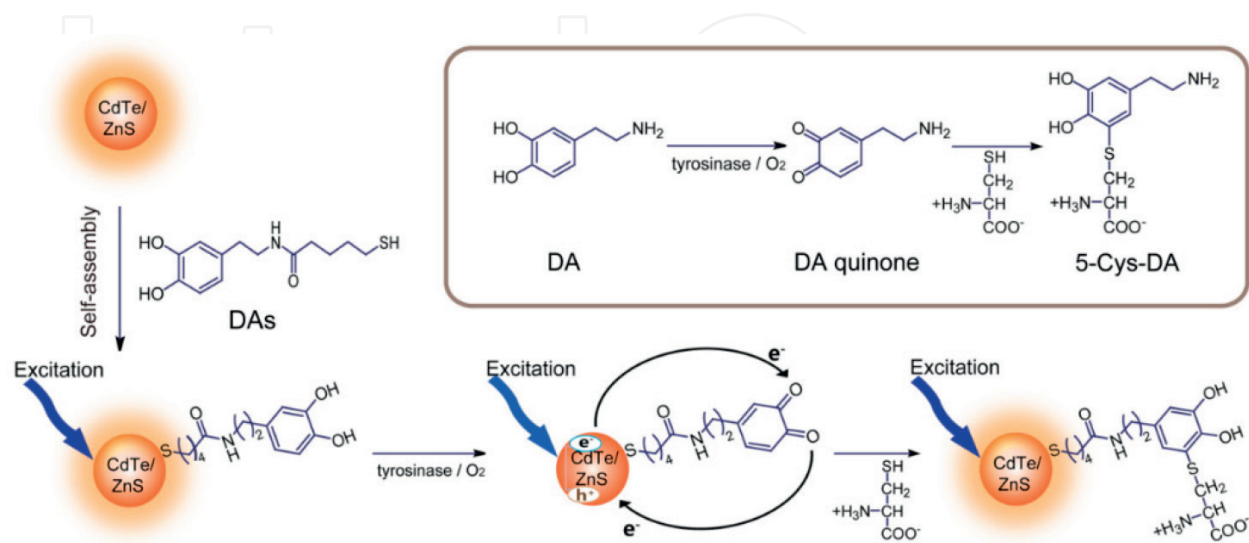


Figure 5. Schematic diagram of self-assembly and FL quenching/recovery characteristics of DAs-functionalized CdTe/ZnS QDs; Inset: schematic of the oxidation of DA and the irreversible interaction between Cys residue and DA quinone. Adapted from [51]. Copyright 2015 American Chemical Society.

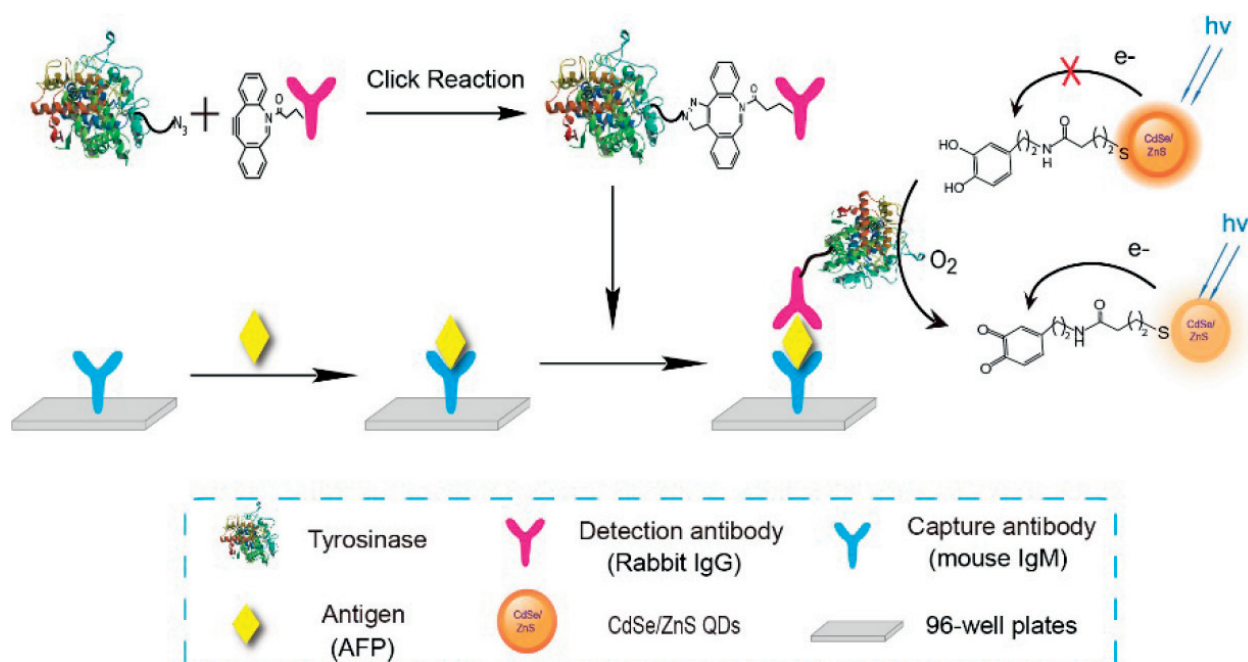


Figure 6. Schematic representation of redox-mediated indirect fluorescence immunoassay for the detection of biomarkers using DAs-functionalized CdSe/ZnS QDs. Adapted from [52]. Copyright 2016 American Chemical Society.

homeostasis may either lead to or result from oxidative stress in cell. In all major examples of neurodegenerative diseases, there is strong evidence that oxidative stress contribute to mitochondrial dysfunction occurs early and acts causally in disease pathogenesis. Thus, this specific fluorescence changes in our proposed system develop a powerful fluorescence sensor to follow the tracks of the neurotransmitter modification.

Inspired by redox-mediated fluorescence strategy, a redox-mediated indirect fluorescence immunoassay was developed for detecting the disease biomarker α -fetoprotein in a model based on DAs-immobilized CdSe/ZnS QDs (**Figure 6**) [52]. In this system, tyrosinase conjugated with the detection antibody was used as a bridge linking the QD fluorescence signals with the concentration of target disease biomarkers; the tyrosinase could catalyze enzymatic oxidation of DA to DA-quinone, resulting in fluorescence quenching in the presence of the analyte. Using this method, the detection limit for AFP was as low as 10 pM. This work provides a new pathway for the detection of disease biomarkers by RMFIA and has good potential for other applications.

5. Conclusion

By using redox-mediated fluorescence strategy, we demonstrated that coupling QDs with redox-active surface ligand is capable of fluorescence detecting of target analytes with high specificity. Ubiquinone-coupled QDs could be used for quantitative detection of ROS and target-specific imaging of transmembrane receptors in living cells. Dopamine as an electron donor could sensitize QDs through different mechanisms for monitoring dopaminergic neurotoxicity. Moreover, the improvement of QD-dopamine bioconjugates as biosensors was used for clinical diagnostic applications. Cumulatively, these results confirm a critical role for redox molecules, and especially quinone, in charge-transfer interactions with QDs for biological application.

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