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Review

Targeted cysteine and glutathione detection in extra/intracellular systems by copper-based fluorescent imaging probes

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ABSTRACT

The three primary biothiols are cysteine (Cys), glutathione (GSH), and homocysteine (Hcy) which plays key functions in a variety of biological processes. Intracellular and extracellular microenvironments are perfectly regulated in the living system, while in case of any fluctuations in the redox, buffer level may lead to several diseases. The unbalance in the extracellular compartment is influenced by the changes in intracellular metabolism and these are correlated with cellular processes such as death, differentiation, and proliferation, in the live system. Therefore, a study was performed to develop copper-based fluorescence probes for the sensitive and selective detection of extracellular and intracellular targets such as cysteine (Cys) and glutathione (GSH) respectively. Conversely, the quenched fluorescence of complex (Probes + Cu) by the coordination of either Cys or GSH, leads to retained Cu^{2+} ion due to its approximate binding with Cys or GSH. In this review, we have segmented the reported probes according to the fluorophore used, analyzed their photophysical characteristics, and highlighted the advantages and disadvantages of each (limit of detection, mechanism).

1. Introduction

Cysteine (Cys), homocysteine (Hcy), and glutathione (GSH) are crucial to maintain the redox balance in biological systems among other biological thiols and take part in intracellular signal transduction [1,2]. Despite their comparable structural and chemical features, they have diverse functions in biological activities. (Fig. 1). They can also act as antioxidant, defending cells and tissues from free radicals and reactive oxygen species (ROS) [3–6]. In all living organisms, both intracellular and extracellular redox buffers are well-regulated [7–9]. The redox buffers can maintain the microenvironment of reduced intracellular and oxidized extracellular compartments [10,11]. The redox buffer of Cys to cystine (Cys/CyssCy) system may occur in the range of 20–300 μM existing in the extracellular matrix [12,13]. In particular, Cys amino acid (AA) is involved in various biological processes specifically cross-linking through disulfide bonds, and also involved in detoxification, secondary protein synthesis, metabolism of the living system [14–19], etc. However, a deficiency of Cys causes several diseases related to fat loss, skin lesions, edema, liver damage, loss of muscle, and hematopoiesis [20–22]. Its elevated level leads to various diseases such as Parkinson's disease, Alzheimer's disease, cardiovascular disease, slow growth in children and rheumatoid arthritis [23–29]. GSH is another important essential thiol-containing amino acid involved in maintaining the redox environment in the biological system [30]. It is an antioxidant, which defends against unsought toxins and free radicals present in intracellular partitions such as mitochondria, nucleus, and cytosol in the concentration range of 2–10 mM [31]. Diseases like liver damage, leukocyte loss, neurological disorder, cancer, etc are directly related to the change in the level of GSH concentration [32–39]. Mostly, the extracellular matrix of Cys is more reducing than the intracellular matrix of GSH. Remarkably, Cys/CyssCy and GSH/GSSG redox couples are dominants in the extracellular and intracellular compartments respectively [40–42]. Indeed, the redox reaction of Cys (8–10 μM) /CyssCy (40–50 μM) corresponds to the potential at −80 mV, however, the pathological cells existing in the extracellular region of Cys/CyssCy redox potential range is −62 to −20 mV [43]. An elevated level of GSH, affects the cell proliferation redox potential at −260 mV, and the redox couple for GSH/GSSG in normal cells is around −120 mV [44]. A balanced redox performance between Cys and GSH is highly essential in a living system, which leads to monitoring human health anxieties.

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