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The role of metals in the next generation of anticancer therapeutics

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Introduction

The contributions that inorganic chemists have made in the fight against cancer have evolved with our understanding of the chemistry of metal complexes and the biology of cancer. Within a decade of the isolation of radium at the turn of the 20th century, radium-based brachytherapy was being explored to treat a variety of cancers [1]. Although radiotherapy remains one of the most important areas in which inorganic chemists can contribute to anticancer therapy, the collection of manuscripts within this special issue is focused on molecular pharmaceutics that elicit an anticancer response by engaging in chemical reactions. The relevance of molecular anticancer chemotherapy was appreciated in earnest following World War II with the realization that the nitrogen mustards used as chemical warfare agents could lead to regression in lymphoma patients [2]. During the same period, it was discovered that folate antagonists, such as methotrexate, could lead to remission of childhood acute lymphoblastic leukemia [3]. It was in the wake of these, and other, discoveries that the anticancer activity of platinum(II) compounds was uncovered, ultimately leading to the clinical approval of cisplatin [4]. Although inorganic compounds had had a long preceding history in medicine, the success of cisplatin was arguably a primary driver of the ensuing efforts to develop metal-based anticancer drugs. These research endeavors ultimately resulted in the FDA approval of two other platinum(II) drugs: carboplatin and oxaliplatin. Similarly structured research programs were launched to uncover other chemotherapeutically active metal complexes, but to date these have only resulted in the approval of three other platinum(II) complexes in regional markets (lobaplatin in China, nedaplatin in Japan, and heptaplatin in Korea). Studies performed in the late 20th and early 21st centuries uncovered a wealth of bioinorganic chemistry and fundamental cancer biology, and chemists responded by developing new strategies to exploit the reactivity of inorganic molecules to treat cancer. This special issue represents a collection of current opinions on the directions in which this field is headed, with particular care taken to ensure that the viewpoints of emerging investigators are reflected. The authors have substantiated the timeliness of these opinions by focusing on publications that have appeared within the past few years.

Overview

Platinum complexes, which helped usher in the modern era of metal-based anticancer agents, continue to be among the most heavily explored. Deng and Zhu describe one of the intensely investigated avenues in platinum anticancer chemistry: platinum(IV) prodrugs with functional axial ligands. Early studies used the additional two ligands within the octahedral coordination sphere of bioactive platinum(IV) complexes to tune their physicochemical properties and pharmacokinetics. Providing many recent examples, Deng and Zhu describe the evolution from biologically innocent to biologically non-innocent axial ligands. They highlight that further work is needed to establish the extent to which platinum(IV) complexes do indeed function as platinum(II)-releasing prodrugs, rather than acting to elicit biological responses directly.

In addition to platinum(IV) prodrugs, bioactive platinum complexes have been formulated as supramolecular assemblies, but the wide array of distinct approaches that are taken can obfuscate the underlying themes that unite these efforts. Jogadi and Zheng provide not only a summary of the recent advances in the exploration of anticancer supramolecular platinum complexes, but also a cogent organizational scheme for understanding how these advances relate to one another. They suggest that the next important challenges that investigators will target include intracellular self-assembly, rational tuning of interactions with biomacromolecules, stimulus-responsive release for tumor targeting, and inclusion of biologics.

Whereas Jogadi and Zheng describe the use of atomically precise supramolecular assemblies, much work has also been performed on larger, polydisperse nanoparticle constructs. Li and Lin provide an overview of the use of such constructs and the advantages that they confer before describing recent developments in the area of nanoparticles that can deliver multiple therapeutic agents: a materials science approach to the molecular formulation approach discussed by Deng and Zhu. They caution that nanoparticle-formulated combination therapy may not be as simple as co-packaging drugs that function synergistically when administered systemically because of differences that can exist in the in vivo behavior of the nanoparticles as compared to the small-molecules.

Instead of molecularly combining a biologically active metal complex with biologically active organic molecules, multiple bioactive metal motifs can be linked together. López-Hernández and Contel provide an assessment of five recent articles that focus on the activity of such compounds in animal models. They propose plausible mechanisms of action for multimetallic species, including platinum complexes tethered to iron(II), ruthenium(II), or gadolinium(III) centers. They also described results obtained with complexes in which gold(I) is tethered to titanium(IV) or ruthenium(II).

A perennial complication faced by platinum drugs, as well as other drugs containing either soft or oxidized metal centers, is deactivation by soft nucleophiles, such as thiols. The thiol that is present at the highest concentration in the intracellular milieu is glutathione, and Nguyen and Do describe strategies that can be taken to modulate glutathione levels to potentiate metallodrug activity. Alternative approaches, including glutathione-activated prodrugs and protected metallodrugs, are also described. Nguyen and Do highlight the need for a means of quantifying glutathione susceptibility that would be comparable across anticancer agents and the importance of synthetic chemists collaborating with biomedical researchers and clinicians from the earliest possible stages of a project.

One broad theme that runs through many of the contributions is the altered metabolism of cancer cells. Regardless of whether it is a cause or a consequence of malignancy, it is a clear hallmark of cancer, and many recent advancements in the area have tried to capitalize on this difference to target cancer cells. The contribution from Vaidya and Patra describes recent developments in the exploration of platinum(II) glycoconjugates as cancer-targeting molecules. Many cancer cells upregulate the expression of glucose transporters, and the glycoconjugate strategy aims to capitalize on this differential transporter expression to increase the preferential uptake of bioactive platinum complexes by cancer cells. Vaidya and Patra predict that the next frontier to be explored will be the use of sugars more complex than the monosaccharaides that have predominantly been studied to date.

The altered metabolism of cancer cells has led many researchers to focus their efforts on targeting mitochondria. Olelewe and Awuah summarize recent work that has been performed on the ability of third-row transition-metal complexes to target this energy-producing organelle. They describe work on lipophilic cationic platinum complexes, cyclometallated gold complexes, and rhenium tricarbonyl complexes that are proposed to localize to the mitochondria. Iridium complexes are described that, based on their structure, can function as either photodynamic therapy agents or inhibitors of mitochondrial topoisomerases. Olelewe and Awuah highlight that more relevant biological models and disease models will help this area of research to progress further.

Tomat highlights that another feature of altered cancer homeostasis is the elevated iron requirements of cancer cells and that this difference can be targeted. Although it is possible that some of the problems associated with early non-specific iron chelation strategies could be improved upon by using organelle-targeting groups and prochelator design, Tomat makes a strong case for the importance of polypharmacology in medicinal inorganic chemistry, stating that, in the future, "specific metal recognition is less likely… than understanding the relevance of other metals to the overall mechanism of action."

In addition to altered metabolism, the iron content of cancer cells is related to stemness, the set of characteristics shared by cells known as cancer stem cells: a population of resilient cells that can serve as a chemotherapy-resistant reservoir that drives relapse and metastasis. Northcote-Smith and Suntharalingam describe metal complexes that have been investigated for their ability to specifically target this sub-population of cells. They describe platinum(IV) complexes that release axial ligands known to target cancer stem cells, as well as other group 10 complexes, with an emphasis on the activation of different cell-death pathways. In addition to copper and iridium complexes, Northcote-Smith and Suntharalingam discuss the cancer stem cell-targeting ability of gallium(III) complexes. They propose that, although the current pool of metal-based anticancer stem cell agents is small, the picture will sharpen as it grows, and as more studies are performed in increasingly sophisticated organism-level disease models.

The anticancer activity of p-block compounds exemplified by the gallium complexes described by Northcote-Smith and Suntharalingam was also described by Hollow and Johnstone. Arsenic trioxide is widely used in the treatment of acute promyelocytic leukemia, but extension to other cancers has had limited success. The use of arsenic-containing nanomaterials represents one strategy to circumvent these difficulties. Specifically, Hollow and Johnstone describe the use of nanoparticulate realgar and arsenene nanosheets as anticancer agents. They caution that although these studies are exciting, increased care must be taken in the exploration of anticancer nanoparticles to ensure that a robust understanding of the roles played by each component of these complex assemblies is obtained.

The previously described articles have focused largely on the development of novel therapeutics that, in many cases, are hypothesized to function via well-established mechanisms of action. Important work is also being performed to identify new targets, as described by Storr and co-workers in their piece on the inhibition of p53 aggregation as a strategy for treating cancer. They begin with an overview of the logic underlying this strategy and then discuss the different ways in which researchers have recently worked towards achieving this goal. They describe stabilizers of folded p53, including arsenic trioxide, as well as inhibitors of protein aggregation, many of which involve regulating levels of Zn, which is crucial for p53 activity.

An exciting new development in cancer therapy involves the induction of immunogenic cell death, which triggers the activity of the adaptive immune response to kill further cancer cells. Arambula and co-workers provide a systematic overview of the metal complexes that are known to trigger immunogenic cell death, but they highlight that there are too few compounds that generate a sufficiently robust response to provide design principles. They suggest that both high-throughput and rational design approaches will be important facets of exploiting this promising new strategy.

Finally, Meier-Menches and colleagues provide an overview of the methods that can be used to establish the mechanism of action by which a drug functions. They provide nice examples where unexpected answers were returned, and we strongly encourage the community to take their message to heart that mechanisms of action cannot be assumed and that even seemingly benign changes in molecular structure can have profound mechanistic implications.

Conclusion

We very much appreciated working with all the authors noted above on assembling this special issue and we hope that you enjoy reading their excellent contributions and appreciating the continued role that metal complexes are poised to make in the treatment of cancer.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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