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Simultaneous Visualization of Endogenous Hcy, Cys, GSH and their Transformation through Different Fluorescence Channels

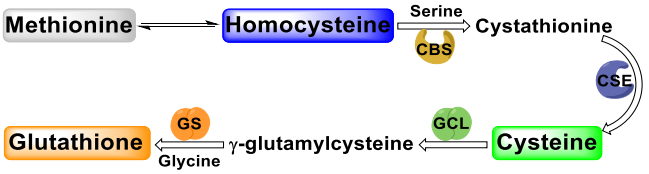
Guoxing Yin,[†,§] Tingting Niu,[‡,§] Ting Yu,[†,§] Yabing Gan,[†] Xinyu Sun,[†] Peng Yin,[,†] Haimin Chen,*[,‡] Youyu Zhang,[†] Haitao Li*[,†] and Shouzhuo Yao[†]*

Abstract: Studying biologically important species simultaneously is crucial to understand cellular functions and the root causes of related diseases. Direct visualization of endogenous biothiols in biological systems is of great value to understand their biological roles. Herein, a novel multi-signal fluorescent probe was rationally designed and exploited for simultaneous sensing of Hcy, Cys and GSH from different emission channels. This probe was successfully applied to the simultaneous discrimination and visualization of endogenous Hcy, Cys, GSH and their transformation in living cells.

The most abundant intracellular biothiols, homocysteine (Hcy), cysteine (Cys), and glutathione (GSH), are widely linked to physiological and pathological processes in complex biological environments.[1] A lot of research has demonstrated that aberrant levels of Cys/Hcy/GSH are related to a wide range of human diseases.[2] As shown in Scheme 1, Hcy, derived from methionine, is condensed with serine catalyzed by cystathionine β-synthase (CBS) to generate cystathionine, which is further converted to Cys by cystathionine γ-lyase (CSE).[3] Cys is one substrate for glutamate cysteine ligase (GCL) and glutathione synthetase (GS) to yield GSH.[4] Therefore, Hcy levels are tightly associated with the levels of Cys and GSH in living systems. Fluctuation in the concentration of one biothiol would influence another. In order to elucidate the complicated relationship between Hcy, Cys, GSH and understand the root causes of their related diseases, it is greatly challenging and significant to simultaneously differentiate and quantify endogenous Cys, Hcy and GSH in living cells and human serum.

Recently, compared to conventional analytical methods,[5] multi-signal fluorescent probes together with confocal fluorescence imaging techniques are widely applied to multicolor imaging due to their simultaneous and discriminative monitor of multiple analytes or dynamic processes for specific analyte as well as the virtues of fluorescent methods, such as noninvasive, relative low cost, high sensitivity and high selectivity.[6] Though a lot of fluorescent probes have been developed to sense and quantify endogenous and exogenous biothiols,[1b, 2b, 7] owing to their similarities in structures and properties and large differences in their concentrations, only several fluorescent probes that could simultaneously detect two or three species of Cys/Hcy/GSH at one time have been reported (Table S1).[3b, 8] To the best of our knowledge, there is no fluorescent probe that could simultaneously differentiate and image endogenous Cys, Hcy and GSH in living cells, partially due to the low concentration of Hcy.[1b] Herein, based on our previous report,[9] we rationally designed a novel multi-signal fluorescent probe with background-free, large fluorescence enhancement and high quantum yield (QY), which could simultaneously image intracellular Hcy, Cys, GSH and their dynamic changes from three different emission channels. This probe exhibited high selectivity and sensitivity for Hcy, Cys and GSH with a low detection limit of 0.7, 0.2 and 1 nM, respectively. This study will greatly improve the understanding of their generations, relationships, functions and metabolisms in biological systems, and promote the early diagnosis, intervention and treatment about their related diseases.

Under the guidance of our previous findings,[9] probe 1, featured with coumarin as fluorophore with twisted *N*,*N*-diethylamino group, will exhibit high quantum yield, fluorescence background-free, and good biocompatibility.[10] And ethyl 2-cyanoacrylate group in the probe would improve its solubility and cell permeability (Scheme 2).[12] Besides, judging from Guo's work and our previous research,[8g, 9] chloro atom in the 4-position of the coumarin moiety could initially be replaced by thiol group of biothiols to afford thio-coumarin derivatives, and the following rearrangement would result in amino/thio-coumarin derivatives. The cyano group at the α position of the Michael addition acceptor enables fast reaction kinetics for thiol addition,[7c,7d] and C=C bond breakage would be occured to form the intermediate of imine/iminium for amino addition (Scheme S2).[8j, 12] Thus, reactions between probe 1 with Cys, Hcy and GSH could yield different products with distinct signal outputs. And the simultaneous discrimination of Hcy, Cys and GSH from different fluorescence channels could be realized.



Scheme 1. The compact relationship between Hcy, Cys and GSH.

Initially, probe 1 was easily synthesized and well-characterized (Scheme S1, Figures S23-S30). Its sensing behavior towards biothiols was examined through UV-vis and fluorescence spectra in DMSO-PBS (pH 7.4, 10 mM, v/v, 4/6) at

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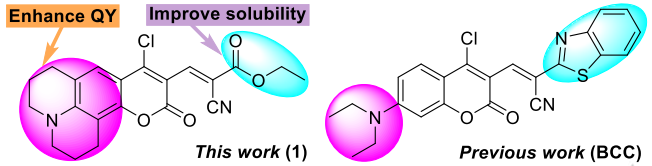
room temperature. As shown in Figure 1a, upon addition of Cys/Hcy/GSH, the initial absorption peak of probe 1 at 527 nm was decreased dramatically. For Hcy, two new peaks at 461 and 378 nm were emerged. Correspondingly, a significant fluorescence turn-on at 467 nm with 457-fold fluorescence increment was observed (λ_{ex} = 375 nm) (Figure 1b). For Cys, an increasing absorption peak at 397 nm was found. And a large fluorescence turn-on with 740-fold increment at 503 nm was observed when excited at 400 nm (Figure 1). Besides, for GSH, the initial absorption peak was decreased and a slight bathochromic shift was displayed. A new peak was found at 502 nm with a 25 nm blue shift, and the fluorescence spectra for probe with GSH demonstrated a 115-fold fluorescence enhancement at 568 nm (λ_{ex} = 500 nm) (Figure 1). Compared to our previous work,[9] probe 1 exhibited more favorable sensing properties, such as improved water solubility, minimal fluorescence background and high quantum yield (Table S2), which are beneficial for fluorescence imaging of endogenous Cys/Hcy/GSH with different concentrations.



Scheme 2. The comparison of probe BCC and probe 1.

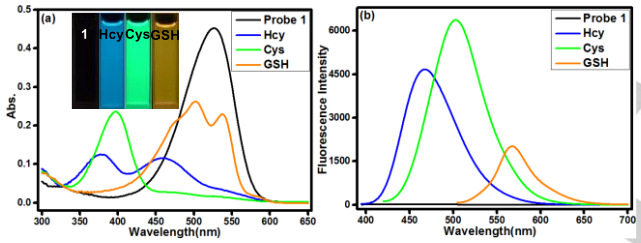


Figure 1. (a) Absorption spectra of probe 1 (10 μM) upon addition of 10 equiv. of biothiols (100 μM) at room temperature for 20 min. (b) The corresponding fluorescence spectra of probe 1 to 10 equiv. of Hcy (λ_{ex} = 375 nm), Cys (λ_{ex} = 400 nm), and GSH (λ_{ex} = 500 nm). Condition: DMSO-PBS (pH 7.4, 10 mM, v/v, 4/6). The inset photos show the color changes of probe 1 (10 μM) in the presence of 10 equiv. of Hcy, Cys and GSH under UV lamp at 365 nm, respectively.

In the following, results from time-dependent UV-vis and fluorescence spectra studies were further demonstrated that probe 1 could selectively discriminate Hcy, Cys and GSH from blue, green and yellow fluorescence channels, respectively (Figures S1-S7). The signals for Hcy, Cys and GSH could reach a plateau within a short time (15 min), which is beneficial for practical applications. The selectivity of probe 1 over other biologically related species were further assessed, including various amino acids, sulfur-containing compounds (Figure S9). Multi-signal outputs of probe 1 were only observed for Hcy, Cys and GSH when excited at 375, 400 and 500 nm, respectively, but there is no obvious fluorescence change to a series of other biologically related species. These results demonstrated the excellent selectivity of probe 1 for the simultaneous discrimination of Hcy, Cys, and GSH. In addition, based on thiol specific addition/rearrangement-cyclization reactions, probe 1 was able to preclude the cross-talk caused by sulfur-containing protein and other reactive sulfur species such as SO_2, H_2S_2 and H_2S, which are existed in living cells (Figure S9). Therefore, probe 1 exhibited superiorities over other fluorescent probes.[2d]

Next, fluorescence titration experiments were conducted carefully with three different channels. As shown in Figure 2, the dose-dependent fluorescence enhancement of probe 1 exhibited good linearity with the concentration of Hcy/Cys in the range from 0 to 30 μM, and the detection limits were calculated to be as low as 0.7 and 0.2 nM based on S/N = 3, respectively. The fluorescence intensities were linearly proportional to the amount of GSH from 0 to 10 μM and 10 to 25 μM with low detection limit (1 nM). Probe 1 was also suitable to be applied to the mixture of Cys/Hcy/GSH with different concentrations (Figures S10-S12). Upon excitation with specific wavelength, each specie from the mixture of Hcy/Cys/GSH could elicit dramatic fluorescence enhancement from specific channel. Furthermore, after sequentially reacted with Hcy/Cys/GSH, probe 1 exhibited significant fluorescence turn-on in the blue, green and red fluorescence channels, respectively (Figures S13). Therefore, probe 1 has the potential to simultaneously discriminate Hcy, Cys, GSH and monitor their transformation from three different emission channels in vitro and in complex biological environments.

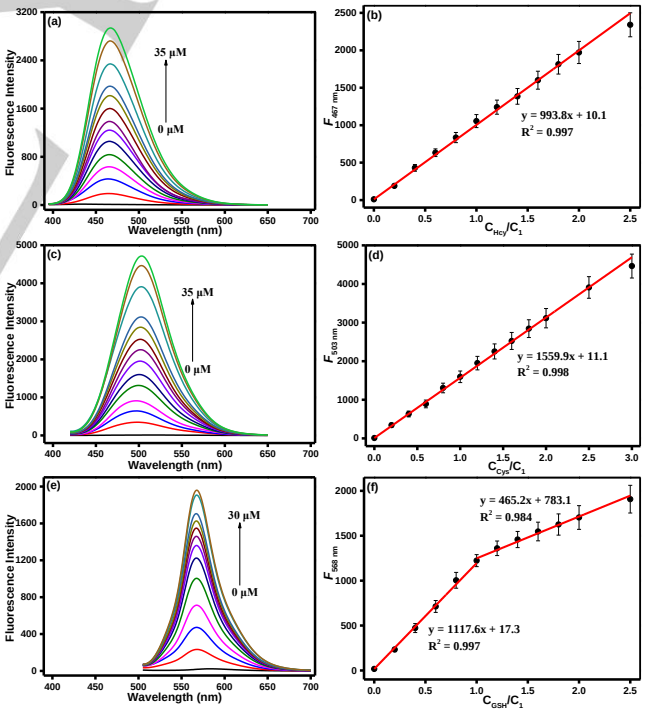


Figure 2. Fluorescence intensity spectra of 1 (10 μM) in the presence of (a) 0 to 35 μM Hcy excited at 375 nm, (c) 0 to 35 μM Cys excited at 400 nm and (e) 0 to 30 μM GSH excited at 500 nm, respectively. The linear changes of the fluorescence intensity of probe 1 at 467, 503 and 568 nm and as a function of (b) Hcy, (d) Cys and (f) GSH concentration, respectively. Condition: DMSO-PBS (pH 7.4, 10 mM, v/v, 4/6) at room temperature for 20 min. Slit (nm): 2.5/2.5.

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In order to understand the reaction mechanism between probe 1 and Cys/Hcy/GSH, several control compounds (C5-C9) were synthesized (Scheme S2), and characterized (Figures S31–S40). Judging from the LC-MS and HRMS spectra from the reactions between probe 1 with Hcy/Cys/GSH and absorption spectra of these control compounds (Figures S8 and S14-S16), reasonable reaction mechanisms were proposed for probe 1 with Hcy/Cys/GSH (Scheme S2).[11] The isolation of these products was failed, which may be due to their instabilities. Further mechanism studies are still investigated in our lab.

Subsequently, simultaneous visualizations of endogenous Hcy, Cys and GSH in living cells using probe 1 were conducted. Concentration of total homocysteine is normally below 15 uM and free homocysteine is minimal,[1b] so there is no report about fluorescence imaging of endogenous Hcy in living cells. Featured with high quantum yield ($QY_{1\text{-Hcy}}$ = 0.13), large fluorescence enhancement (457 fold for Hcy) and high sensitivity (LOD = 0.7 nM for Hcy), probe 1 would be suitable to monitor endogenous Hcy in living cells. In the advantage of low toxicity and good cell permeability of probe 1 (Figure S17), pretreated with N-ethylmaleimide (NEM, scavenger of SH compounds), almost no fluorescence could be observed after incubated with probe 1 (Figure S18, A1-A3). While, after subsequently treated with Hcy, Cys and GSH respectively, blue, green and red fluorescences were observed from three different emission channels (Figure S18, B-D, and Figure S19), which demonstrated that fluorescence imaging of Hcy, Cys and GSH simultaneously could be achieved with high selectivity. After cells were only incubated with probe 1, blue, green and red fluorescence images were obtained for the monitor of cellular Hcy, Cys and GSH in different living cells, respectively (Figure 3). These results exhibit excellent perspective for the simultaneous and quantitative fluorescence analysis of these important biothiols in living cells and human serum.

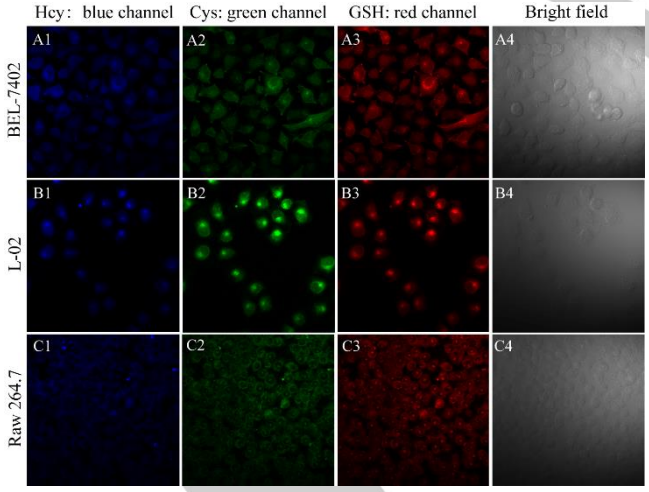

Figure 3. (A) BEL-7402, (B) L-02 cells and (C) Raw 264.7 were incubated with probe 1 for 30 min, then imaged. (A4-C4) represent the bright field images of A1-C1, respectively. (λ_{ex} = 405 nm, λ_{em} = 421 - 475 nm for the blue channel; λ_{ex} = 458 nm, λ_{em} = 500 - 550 nm for the green channel; and λ_{ex} = 543 nm, λ_{em} =552 - 617 nm for the red channel). Scale bar: 20 μm.

Dynamic fluorescence imaging for biothiols was further conducted. NEM was firstly used to eliminate SH-containing compounds and proteins in living cells. When only incubated with probe 1 in living cells, almost no fluorescence was observed from three emission channels up to 120 min (Figure S20). However, after incubated with exogenous Hcy and probe 1, blue and green fluorescence could be observed from different channels after 30 min. Green fluorescence was weakened along with the prolonged incubation time. While red fluorescence will be appeared after incubated for 60 min, then weakened (Figure 4). Meanwhile, when cells were incubated with exogenous Cys and probe 1, fluorescence changes could be observed from green and red fluorescence channels (Figure S21). These results demonstrated the transformation for Hcy, Cys and GSH was proceeded. And dynamic fluorescence images of Hcy/Cys/GSH were successful for the first time. In addition, it was found that this probe could be used to detect Hcy and Cys in algal cells. *Pyropia haitanensis* was taken as the experimental object. When it was stimulated by different stresses, different antioxidant states within the cells could be reflected from fluorescence images, but the red fluorescence was disturbed due to the effect of algal phycoerythrin (Figure S22).

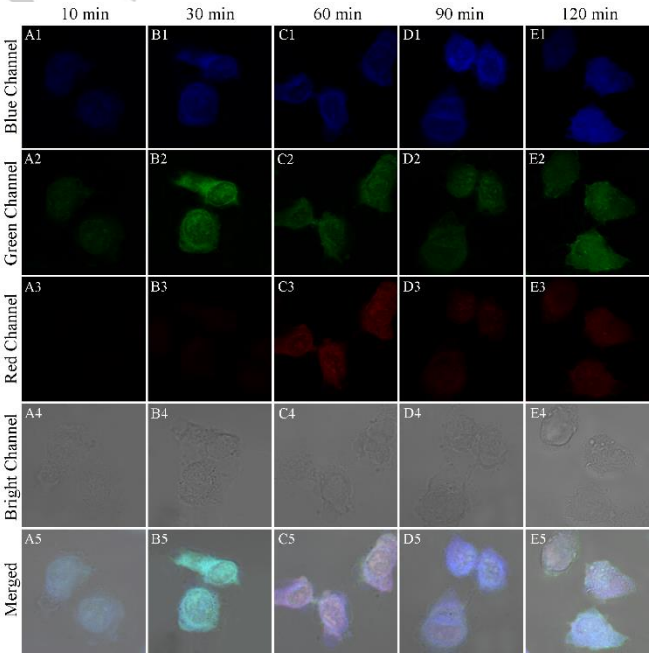

Figure 4. Confocal fluorescence images of Hcy in BEL-7402. (A-E) Cells were pretreated with NEM (0.25 mM, 30 min), then treated with probe (5 μM, 30 min), Hcy (100 μM) for 10, 30, 60, 90 and 120 min respectively, then imaged. (λ_{ex} = 405 nm, λ_{em} = 421 - 475 nm for the blue channel; λ_{ex} = 458 nm, λ_{em} = 500 - 550 nm for the green channel; and λ_{ex} = 543 nm, λ_{em} = 552 - 617 nm for the red channel). Scale bar: 10 μm.

In conclusion, a novel multi-signal fluorescent probe 1 has successfully designed and synthesized. Based on different reactions between probe 1 with Cys/Hcy/GSH, simultaneous discrimination and imaging of endogenous Hcy, Cys, GSH and their transformation via three emission channels in different living

cells was achieved for the first time. This probe also could be used to image Hcy and Cys in plants. More importantly, this research will promote the design of multi-signal probes and greatly improve our understanding about cellular functions and the root causes of disease, which are related with Cys/Hcy/GSH.

Acknowledgements

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Conflict of interest

The authors declare no competing financial interests.

Keywords: endogenous biothiols • transformation • fluorescent probe • simultaneous sensing

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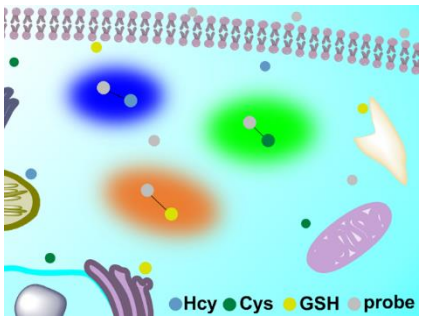

A multi-signal fluorescent probe was exploited for simultaneously differentiating and sensing of endogenous homocysteine, cysteine, glutathione and their transformation in living cells.

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