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Review

Recent progress on the development of glutathione (GSH) selective fluorescent and colorimetric probes

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ABSTRACT

Glutathione (GSH) plays a key role in many cellular functions. Abnormal levels of GSH is considered to be sign of many diseases. As a result, various fluorescent imaging probes and/or chemosensors for GSH have been developed. Compared to other analytical methods, fluorescence has unique merits, such as excellent detection limits and sensitivity for use in imaging cells, tissues and small animals. However, colorimetric probes undergo distinct color changes, which in most cases can be detected by using the naked eye. This review of studies aimed at the development of GSH probes is presented in a format that is organized by structural features and chemical reactions of the probes. The topics include probes that are based on nanoparticles or nanocomposites, metal ion displacement and coordination and chemical reactions. The reaction based probes are further classified into probes that undergo cleavage of sulphonamide, sulfonate ester and related functional groups, Se—N bond cleavage, aryl substitution reactions, disulfide bond cleavage followed by cyclization, Michael additions, and other processes.

Contents

Abbreviations: GSH, glutathione; Cys, cystein; Hcy, homocystein; NPs, nanoparticles; CL, chemiluminescence; PEC, photoelectrochemical; MB, magnetic beads; CDC, carbon dot cluster; AuNPs, gold nanoparticles; ACD, anionic carbon dots; PFR, phenol formaldehyde resin; N-GQD, nitrogen-doped graphene quantum dot; ICT, intramolecular charge transfer; PET, photoinduced electron transfer; FRET, Förster resonance energy transfer; CTAB, cetrimonium bromide; QY, quantum yield; IFE, inner-filter effect; ESIPT, excited-state intramolecular proton transfer; NIR, near-infrared; NEM, *N*-ethylmaleimide; AD, Alzheimer's disease; LOD, limit of detection; BODIPY, Boron dipyrromethene difluoride; DNBS, 2,4-dinitrobenzenesulfonyl; NBD, 7-nitrobenzo-2-oxa-1,3-diazole; MOF, metalorganic frameworks; DFT, density functional theory; TMB, 3,3′,5,5′-tetramethylbenzidine; TMPyP, 5,10,15,20-tetrakis (1-methyl-4-pyridinio)porphyrin.

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1. Introduction

Glutathione (GSH, γ-glutamyl-cysteinyl-glycine), the most abundant thiol in cells, plays a key role in many cellular functions, especially those that govern the redox state of living cells [1]. In addition, GSH serves as an antioxidant to protect cells by trapping free radicals [2]. Accordingly, GSH is known to play a key role in the control of oxidative stress in redox homeostasis, which involves the interconversion of reduced sulfhydryl (GSH) and oxidized disulfide (GSSG) forms [3]. Abnormal levels of GSH also serve as signals for many diseases, including various human diseases such as AIDS, cancer, liver and lung damage and Parkinson's disease [4–6].

Owing to its importance, GSH has been the target of numerous studies aimed at developing fluorescent imaging probes and chemosensors [7–9]. Compared to other analytical methods, those that are based on fluorescence have several merits, such as excellent detection limits and applicability to image cells, tissues and small animals [10–13]. On the other hand, colorimetric probes induce distinct color changes that can be detected even by using the naked eye. Various approaches have been utilized to develop effective GSH probes. For example, MnO_2 nanosheets, which are efficient quenchers, have been used along with fluorescent nanoparticles (NPs) to construct probes. In this system, fluorescence of NPs is regenerated upon addition of GSH as a consequence of GSH promoted reduction MnO_2 to Mn^{2+}. Other common approaches take advantage of the strong nucleophilicity and strong metal ion affinities of this thiol.

In this review, we discuss recent contributions that have been made to the development of GSH selective fluorescent and colorimetric probes. Even though the probes undergo similar emission changes in the presence of the three biothiols such as GSH, Cys (cysteine) and Hcy (homocysteine), they are applicable to imaging GSH in the cells owing to its higher concentration than those of the other biothiols. Specifically, because the concentration of GSH in mammalian cells is in the range of 1–10 mM, which is much higher than that of Cys (30–200 μM) and Hcy (5–15 μM), the other biothiols do not interfere with detection of GSH even when the probes display similar reactivities towards GSH, Cys and Hcy. Most probes that take advantage of the high nucleophilicity of GSH operate irreversibly and are called "reaction based probes" or "chemodosimeters". However, a few reversible fluorescent probes with appropriate dissociation constants (K_d) have been recently investigated as GSH selective sensors.

Although reviews of biothiol sensors have been published to date, most focus on small molecule and reaction based probes. Importantly, no comprehensive review for GSH selective probes has been published thus far. This review covers contributions to the development of GSH probes from various groups in the 2010–2017 period, but a few noteworthy examples arising during 2005–2009 are also included. The presentation is organized according to the structural features and chemical reactions of the probes (Fig. 1). Following this format, the coverage focuses on strategies for the development of GSH probes that are based on nanoparticles and nanocomposites, metal ion displacement and coordination, and chemical reactions. The review of reaction based probes is further subdivided into those that rely on cleavage of sulphonamide, sulfonate ester and related functional groups, Se—N bond cleavage, aryl substitution reactions, disulfide bond cleavage and cyclization, and Michael additions.

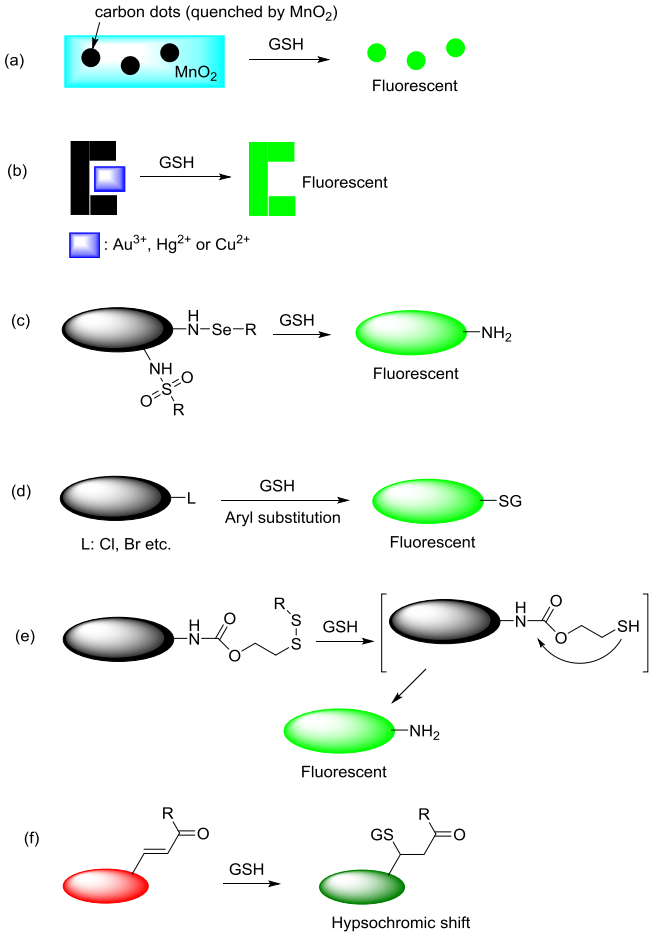

Fig. 1. Representative approaches to sense GSH. (a) Nanoparticle or nanocomposite based probes, (b) metal ion displacement approach, (c) probes based on the cleavage of sulphonamide, Se—N bond etc., (d) probes based on aryl substitution reaction, (e) probes based on the disulfide bond cleavage and cyclization, (f) Michael addition based probes.

2. Nanoparticle and nanocomposite based probes

Nanoparticles and nanocomposites have been extensively investigated for use as fluorescent and colorimetric probes [14,15]. In this section, we discuss the use of Au^{3+} and carbon dot cluster (CDC) combinations, carbon dots–MnO_2 nanocomposites, and carbon quantum dots (CDs)-fluorescent dye-Hg^{2+} hybrid systems as the basis for "off-on" type fluorescent probes for GSH.

A novel isoluminol-H_2O_2-Co^{2+} based chemiluminescence (CL) probe, relying on the reaction scheme shown in Fig. 2, was developed by Ding et al. [16]. This sensor, which utilizes CL arising from the isoluminol-H_2O_2-Co^{2+} system as a light source, was employed to image the biothiol GSH in cancer cells. The probe is comprised of an isoluminol moiety linked to polystyrene microspheres (PSMs) conjugated to magnetic beads (MB) through thiolated DNA. After magnetic separation, GSH cleaves the disulphide bond of the conjugate enabling Co^{2+} to promote the light producing CL reaction between the isoluminol moiety and H_2O_2, and PEC detection