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ARTICLE TYPE

A highly sensitive and selective fluorescent probe for fast sensing of endogenous HClO in living cells

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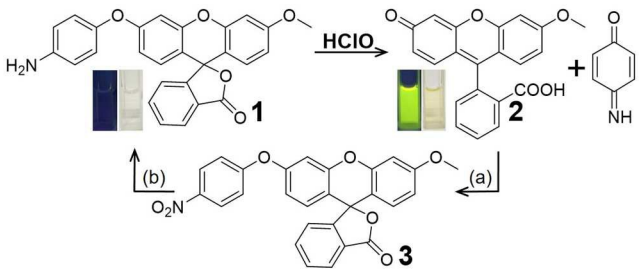
A new fluorescence probe was developed for HClO detection in physiological conditions, which displayed fast response ($t_{1/2}$ < 30 s) and large *off-on* (> 1000-fold) toward HClO with high sensitivity and selectivity. The probe was successfully applied for detection of both exogenous and endogenous HClO in living cells. Using the probe-based tool, we could observe the H_2S-induced HClO biogenesis in living cells for the first time.

Reactive oxygen species (ROS), including hydrogen peroxide (H_2O_2), hydroxyl radicals ($^{\bullet}OH$), peroxyl radicals ($ROO^{\bullet}$), singlet oxygen ($^1O_2$), superoxide anion radicals ($O_2^{\bullet-}$) and hypochlorous acid (HOCl), play important roles in various biological and pathological progresses.[1] HClO, one of the most important ROS, is known to be generated from the reaction between H_2O_2 and Cl^- catalysed by myeloperoxidase (MPO) *in vivo*.[2] As an important microbicidal effector, regulated production of HOCl is helpful for host innate immunity to cope with microbial invasion.[3] Excessive production of HClO, however, is closely related to numerous diseases, such as neuron degeneration, cardiovascular diseases, inflammatory diseases, cystic fibrosis and certain cancers.[4] Thus, it is of great value to develop efficient methods to detect HClO *in vivo* as well as to explore its biological functions.

Fluorescence-based methods are highly desirable and sensitive for *in-situ* and real-time visualization of HClO in living biological systems. As an ideal method, fluorescent probes were widely used to detect the biological HClO.[5-9] These fluorescent probes are majorly based on the specific HClO-induced chemical reactions. For instance, a deformylation reaction-based probe was reported for *in vivo* imaging of HClO.[6] Yoon *et. al*. reported the first fluorescent probe for HClO based on the selective oxidation of a B-H bond.[7] Peng *et. al.* developed an "enhanced PET"-based probe for imaging elesclomol-induced HClO in cancer cells.[8] Moreover, the oxidation of catechol was also applied for design of fast-response HClO probe.[9] Though these great successes have been achieved, we still need to develop advanced probes with high sensitivity, high selectivity and fast-response properties for real-time detection of low-concentration endogenous HClO in living biological samples. Moreover, such probe-based tools will further enable exploration of ROS biology, which is still at the infant status.

We have been interested in development of fluorescent probes for H_2S and biothiols for some time.[10] Based on the probe-based tools, the H_2O_2-induced H_2S biogenesis was observed in living cells.[11] We therefore hope to investigate the possible crosstalk between H_2S and other ROS such as HClO. Herein, the fast oxidation of *p*-aminophenyl ether moiety was employed as the receptor for HClO,[5b] and a highly sensitive and selective fluorescence probe **1** for HClO was developed. The probe **1** showed fast response ($t_{1/2}$ < 30 s) and very low detection limit for HClO (0.65 nM), which was successfully used to observe the H_2S-induced HClO biogenesis in living cells for the first time.

To realize large fluorescence response, we chose methoxyfluorescein as fluorophore, which displayed very large *off-on* from the spirocylized conformation to the π-conjugation conformation.[12] As shown in Scheme 1, probe **1** was synthesized from facile two-step reactions with good isolation yields, and was well characterized by ^1H NMR, ^{13}C NMR and high-resolution mass spectra (HRMS) (see ESI). As expected, the spirocylized probe **1** was colorless and non-fluorescent. After reaction with HClO, the spirocyclic structure was unlocked and the green fluorescence of **2** is released so as to achieve more than 1000-fold fluorescence enhancement.



Scheme 1. Synthesis of probe **1** for HClO detection. (a) *p*-fluoronitrobenzene, NaH, Cs_2CO_3, 86%; (b) $SnCl_2•2H_2O$, concd. HCl/H_2O_2, 49%. Inset: photos of **1** (20 μM) in the absence or presence of HClO (1 eq.) in PBS buffer (50 mM, pH 7.4 containing 5% EtOH) under 365 nm UV lamp or daylight.

With the probe **1** in hand, we examined the absorption and fluorescence spectra of **1** with HClO in buffer (pH 7.4). **1** (20 μM) showed no obvious absorption peak due to separation of the π-conjugation system, while addition of HClO (1 eq.) triggered new absorption profiles with maxima at around 465 nm (Fig. 1A), implying fluorophore **2** was produced.[13] The reaction products were confirmed by HRMS (Fig. S1), and the colour of the reaction solution changed from colorless to yellow (scheme 1). **1** (5 μM) was non-fluorescent, while a strong emission at around

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515 nm was observed immediately when HClO (1 eq.) was added (Fig. S2). As shown in Fig. 1B, the reaction of **1** with HClO (1 eq.) almost finished within 5 min with $t_{1/2}$ < 30 s, implying that **1** was a very fast-response probe for HClO detection. This property was significant because of the short lifetime of endogenous HClO in living biological systems. The fluorescence increase at 515 nm was found to be up to 1046-fold, which is one of the largest *off-on* probes for HClO.[5-9] Such large emission response could provide a high signal to noise ratio for HClO detection in living cells. The result for stability showed that **1** was very stable within 30 min in PBS buffer (Fig. 1B).

Considering the low concentration of HClO in biological systems, excellent sensitivity for a fluorescent HClO probe is necessary. To gain detailed information about the sensitivity of **1**, the emission spectra was closely monitored by addition of various low concentrations of HClO into the probe for 10 min (Fig. 1C). The emissions at 515 nm were linearly related to the concentrations of HClO from 0.1 to 1.0 μM (Fig. 1D). The detection limit was determined to be 0.65 ± 0.01 nM using the 3σ/k method,[14] which is comparable to the most sensitive HClO probe (0.33 nM).[5c] Such nanomolar low detection limit should be beneficial to the detection of endogenous HClO.

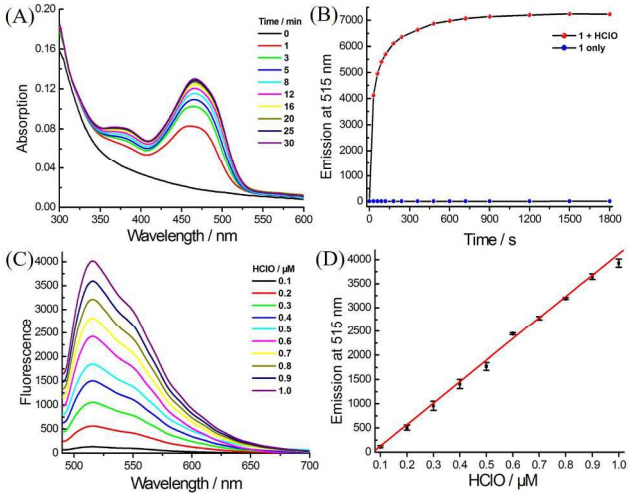

Fig. 1. (A) Time-dependent absorption spectra of **1** (20 μM) toward HClO (20 μM). (B) Time-dependent emissions of **1** (5 μM) at 515 nm in the presence or absence of HClO (5 μM). (C) Fluorescent spectra of probe **1** (5 μM) with diverse low concentrations of HClO (0.1-1.0 μM). (D) Linear relationship (r = 0.9989) between emissions at 515 nm and concentrations of HClO. All experiments were performed in PBS buffer (50 mM, pH 7.4 containing 5% EtOH) at room temperature.

One of the most important capabilities for a fluorescent probe to detect HClO is to exhibit distinguishable response toward HClO over other ROS species and analytes. To evaluate the specific nature of **1** for HClO, it was incubated with various ions, RSS, RNS and ROS in PBS buffer (pH 7.4) separately, and the fluorescence increase at 515 nm was recorded (Fig. 2). Among all species, only $^{\bullet}$OH, ^{t}BuOO$^{\bullet}$ and $ONOO^-$ triggered very slight fluorescence response. However, the fluorescence increase for $^{\bullet}$OH (20 eq.), ^{t}BuOO$^{\bullet}$ (20 eq.) and $ONOO^-$ (4 eq.) were only 15, 14 and 32 fold, respectively, which is extremely lower than the response caused by HClO (1 eq., 1046 fold). Specially, no obvious fluorescence increase was observed when Na_2S (30 eq.) was added (lane 11). These results clearly demonstrated the superior selectivity of **1** toward HClO over other analytes.

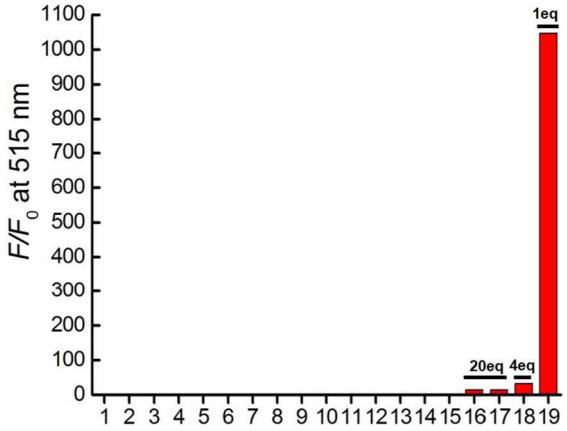

Fig. 2. Relative emissions of **1** (5 μM) toward various ions, RSS, RNS and ROS at 515 nm. Lanes from 1 to 19: Fe^{2+} (100 μM), Zn^{2+} (100 μM), Mg^{2+} (100 μM), SO_3^{2-} (100 μM), HSO_3^- (100 μM), $S_2O_3^{2-}$ (100 μM), SO_4^{2-} (100 μM), Cys (500 μM), Hcy (500 μM), GSH (5 mM), Na_2S (150 μM), H_2O_2 (100 μM), ^{t}BuOOH (100 μM), O_2^- (100 μM), NO_2^- (100 μM), $^{\bullet}$OH (100 μM), ^{t}BuOO$^{\bullet}$ (100 μM), $ONOO^-$ (20 μM), HOCl (5 μM). Experiments were carried out in PBS buffer (50 mM, pH 7.4 containing 5% EtOH) at room temperature for 10 min.

To investigate the effects of pH values on the detection of HClO, time-dependent fluorescence response of **1** (5 μM) with HClO (1 eq.) in PBS buffer at different pH values was examined (Fig. S3). **1** was nonfluorescent at all tested pH values. After reaction with HClO, the solution of **1** exhibited large turn-on for a wide range of pH from 4.5 to 9.5, and the turn-on fold at pH 6.5-7.5 was higher. For the response rate, **1** reacted with HClO relatively faster at lower pH values. These results indicated that the probe **1** was suitable for use at physiological pH. The cytotoxicity of **1** was also evaluated using RAW 264.7 cells (mouse macrophage cell line) by methyl thiazolyl tetrazolium (MTT) assay (Fig. S4). **1** did not show much obvious cytotoxicity at 0.1-10 μM range within 24 h, implying that **1** should be suitable for bioimaging of HClO in living cells.

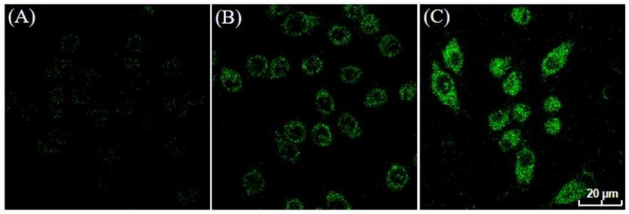

Fig. 3. Confocal microscopy images of exogenous HClO detection in living RAW 264.7 cells using **1**. Cells were incubated with (A) **1** (5 μM) alone for 30 min; (B) **1** (5 μM) for 30 min and then NaClO (5 μM) for another 30 min; (C) **1** (5 μM) for 30 min and then NaClO (20 μM) for another 30 min. Emissions were collected at green channel (500-600 nm) with 458 nm excitation. Scale bar, 20 μm.

To explore the biological applicability of **1**, we firstly examined whether **1** could be used to detect intracellular HClO in living cells. RAW 264.7 cells were incubated with **1** (5 μM) for 30 min, washed by PBS buffer, then treated with different

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concentrations of NaClO (5 or 20 μM) for another 30 min and imaged using a confocal fluorescence microscopy immediately (Fig. 3). Cells incubated with **1** alone showed fairly weak fluorescence, while bright green fluorescence was observed upon addition of 1 eq. NaClO, and more remarkable fluorescence appeared when treated by 4 eq. NaClO (Fig. 3B-C and Fig. S6). These results indicated that **1** could be applied to detect intracellular HClO in a concentration-dependent fashion.

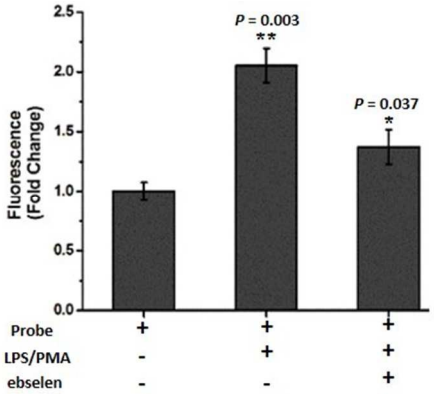

Fig. 4. The relative fluorescence of confocal microscopy images for detection of LPS/PMA-stimulated endogenous HClO in living RAW 264.7 cells using **1**. $N = 3$ fields of cells, error bars are ± sd.

For detection of the endogenous HClO using **1**, RAW 264.7 cells were stimulated with lipopolysaccharides (LPS, 1 μg/ml) for 12 h followed by phorobol myristate acetate (PMA, 1 μg/ml) for 1 h to generate HClO.[6] As shown in Fig. S8B, obvious increase in fluorescence was observed after cells were stimulated with the LPS/PMA. Ebselen, a ROS scavenger that could decrease the HClO level, was used in the control experiment. The LPS/PMA-treated cells displayed fairly weaker fluorescence in the presence of ebselen (Fig. S8C). The relative emission (Fig. 4) clearly showcased that stimulation of LPS/PMA could trigger about 2.1-fold fluorescence increase, which was higher than the ebselen-treated control group (about 1.3 fold). Inspired by Peng's work,[8] **1** was also used to detect elesclomol-induced HClO in living cancer cells. As expected, notable increase in fluorescence was observed after MCF-7 cells were treated with elesclomol (2 μM) for 1 or 2 h (Fig. S9). These results elucidated that **1** could be used for imaging of endogenous HClO in living cells.

Encouraged with the above results, we further employed the probe **1** for investigation of possible crosstalk between H_2S and HClO in living cells. To this end, cells were treated with H_2S (150 μM) for 1 h, washed with PBS buffer, and then incubated with **1** (5 μM) for 30 min. To our delight, H_2S-treated cells exhibited remarkable green fluorescence with the mean intensity about 3.3-fold higher than that of **1**-stained cells (Fig. 5A, B and D). While the ebselen-treated cells in the control group displayed much weaker fluorescence, showing around 1.8-fold fluorescence increase than that of **1**-stained cells (Fig. 5C and D). To further investigate the H_2S-induced HClO biogenesis, concentration-dependent experiments were carried out and the order of incubation was also studied. We found that H_2S-treated cells all displayed strong fluorescence when 50-150 μM H_2S was added first (Fig. S11). When **1** was added first, H_2S-treated cells also showed stronger fluorescence than those incubated with **1** alone. Taken together, these data clearly demonstrated that endogenous HClO could be generated under the simulation of exogenous H_2S in living cells. Previously, we reported a dual-response fluorescent probe to clarify the H_2O_2-induced H_2S biogenesis in living cells.[11a] Herein, we discovered that the living cells could generate HClO spontaneously to deal with the reductive pressure caused by exogenous H_2S. We supposed that the redox atomosphere in cells should be balanced to maintain the normal cell growth. The biobalance proposals include the possible mutual inducement on the production of both ROS and RSS.[15] Our finding in this work should be helpful for further understanding the intracellular redox homeostasis.

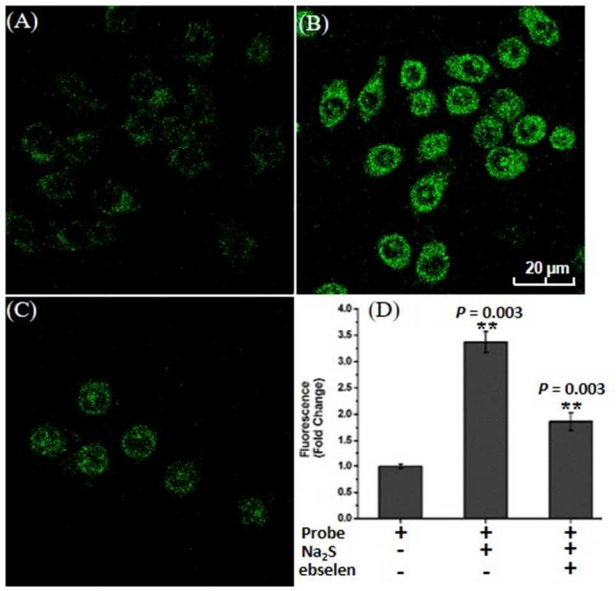

Fig. 5. Confocal microscopy images of H_2S-induced endogenous HClO detection in living RAW 264.7 cells using **1**. Cells were incubated with (A) **1** (5 μM) alone for 30 min; (B) H_2S (150 μM) for 1 h, then **1** (5 μM) for 30 min. (C) Cells were pretreated with ebselen (100 μM) for 30 min. (D) The mean fluorescence and relative ratio for images A-C. Emissions were collected at green channel (500-600 nm) with 458 nm excitation. Scale bar, 20 μm. $N = 3$ fields of cells, error bars are ± sd.

In summary, we report a new fluorescent HClO probe **1**, which displayed very fast response ($t_{1/2} < 30$ s) toward HClO (1 eq.) and possessed high selectivity over other analytes. Due to the ring-opening reaction of methoxyfluorescein, **1** showed very large fluorescence *off-on* (1046-fold) upon reaction with HClO. High sensitivity of **1** with a detection limit as low as 0.65 nM was beneficial to detection of endogenous HClO in living cells. Importantly, using the probe **1**, we revealed the H_2S-induced endogenous HClO biogenesis in living cells for the first time, which could help to understand the intracellular redox homeostasis. This probe should be an excellent tool for further exploring the biological functions of HClO as well as its crosstalk with other intracellular molecules.

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Notes and references

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‡The authors pay equal contributions to this work.

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Coverpicture

A highly sensitive and fast-response fluorescent probe for HClO detection was developed and employed to reveal the H_2S-induced HClO biogenesis in living cells.