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Inorganic Self-assembly: Going Bio

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The use of self-assembly for building complex functional structures is a current topic of interest in supramolecular chemistry. In this context, the use of biomolecule-based building blocks has paved the way for the development of intracellular assemblies. Currently, the potential functionality of such assemblies in biomedical applications is being disclosed. On the other hand, the use of inorganic (metal-based) building blocks is still in its infancy. The construction of inorganic self-assemblies *in-bio* is particularly challenging and demands great efforts to reach applications. However, the plethora of thinkable advantages related to the use of inorganic self-assembly in living cells must fuel new discoveries in this area. This Concept reviews the current advances, perspectives, and challenges in inorganic self-assembly in living systems.

Introduction

Supramolecular chemistry was developed by the hand of inorganic chemistry. The fundamental works of Cram, Lehn, and Pedersen have strong connections to inorganic and coordination chemistry.[1] The developments in the understanding of non-covalent interactions and the applications of tools from organic and inorganic chemistry have moved from the relatively simple macrocyclic hosts-guest complexes[2] to highly engineered molecular designs. On one hand, discrete entities such as the mechanically interlocked molecules (rotaxanes, catenanes, and knots),[3,4] or the supramolecular coordination complexes (metallacages, metallacycles, helicates, etc.) have been reported.[5,6] On the other hand, the creation of supramolecular polymers[7] and networks with further dimensionalities, such as Metal-Organic Frameworks (MOFs)[8,9] or the Hydrogen-Bonded Organic Frameworks (HOFs)[10] have also been achieved. Further, the dynamic nature of non-covalent bonds has been used to impair supramolecular systems with functionality, motion, and stimuli-responsive behaviors, leading to the creation of molecular machines.[11–13]

Self-assembly is one of the central paradigms (if not the central) of supramolecular chemistry. It is based on the codification of information[14] through the chemical design of the assembling entities and the media in which they interact,[15,16] and the posterior translation of that information by recognition operations that ultimately yield characteristic structures, whose formation is directed by thermodynamical and kinetical factors.[17,18] It is worth noting that self-assembly is not a concept bound to the molecular level and can be identified virtually at all levels of complexity of the matter.[19] Thus, self-assembly is the tendency of discrete entities of the same or diverse nature to spontaneously interact with each other to form ordered structures of higher complexity.[19,20] Despite being prevalent in nature, only after the emergence of supramolecular chemistry the design and control of self-assembly became an important topic.

Living organisms are the most complex self-assembled structures. The cells, as their constitutive units, are complex self-assemblies whose function is in many ways based on the dynamic stimuli-responsive organization of hierarchically assembled constructs. Although many of fundamental chemical pathways in cells are well-known, we are far from fully describing cells' complex function and the way in which these self-replicative, self-assembled, and out-of-equilibrium systems emerged is still mysterious.[21] The astonishing complex function of cells has inspired supramolecular chemists to generate artificial systems featuring complex self-assembly pathways, stimuli-responsive and dissipative behavior.[22–26] The so-called biomimetic self-assembly[27] has produced amazing examples, but still their complexity is far from that of living systems.[28–31] The advances and challenges in the different branches of this area have been recently summarized in different reviews and critical works.[32–38]

Bioorthogonal chemistry – a term coined by Carolyn Bertozzi, that describes the use of living cells' milieu as a reaction flask – has been one of the main achievements of the chemistry of this century, as recognized by the 2022 Nobel Prize in Chemistry.[39] Nowadays, it is possible to extend this concept and envision the emergence of other bioorthogonal processes,[40] for example bioorthogonal self-assembly: namely, the self-assembly of exogenous materials into the living environment (*in-bio*). Many of the existing reports of the latter harvest from the cellular machinery, i.e. enzyme-instructed self-assembly (EISA),[41,42] to chemically activate the building blocks, triggering the self-assembly. This strategy has been adopted in order to gain some spatial-temporal control over the self-assembly process, which is an important challenge.[43] Also, most of the available examples are based on biomolecules to avoid undesirable toxicity and ensure the biocompatibility of the process.[44–46] Indeed, the scarceness of examples portraying metal-containing building blocks can be due to the reactivity that metallic

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centers typically exhibit in biological conditions, which is nevertheless responsible for their usefulness in medicinal chemistry, i.e. it is the reason for both the compounds' therapeutic and toxic effects.[47–50] Overall, finding inorganic building blocks that are capable of self-assembly in biological conditions in a controlled manner, without disturbing the cellular machinery, is challenging. On the other hand, non-bioorthogonal intracellular self-assembly, i.e. bioactive self-assembly, can be envisioned as a tool to inhibit, modify or even fix cellular mechanisms associated with some diseases.

Herein, the recent advances in the self-assembly of inorganic exogenous building blocks into living cells and even organisms are summarized, organizing them either as bioorthogonal or bioactive. Finally, a vision of the potential of inorganic self-assembly in biomedical applications is provided. It is worth noting that this concept considers only assemblies formed by non-covalent interactions, and thus biomineralization process are not considered in the scope of this work.[51]

Bioorthogonal self-assembly

Bioorthogonal processes are expected to not considerably disturb cellular functionality. However, relatively small changes can occur; in this sense, this category includes examples of self-assembly in cells in which disturbance of neither the cellular processes nor viability has been observed. In most cases, the true biorthogonality of the process may need further assessment.

Peptide-based targeting moieties are used extensively in radiopharmaceuticals.[52,53] It is not surprising that the first example of intracellular self-assembly containing metal complexes arose from that field given the emergency of peptide-based EISA. In detail, Cao et al.[54] designed a Gd-DOTA-bearing peptide (DOTA = 2,2′,2″,2‴-(1,4,7,10-tetraazacyclododecane-1,4,7,10 tetrayl)tetraacetate) for Magnetic Resonance Imaging (MRI) that contains a furin-cleavable motif and a disulfide group in vicinal positions, and a terminal carbonitrile group. Upon internalization, disulfide reduction and furin-cleavage of the parent molecule generate a 1,2-aminothiol (cysteine) moiety that undergoes condensation with the carbonitrile of another molecule, producing dimeric cyclic molecules that self-assemble by π-stacking interactions forming nanoparticles (NPs, Figure 1a). The formation of the nanostructures increases the local concentration of Gd and enhances the relaxivity in comparison with the monomer, permitting the MRI of furin overexpressing MDA-MB-468 cells (triple negative breast adenocarcinoma) in mouse xenografts.[54] More recently this same approach has been applied with a ^{68}Ga-containing peptide used for positron-emission tomography.[55]

A glutathione(GSH)-activated and luminescent ruthenium(II) compound – based on the condensation-guided self-assembly showed in the previous examples (Figure 1a) – was designed also by the group of Liang,[56] to form aggregates inside GSH-rich environments (ca. 10 mM), such as those found in cancer cells. In these conditions, the monomeric compound trimerizes (Figure 1b) and later aggregates in 150 nm NPs. The aggregated form does not show quenching of the emission and accumulates into the cells allowing persistent imaging, and thus was proposed to image thiol-rich cellular environments.[56] As cysteine–carbonitrile condensation reaction was responsible for the trimerization step, the use of an excess of carbonitrile-containing ligand was applied in order to deplete naturally

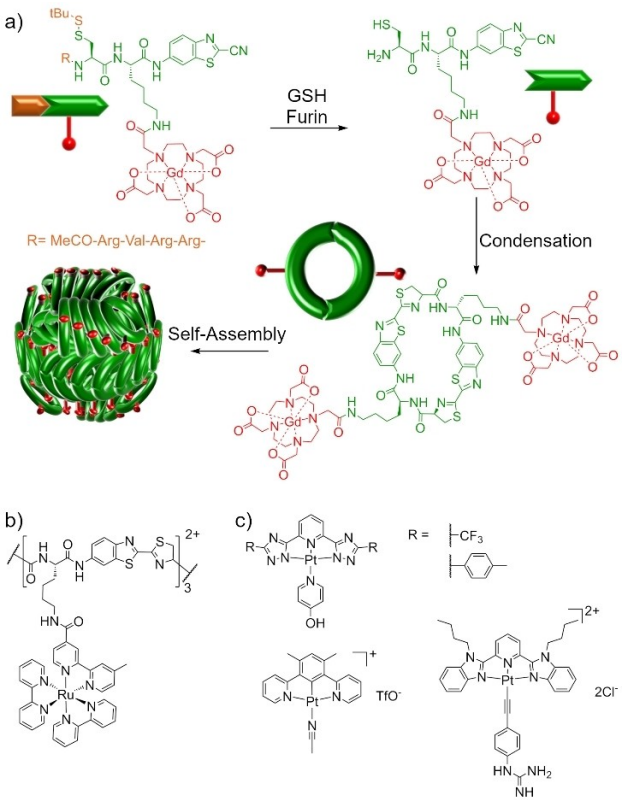

Figure 1. a) Self-assembly of Gd-DOTA-containing peptides triggered by furin and GSH, the activated peptide undertakes a cysteine–carbonitrile condensation reaction before the self-assembly process. b) Trimeric species formed after GSH activation of a Ru-containing peptide that self-assembles into NPs inside cells. c) Neutral platinum(II) compounds proposed by De Cola[59] as aggregation-based imaging agents (top) and cationic Pt(II) compounds reported to self-assemble preferentially into the nucleus by the group of Yam[61,62] (bottom).

Guillermo Moreno-Alcántar got his PhD from Universidad Nacional Autónoma de México, in 2018 in the group of Prof. Hugo Torrens. From 2018 to 2020, he was a Postdoctoral Fellow in the group of Prof. Luisa De Cola in Strasbourg where he studied the control of self-assembly processes of luminescent coordination compounds in complex environments. Since 2021 he is a Research Fellow of the Alexander von Humboldt Foundation at the Technical University of Munich, hosted by Profs. Angela Casini and Roland Fischer. His research interests span from the fundamental study of non-covalent interactions in metal-containing systems to the biomedical applications of metal-based self-assemblies.

occurring cysteine that interferes with the system. Further design of this kind of chemically activated aggregation-based system is challenging, as many potential interferents exist in the cellular milieu.

The potential advantages of the dynamic nature of the self-assembly processes for fluorescence imaging applications were early suggested by the group of De Cola,[57] that first exploited the advantageous aggregation-induced emission enhancement[58] of Pt(II)[59] and Re(I)[60] complexes (Figure 1c) for the imaging of cells. However, in these pioneering works, it was not possible to establish if the reported compounds were internalized in the cells as monomers or aggregates, and thus, the intracellular nature of the observed self-assembly was not fully elucidated. Recently the group of Yam,[61,62] has reported that similar square planar Pt(II) coordination and organometallic complexes are capable of self-assembly inside living cells (Figure 1c). Importantly, due to the positive charge of the studied compounds, they tend to aggregate in the vicinity of nucleic acids, in particular into the cell nucleus.[61,62]

In 2021, we were able to control the spatiotemporal activation of the self-assembly process of an amphiphilic Pt(II) compound (**Pt_{AC}**).[22,63] In our case, the supramolecular encapsulation of the compound into redox-degradable organosilica cages (OSCs)[64] permitted to halt, and re-activate the complex self-assembly pathway on-demand, by the application of a reducing agent (Figure 2a).[63] Using the OSCs allowed us to transport the metastable aggregated form of the compound into the cell milieu. Once internalized, GSH degrades the OSCs, triggering the self-assembly process. Through the different luminescence of the diverse aggregation stages, we were able to monitor the evolution of the aggregates inside living HeLa cells (cervical adenocarcinoma). After 48 h of incubation, the cells displayed micrometric luminescent supramolecular assemblies of the compound (Figure 2b). Surprisingly, despite the large size of the formed assemblies, the bioavailability of the cells was not affected.[63]

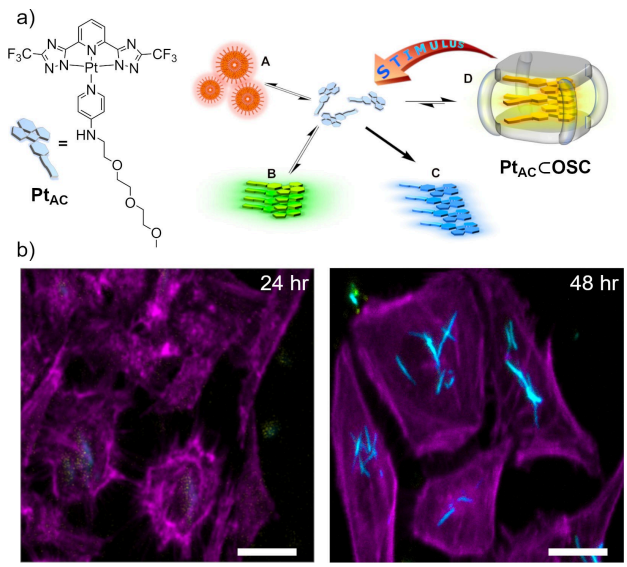

Figure 2. a) Complex self-assembly pathway of Pt_{AC}, including diverse stages metastable micelles (A), metastable rods (B) and thermodynamically stable fibers (C) with different emission colors.[22,63] The compound can be sequestered into OSCs (D), freezing the self-assembly. The OSCs can be degraded on-demand applying a reductive agent as stimuli, restarting the self-assembly process. b) Fluorescence confocal microscopy images showing the time-dependent formation of Pt_{AC} aggregates inside HeLa cells. The membrane was stained with phalloidin 647. Scale bars = 20 μm. Adapted with permission from Ref. [63] Copyright 2021 American Chemical Society.

Bioactive self-assembly

In contrast with bioorthogonal processes, bioactive self-assembly occurs when there are marked effects over either the viability of the biological entities or their biochemical homeostasis, induced by the self-assembly process itself. This type of self-assembly has already been proposed as a way to produce a new generation of supramolecular drugs and some interesting examples have arisen from the inorganic chemistry field.

Gold nanoparticles (GNPs) have attracted attention due to their pharmacological potential. They can be applied in photodynamic, and photothermal therapy (PDT and PTT, respectively) and photoacoustic imaging for cancer treatment and detection, as well as in bioorthogonal catalysis.[65,66] Although small GNPs (< 5 nm in size) have shown superior properties,[67,68] they do not benefit from the enhanced permeability and retention effect of larger systems, and thus, they need to be targeted not to escape the tumour.[69] The group of Rotello introduced the intracellular formation of supramolecular GNPs aggregates as a way to regulate exocytosis.[70] In this first example, the supramolecular aggregation of quaternary ammonium-bearing 2 nm GNPs was induced by the addition of the cucurbit[7]uril (CB7). Aggregation was triggered by the formation of inclusion complexes between CB7 and the quaternary ammonium groups increasing the intracellular retention of the GNPs.[70] Using a similar approach, the group of Ji designed a GSH-based stimuli-responsive system. They functionalized 16 nm GNPs with a β-cyclodextrin (β-CD) host and incubated the particles together with bis-ferrocenium polyethylene glycol in HepG2 cells (hepatocellular carcinoma).[71] Upon GSH-mediated reduction of ferrocene um to ferrocene, the latter forms a host-guest complex with the β-CD in the NPs, causing aggregation and preventing the cellular escape of the GNPs (Figure 3a).

Interestingly, the formed self-assembly induced apoptosis in HepG2 cells compared with the separated GNPs and crosslinker.[71] In contrast, in the study of Rotello, the viability of MCF-7 cells (breast adenocarcinoma) was not affected by the aggregation. Following up on these promising results, more recent works have used DNA-RNA complementary pairing to cause Controllable Aggregation-Induced Exocytosis Inhibition (CAIEI).[72] In one case, a pair of 60 nm GNPs bearing molecular beacons which are designed to be complementary to miRNA-21. This micro-RNA is typically overexpressed in cancer cells, and thus the crosslinking and accumulation of the NPs is projected to occur preferentially in tumour tissue as exemplified in MCF-7 cells. No intrinsic cytotoxicity was observed upon aggregation, however, the aggregates were successfully used as sensitizers for PTT.[72] A similar system using a pair of DNA-

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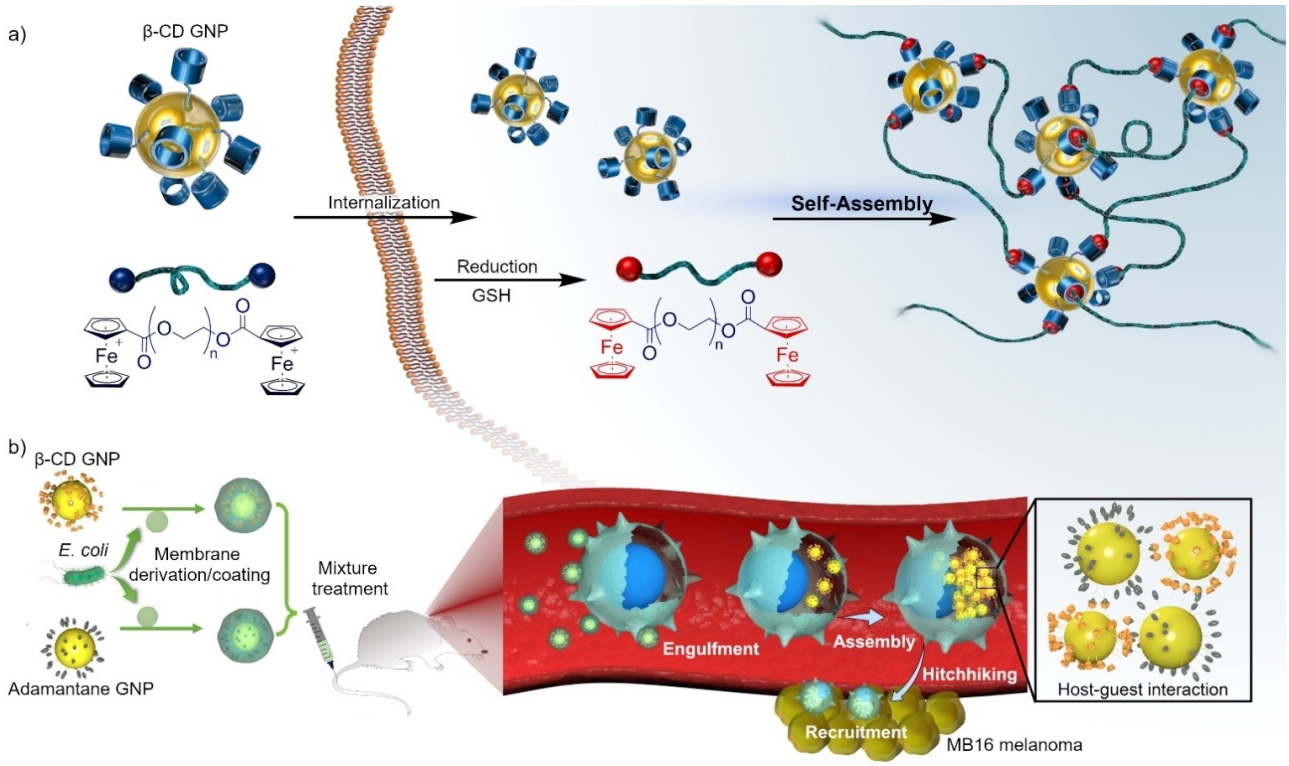

Figure 3. a) Self-Assembly of β-CD-functionalized NPs via supramolecular crosslinking with bis(ferrocene)polyethylene glycol, upon internalization GSH reduces ferrocenium causing the formation of the supramolecular aggregates preferentially in GSH rich environments as the cytosol of cancer cells.[71] b) Hitchicking strategy propossed by the group of Wang, E. coli desguised GNPs with complementary host-guest functionalization are fagocyted by immune cells. Due to CAIEI the NPs are carried via inflammatory tropism to the tumour site. From [74]. © The Authors, some rights reserved; exclusive licensee AAAS. Distributed under a CC BY-NC 4.0 license http://creativecommons.org/licenses/by-nc/4.0/. Reprinted with permission from AAAS.

functionalized 16 nm GNP, which merged sequences are complementary to cancer-related surviving mRNA, was used to form GNP aggregates in HepG2 cells. In this case, a decrease of cell viability and upregulation of apoptotic pathways was observed due to the formation of aggregates, which were also photothermic active.[73]

A further application of the CAIEI of GNPs has been recently reported by Gao, Wang, and collaborators.[74] GNPs were functionalized either with adamantane or β-CD and coated with *Escherichia coli* outer membrane vesicles to promote their phagocytosis by immune cells. Upon uptake by phagocytic immune cells, the bacterial membrane is degraded, and intracellular GNPs aggregation – due to the formation of the inclusion complex of adamantane in β-CD – prevents exocytosis. The immune cells carrying PTT-active aggregates move due to inflammatory tropism to the tumour site, where PTT is applied (Figure 3b). Increased delivery of the aggregates to the tumour was triggered by an exacerbated immune response caused by previous PDT treatment. The therapy was effective in depleting B16 (murine melanoma) tumours in mice xenografts.[74] Although the application of GNP aggregates in PTT is promising, their distinct effects on the viability of cancer and healthy cells need to be further studied to disclose the implications of the formation of self-assemblies and their possible application in the treatment of cancer.

Besides the cytosolic environment, which contains many attractive molecules that can act as stimuli in *smart* self-assembly processes, cell membranes constitute another interesting environment, as not only do they provide a biphasic hydrophobic environment with distinctive chemistry, but also play a key role in maintaining cell homeostasis. In this context, the assembly of polymeric 3D and 2D MOFs in the cell membrane has drawn attention. In 2016 the group of Falcaro[75] achieved the formation of a synthetical cytoskeleton made from a MOF (zeolitic imidazolate framework-8, ZIF-8, Figure 4a), differently from previous reports of mineralization of cell membranes,[76,77] the MOF allows transport of nutrients and warrants the bioavailability of the yeast cells. However, the coated cells were unable to proliferate, indicating that the shell causes a state of latency, disturbing the natural cell cycle.[75] Latterly, a similar MOF coating has been modified to encapsulate protective antitrypsin, which upon the release from the protective MOF layer is capable of inhibiting proteasome enzymes transforming the environment from cytotoxic to biocompatible.[78]

More recently, Ohtani, Hayami, and co-workers demonstrated the generation of pseudo-membrane jackets formed by coordination-driven self-assembled domains.[79] To this end manganese complex lipids $[MnN(NC)_4((dabco\text{-}C_{16}H_{33})_2)]$ (**MC**, Figure 4b) were incorporated into the membranes of Chinese

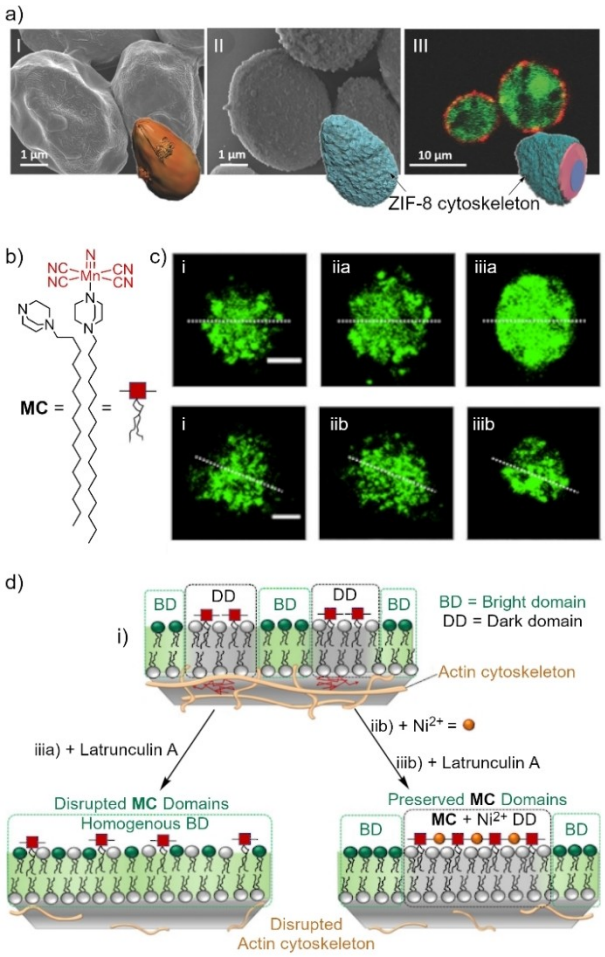

Figure 4. a) Scattering electron microscope images of native (I) and ZIF-8-coated (II) yeast cells and (III) confocal scanning laser microscopy showing the cross section of living yeast cells (green) with the ZIF-8 cytoskeleton (red-labeled). Adapted from Ref. [75] Copyright (2016) with permission from Wiley-VCH GmbH. b) Structure of the membrane intercalator (MC) used for generating membrane jackets in hamster ovary cells. c) and d) effect of the disruption of the actin cytoskeleton over the dark patches generated by MC (i,iia): in the presence of Ni^{2+} the patches are not disturbed (iib). Upon addition of Latrunculin A actin fibers are damaged, causing the patches of MC to dissipate (iiia), in the presence of Ni^{2+} the patches remain also after treatment with Latrunculin A (iiib) due to the crosslinking effect of the metal ion. Adapted from Ref. [79] Copyright (2020) with permission from Wiley-VCH GmbH.

hamster ovary cells which have been labeled with a fluorescent lipid. The inclusion of metal-complex lipids produced dark domains, indicating a high concentration of metal-containing lipids (Figure 4c–d). The disruption of the actin cytoskeleton allowed the homogeneous redistribution of the metal complexes in the membrane. Interestingly, the addition of a second metal center (Ni^{2+}) fixed the domains independently from the state of the actin fibers due to the formation of 2D MOFs. Moreover, the presence of the metal-containing domains can enhance the cellular calcium intake probably in response to ATP stimulation of P2-purinoceptors[79] which are involved in important physiological processes such as the synapsis and the regulation of immune response.[80]

Challenges and perspectives

The last decade has marked an increasing interest in the generation of self-assembled structures inside living organisms. Chemical and supramolecular strategies have been successfully used to this end allowing both therapeutic and imaging-related applications, however, the vast majority of the available examples of self-assembly inside living systems are based on organic compounds, in many cases biomolecules.[44–46]

Inorganic building blocks, such as coordination and organometallic metal complexes, or even metal clusters or NPs are among the most prominent agents used with both imaging and therapeutic ends in medicinal chemistry.[50,81–83] In the design of therapeutic self-assemblies, comparative studies within healthy and diseased models are a pending matter to pursue. Besides, the use of inorganic building blocks for the generation of supramolecular assemblies into the living milieu would undoubtfully uncover further applications in these areas. Moreover, the use of intracellular coordination-driven self-assembly which could derive in important imaging or therapeutic applications is still unexplored.[38,83–85] For instance, when compared to purely organic building blocks the possibilities of self-assembly of metal-organic entities are enriched by the extended toolbox of available non-covalent interactions,[86] for example, coordination bonds or metallophilic contacts,[87,88] which further generate aggregates with attractive properties.[59,89] The design of building blocks that self-assemble under these principles could render the assembly process selective in complex biological matrices. Moreover, the possibility of modulating the strength of these interactions[90,91] should be applied to generate stimuli-responsive and adaptative materials. In this sense, the dynamic nature of supramolecular assemblies has not been fully exploited,[45,92,93] for example, the stimuli-responsive behavior of supramolecular materials can be used to image and report in real-time cellular processes.[94] Supramolecular engineering of stimuli responsible and dissipative processes that use cell metabolites as fuels is needed to this end.[95,96] All in all, inorganic self-assembly has just entered bio-systems and the upcoming years will show once again what the invaluable union between inorganic and supramolecular chemistry has still to offer.

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Conflict of Interest

The authors declare no conflict of interest.

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Correction added on April 20, 2023, after first online publication: The copyright statements to the caption of Figure 3b was corrected from "Adapted under terms of the CC-BY license.[74] Copyright 2022, The Authors, published by American Association for the Advancement of Science." to "From [74]. © The Authors, some rights reserved; exclusive licensee AAAS. Distributed under a CC BY-NC 4.0 license http://creativecommons.org/licenses/by-nc/4.0/. Reprinted with permission from AAAS."