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Current Opinion in Chemical Biology

Approaches to the design of catalytic metallodrugs

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Metal ions are known to act as catalytic centres in metallo-enzymes. On the other hand, low-molecular-weight metal complexes are widely used as catalysts in chemical systems. However, small catalysts do not have a large protein ligand to provide substrate selectivity and minimize catalyst poisoning. Despite the challenges that the lack of a protein ligand might pose, some success in the use of metal catalysts for biochemical transformations has been reported. Here, we present a brief overview of such reports, especially involving catalytic reactions in cells. Examples include C–C bond formation, deprotection and functional group modification, degradation of biomolecules, and redox modulation. We discuss four classes of catalytic redox modulators: photosensitizers, superoxide dismutase mimics, thiol oxidants, and transfer hydrogenation catalysts. Catalytic metallodrugs offer the prospect of low-dose therapy and a challenging new design strategy for future exploration.

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Current Opinion in Chemical Biology 2015, **25**:172–183

This review comes from a themed issue on **Biocatalysis and biotransformation**

Edited by **Thomas R Ward** and **Valentin Köhler**

For a complete overview see the Issue and the Editorial

Available online 12th March 2015

http://dx.doi.org/10.1016/j.cbpa.2015.01.024

Introduction

Metal-based catalysts, metallo-enzymes, are well known in natural biological systems. These are often based on transition metal ions surrounded by proteins, with sites carefully designed to allow the selective recognition of substrates, protecting somewhat the metal ion from poisoning. Examples include manganese, iron, copper, zinc and molybdenum in all major classes of enzymes: oxidoreductases, transferases, hydrolases, lyases, isomerases and ligases.

The potential value of using natural metallo-enzymes or synthetic metal catalysts as drugs has already been recognized. The enzyme SOD for example has been in clinical trials as an oral agent for the treatment of age-related macular degeneration (NCT00800995) [1]. Interestingly the Mn^{II} MRI contrast agent Mangafodipir (MnDPDP) also possesses SOD activity, and Calmangafodipir ($Ca_4Mn(DPDP)_5$) is in Phase II clinical trials (NCT01619423) for treatment of metastatic colorectal cancer [1].

Metallo-drugs with catalytic properties can potentially be administered in smaller doses and with lower toxicity. Furthermore, catalytic drugs are likely to have novel mechanisms of action which might circumvent the development of drug resistance. However, low-molecular-weight catalysts are known to be easily poisoned in the presence of nucleophiles [2]. Retaining the activity of metal-based catalysts in biological media is, therefore, challenging on account of the presence of many biomolecules. Despite the difficulties, four major groups of 'catalytic metallodrugs' have been explored recently with some remarkable successes, those relating to C–C bond formation, deprotection and functional group modification, degradation of biomolecules, and redox modulation. We discuss four classes of catalytic redox modulators: photosensitizers, superoxide dismutase mimics, thiol oxidants and transfer hydrogenation catalysts. The potential of these catalytic systems to progress from model reactions, to cellular and eventually *in vivo* activity and to become approved drugs, is of particular interest (Table 1).

Formation of C–C bonds

Reactions such as azide–alkynyl cycloadditions [3], Suzuki–Miyaura [4–7] or Sonogashira [8] cross-couplings have been explored as synthetic tools for C–C bond formation *in vitro* and *in vivo*. For example, Pd^0 nanoparticles can carry out Suzuki–Miyaura cross-coupling reactions inside living cells. The nanoparticles can be delivered to cells encapsulated in polystyrene microspheres, once inside cells, the nanoparticles can be used for fluorescent labelling [4]. Palladium(II) compounds such as $[Pd(OAc)_2(ADHP)_2]$ (ADHP = 2-amino-4,6-dihydroxypyrimidine), can also catalyse Suzuki–Miyaura cross-coupling and have been used to label modified I-containing proteins on cell surfaces with fluorescent tags bearing boronic acid in *Escherichia coli* [5–7]. Similarly, the complex $[Pd(OAc)_2(N,N\text{-dimethylADHP})_2]$ has been used for fluorescent-labelling of homopropargylglycine-modified ubiquinone and peptides *via* a copper-free Sonogashira reaction [8]. Copper-free Shonogashira in modified *E. coli* and Shigella cells has also been performed using $Pd(NO_3)_2$ to fluorescently label allyl-containing proteins [9]. Copper(I) has been used to perform azyl–alkyne cycloadditions in combination with ligands such as TBTA, THPTA, BTTAA or BTTES (Figure 1). Using such a method, different cell membrane proteins

Table 1

Examples of metal catalysis studied *in cellulo* or *in vivo*

Metal complex	Reaction	Function/use	Cell system
C–C bond formation			
Cu(I)-TBTA (or similar)	Azyl–alkine cycloadditions	Labelling of modified proteins containing alkyne or azyl groups	*E. coli*, HeLa, CHO, Jurkat cells, Zebra fish
$[Pd(OAc)_2(ADHP)_2]$	Suzuki–Miyaura cross coupling	Fluorescence labelling of cell-surface proteins	*E. coli*
$[Pd(OAc)_2(DMDHP)_2]$	Cu-free Sonogashira	Labelling of alkyl-containing proteins	*E. coli*
$Pd(NO_3)_2$	Cu-free Sonogashira	Labelling of alkyl-containing proteins	Shigella cells
Pd^0 nanoparticles	Suzuki–Miyaura cross coupling	Fluorescence labelling	HeLa cells
Deprotection and functional group modifications			
Pd^0 nanoparticles (PET microspheres)	Carbamate cleavage	Activation of pro-fluorophores protected by carbamates	HeLa cells
Pd^0 nanoparticles (PET macrospheres)	Carbamate cleavage Dealkylation of amines	Activation of pro-fluorophores or pro-drugs	Zebra fish
$[Pd(dba)_2]$, $[(Allyl)PdCl]_2$	Carbamate cleavage	Activation of pro-fluorophores protected by carbamates; selective activation of proteins containing lysine protected aminoacids	HeLa, HEK293T, CHO, CaCo-2, A549, NIH3T3 cells
[Fe(TPP)Cl]	Reduction of aromatic azides	Activation of azides/fluorescence imaging	HeLa cells, zebra fish, *Caenorhabditis elegans*
$[Cp^*Ru(\eta^6\text{-pyrene})]PF_6$	Carbamates cleavage	Activation of pro-fluorophores protected by allyl-carbamates	HeLa cells
$[Cp^*Ru(COD)Cl]$	Carbamates cleavage	Activation of pro-fluorophores protected by allyl-carbamates	HeLa cells
$[CpRu(QA)(\eta^3\text{-allyl})]PF_6$	Carbamate cleavage	Activation of pro-fluorophores or pro-drugs protected by allyl-carbamates	HeLa cells
Degradation of biomolecules			
Cu(II)-ATCUN-R	Cleavage of RNA	Hepatitis C and HIV	Huh7 cells (Hepatitis C) Jurkat cells (HIV)
Ni(II)-ATCUN-R	Cleavage of RNA	Hepatitis C and HIV	Huh7 cells (Hepatitis C) Jurkat cells (HIV)

have been labelled with fluorescent tags in *E. coli*, HeLa, CHO and Jurkat cells [10,11]. More interestingly, the reaction was also executed successfully in mammalian cells and embryonic zebra fish [12]. This topic has been extensively reviewed recently [13–15].

Deprotection and functional group modification

This area of research is remarkably young with only limited examples, but shows much promise. Examples are the Pd^0 nanoparticles mentioned above for the Suzuki–Miyaura reaction [4]. Such particles encapsulated in polystyrene microspheres catalyse the cleavage of allyl-carbamate protected groups [4]. The catalytic reaction is effective in HeLa cells where allyl-carbamate-protected-rhodamine 110 was administered before the administration of the nanoparticles, giving intense fluorescence after the liberation of rhodamine 110 [4].

A similar approach has also been used for the activation of drugs such as modified 5-fluorouracyl, protected at the N1 with allyl, propargyl or benzyl groups. The modified drug was administered and activated in zebra fish by Pd^0 nanoparticles attached to macrospheres of polystyrene (150 μm diameter, larger than human cells). The Pd^0 nanoparticles are capable of catalysing the extracellular dealkylation of the N-alkyl fluoracyl [16••]. The same Pd^0 nanoparticles also activated pro-drugs protected with carbamates such as gemcitabine [17].

Meggers *et al.* have reported a series of compounds which are capable of cleaving carbamates in protected amines, using Ru^{II} compounds instead of Pd^0, for example, $[(Cp^*)Ru(COD)Cl]$ (COD = cyclooctadiene) (Figure 1) [18,19] and $[(Cp^*)Ru(\eta^6\text{-pyrene})]PF_6$. The latter is inactive until irradiated with light (λ = 330 nm) and further releases the pyrene moiety. Both complexes activate a derivative of rhodamine 110 protected with allyl-carbamates in HeLa cells (Figure 1). However, the presence of thiols is required [19,20]. More recently, the catalytic cleavage of allyl-carbamates in cells has been greatly improved by the use of the Ru^{IV} complexes such as $[CpRu(QA\text{-}R)(\eta^3\text{-allyl})]PF_6$ (QA = 2-quinolinecarboxylate; R = π-donating groups). These also activate protected fluorophores and protected anticancer drugs such as N-(allyloxycarbonyl) doxorubicin, inside HeLa cells [21].

Chen *et al.* have recently reported the use of four Pd compounds as catalysts for the deprotection of carbamates. These compounds were tested for the deprotection of allyl-carbamate-protected and propargyloxy-carbamate-protected rhodamine 110 and also protected