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Synthetic fluorescent probes to map metallostasis and intracellular fate of zinc and copper

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ABSTRACT

The intracellular tracking of zinc and copper, metals essential for life, is nowadays pivotal to unravel the complex mechanism that involves the physiological or pathological role of such elements. Traditional methods to determine cellular copper and zinc levels, including those based on the use of fluorescent probes, are aimed at scrutinizing the metallome, to identify both the individual species and their concentrations. The metallome, however, is also a nonstatic concept, as it responds to environmental perturbations in biologically relevant pathways, with highly dynamic spatiotemporal changes. Through an overview of improvements and limits of the state of the art of synthetic fluorescent probes for the detection of intracellular zinc and copper, we report here new routes for the design and the synthesis of novel metal coordination compounds able to overcome the present weaknesses for a new concept of dynamic metallostasis.

1. Introduction

1.1. The biological role of zinc and copper in the cell

Inorganic cofactors are pivotal to physiological processes and play central roles in protein and nucleic acid biochemistry [1]. The biology of metal ions is primarily due to the diverse reaction types, their ability to act as redox centers, the ability of their complexes to transport oxygen, and their ability to act as molecular sensors in signal transduction. Structural analyses of proteins estimated that approximately 33–47% are metal bound, and roughly half of them contain metals in the catalytic sites [2].

Plasma and cells contain d-block metal ions both firmly complexed in metalloproteins and loosely bound in a series of labile complexes with other proteins or low molecular weight ligands in competitive chemical equilibrium [2e–g]. However, the cellular level of unbound metal ions is very low. Such a low total metal concentration in the cell influences the distribution of metals bound to different ligands, depending on the thermodynamic stability constants. Moreover, it is relevant to mention the issue of chemical speciation, when a metal ion might exhibit different coordination environments at the same binding site of the ligand [2h–i].

Ion-specific channels tightly regulate the dynamic concentration of various metals inside cells. When homeostasis is lost, mismetabolism of s- and d-block elements can contribute significantly to pathogenesis of several diseases [3–5]. For example, the neurobiological implications of s-block metal ions, including Na^+, K^+, Ca^{2+}, and Mg^{2+}, have been widely studied [6].

In recent years, d-block metals have received more attention because of their implications in neurophysiology and neuropathology, with particular regard to aging and neurodegenerative diseases. In brain tissue, d-block metal concentration is approximately 10,000-fold higher than the concentration of neuropeptides and normal neurotransmitters, so d-block metals are essential elements for the brain. Specifically, neurodegenerative disorders, Alzheimer disease, prion disease, Parkinson disease, and amyotrophic lateral sclerosis, have been related to an alteration of some metal concentrations (metal-ion hypothesis): manganese, iron, copper, and zinc [7]. Among the d-block elements, $Cu^{+/2+}$ and Zn^{2+} are crucial because they are present as important cofactors of various enzymes and numerous proteins.

In recent decades, numerous efforts have been aimed at tracking copper (in the Cu^+ and Cu^{2+} oxidation states) and zinc (Zn^{2+}) in living cells under normal and pathological conditions to understand the link between dyshomeostasis of these metal ions and the occurrence of a pathological condition.

1.2. Static and dynamic metallome concepts

Traditional methods to scrutinize the copper and zinc levels in the cell (atomic absorption spectroscopy, inductively coupled plasma-mass spectrometry, laser ablation, and more recently, synchrotron X-ray microscopy) as well as most of the studies based on the use of fluorescent probes are aimed at determining the identities of the individual complex species (i.e., qualitative metallomics) and their concentration (quantitative metallomics).

A recent metallomic study of prokaryotic systems highlighted the limits of current knowledge and suggested that the bioinorganic physiology of eukaryotes is indeed more complex than previously recognized [8].

The metallome [9] can be a static concept, covering the significant issues of (1) how an element (metal or metalloid) is distributed among the cellular compartments of a given cell type, (2) its coordination environment, and (3) the concentrations of the individual metal species present.

The metallome, however, can also be a dynamic concept, by analogy to the proteome or metabolome, in the sense that it responds in biologically important ways to environmental changes, with an infinite number of possible variations, both spatially and temporally. A wide network of metal transporters and chaperones, together with transcription factors and metallothioneins, however, guarantees the intracellular metallostasis (metal homeostasis) [9] of biometals as copper and zinc ions, whereas different, tightly regulated, trafficking pathways allow for the metal ion partner recognition and subcellular localization [10]. The determination of cellular metal trafficking with spatial and temporal resolution, oxidation state specificity, and bioavailability is an important goal to understand the homeostasis of metal ions in physiological and, in particular, pathological conditions.

1.3. Scope of this review

The main spectroscopic tools to detect important analytes in vivo and in vitro are magnetic resonance imaging [11] and laser scanning confocal microscopy [12], respectively.

In this review we focus on intracellular cations, specifically copper and zinc, and their mapping by laser scanning confocal microscopy using synthetic fluorescent probes. An overview is given of the existing reporters for tracking copper and zinc trafficking, both inside and outside cells, starting from the first-generation sensors and including the newest, state-of-the-art, ones. The other two important classes of metallosensors – namely,