Coordination Chemistry Reviews xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Coordination Chemistry Reviews

journal homepage: www.elsevier.com/locate/ccr

Review

Bright lights down under: Metal ion complexes turning the spotlight on metabolic processes at the cellular level ☆

Todd A. Gillam [a], Martin J. Sweetman [a,b], Christie A. Bader [c], Janna L. Morrison [d], John D. Hayball [b,e], Doug A. Brooks [c], Sally E. Plush [a,f,*]

[a] School of Pharmacy and Medical Sciences, University of South Australia, Adelaide, SA 5000, Australia
[b] Experimental Therapeutics Laboratory, Hanson Institute and Sansom Institute, School of Pharmacy and Medical Sciences, University of South Australia, Adelaide, SA 5000, Australia
[c] Mechanisms in Cell Biology and Disease Research Group, School of Pharmacy and Medical Sciences, Sansom Institute for Health Research, University of South Australia, Adelaide, Australia
[d] Early Origins of Adult Health Research Group, School of Pharmacy and Medical Sciences, Sansom Institute for Health Research, University of South Australia, Adelaide, South Australia 5000, Australia
[e] Robinson Research Institute, Discipline of Obstetrics and Gynaecology, School of Medicine, University of Adelaide, SA 5005, Australia
[f] Future Industries Institute, University of South Australia, Mawson Lakes, SA 5095, Australia

ARTICLE INFO

Article history:
Received 29 September 2017
Received in revised form 20 November 2017
Accepted 21 November 2017
Available online xxxx

ABSTRACT

The widespread uptake and use of emissive metal ion complexes for investigating cellular structure, composition and function, is evidence of the effectiveness and vast potential for this type of imaging probe. Metal ion complexes provide significant advantages over their organic fluorophore counterparts, including long emission lifetime, resistance to photobleaching and the capacity to readily modify their peripheral chemistry to target specific organelles, signalling pathways and individual molecules. This review will discuss recent progress in the development and use of metal ion complexes, specifically for studying metabolic diseases at the cellular level. Advanced metal ion complexes for organelle imaging and the detection of biorelevant species, to elaborate complexes for understanding cellular mechanisms and recent therapeutic applications will be reviewed. To align with the special issue, Coordination Chemistry Reviews: Coordination Chemistry in Australia, the work of Australian researchers actively engaged in this field is featured prominently, along with key developments from the global research community.

Contents

☆ Author ORCID IDs: 0000-0003-2611-1991 (Todd A. Gillam), 0000-0002-9074-2125 (Martin J. Sweetman), 0000-0002-4653-912X (Christie A. Bader), 0000-0002-8602-8519 (Janna L. Morrison), 0000-0002-3089-4506 (John D. Hayball), 0000-0001-9098-3626 (Doug A. Brooks), 0000-0002-9999-9154 (Sally E. Plush).
* Corresponding author at: School of Pharmacy and Medical Sciences, University of South Australia, Adelaide, SA 5000, Australia.
E-mail address: sally.plush@unisa.edu.au (S.E. Plush).

https://doi.org/10.1016/j.ccr.2017.11.026
0010-8545/

1. Introduction

Australia has a rich history in the research and application of metal ion complexes in biology, from the pioneering work of Francis Dwyer in the 1950s, to the current developments of our international research collaboration, showing heterogeneous arrangement of polar lipids within the matrix of cellular lipid droplets [1–3]. In recent times, there has been considerable research effort directed towards using metal ion complexes to enhance the understanding of intracellular processes and, in particular, in relation to disease pathogenesis [4]. The combination of advanced imaging techniques and the synthesis of highly emissive, novel metal ion complexes is now allowing researchers to visualise and identify subcellular components in unprecedented detail [5,6]. This, coupled with the availability of responsive bio-analytical metal ion complexes that selectively report the detection of specific metabolites, is allowing researchers to understand biological mechanisms as never before [7]. It is envisaged that understanding these mechanisms will lead to the development of accurate and early diagnosis of pathogenic conditions and vital medical breakthroughs with the development of targeted therapeutics.

A significant area of research where the use of metal ion complexes will provide valuable new insights is in understanding metabolic processes. The World Health Organisation (WHO) has identified that annually there are 40 million deaths, which equates to 70% of all deaths worldwide are due to noncommunicable diseases including cancer, cardiovascular disease, chronic lung disease and diabetes [8]. An underlying link between these diseases is altered cellular metabolism. To address the impact of metabolic disease in the population, research efforts are focused on discerning the mechanistic basis of these pathologies at a molecular level. The detailed understanding of the mechanisms underpinning the pathogenesis of cancer or diabetes, and the effective targeting of diseased cells with therapeutic agents, may provide a paradigm shift in how diagnosis and treatment are practiced.

Presently, a range of diagnostic and investigative tools exist, such as fluorescence microscopes and magnetic resonance imaging (MRI) instruments, that allow detection and imaging of diseased cells and tissue. These techniques require the cells to be appropriately identified and labelled, where chemical probes provide both selective targeting and contrasting features that allow differentiation from endogenous biological material. The current key methods for whole body imaging of disease tissues include positron emission tomography (PET) and MRI, both of which provide excellent spatial resolution as whole-body imaging platforms. Metal ion complexes of gadolinium are particularly effective contrast agents for MRI due to their effect on the T1 relaxation times on surrounding nuclei [9]. At the cellular and subcellular level, fluorescence microscopy and flow cytometry are routinely used to image and track (in real-time) specifically labelled cells, organelles, biomolecules and metabolites of interest.

Metal ion complexes are uniquely positioned as imaging agents for disease because they possess the necessary physical and chemical properties for detailed imaging. The ability to alter the chelating ligands of the metal ion complex can facilitate the selective accumulation of the complex in diseased tissues (such as tumours), cells or organelles of interest [10–12]. In terms of investigating the fundamental mechanisms of metabolism, fluorescence microscopy is more commonly used than MRI or PET, although the uses vary between research and clinical settings. To date, fluorescence microscopy for cellular imaging has largely utilised emissive agents based on organic fluorophores, such as small fluorescent molecules or fluorescently labelled antibodies. Organic fluorophores suffer significant limitations however, including photobleaching and short emissive lifetimes (nanoseconds). Fluorescently labelled antibodies offer high substrate labelling specificity, though unfortunately require cell fixation for imaging, which does not permit the visualisation of dynamic cellular processes. In contrast, emissive metal ion complexes exhibit high quantum yields, long-lived visible emission (milliseconds rather than nanoseconds) and are resistant to photo-bleaching [13]. Careful construction can also yield metal ion complexes with a certain level of selectivity for labelling specific cells or organelles [4]. Importantly, many emissive metal ion complexes that have been developed allow live cell imaging, as such they are particularly applicable to visualising live-dynamic processes which may be altered in disease [14,15].

Emissive metal ion complexes provide an ideal platform for the development of cellular imaging agents for both fluorescence microscopy and flow cytometry [13,16–18]. Fluorescence microscopy is particularly useful for observing discrepancies in cellular morphology, while flow cytometry can rapidly differentiate selectively labelled cells from within a mixed population. Metal ion complexes have also been developed that function to report on the presence of key metabolites, providing greater insights into cellular functions. Additionally, many metal ion complexes provide an excellent platform for multimodal imaging that may combine Fourier transform infrared (FTIR), Raman mapping, PET or MRI [19,20]. Due to the metal centre, these complexes are also useful analytes for inductively coupled plasma mass spectrometry (ICP-MS), allowing their cellular uptake to be accurately quantified [21,22]. ICP-MS is regarded as the most reliable method for the accurate determination of metals, with sensitivity in the parts per trillion range [23]. Fortunately, emissive metal ions used in imaging agents are a rarity within the cellular matrix and can be separated from an organic matrix by acidic or microwave digestion of biological samples, reducing matrix interferences.

The favourable emissive characteristics (photo-bleaching resistance and long emissive lifetimes) and potential biocompatibility (live cell imaging) of metal ion complexes has accelerated the exploitation of this type of probe by biologists. It is now highly relevant for chemists to pursue with earnest, the synthesis of metal ion complexes furnished with ligands and moieties that will enable highly specific interactions with relevant biomolecules. Biologists require imaging agents with novel biological specificities and substrate specific responses, to allow the visualisation of the intricate subcellular processes involved in different disease conditions. Due to the chemical structure and photophysical properties of this class of compounds, metal ion complexes offer great potential for developing selective, sensitive, compatible and versatile imaging agents to study cellular mechanisms at the molecular level.

Luminescent metal ion complexes are derived from two distinct categories. Firstly, low-spin transition metal complexes, such as Re (I), Ru(II), Ir(III) and Pt(II) [24,25]. Secondly, complexes of optically emissive lanthanoid(III) ions, such as Eu(III) and Tb(III), which are

Please cite this article in press as: T.A. Gillam et al., Bright lights down under: Metal ion complexes turning the spotlight on metabolic processes at the cellular level, Coord. Chem. Rev. (2017), https://doi.org/10.1016/j.ccr.2017.11.026