Atomic Spectroscopy

Letter

Metallomics for the Screening of COVID-19 and Metallodrug Development

Jiating Zhao,[a,b,#] Liming Wang,[a,b,#] Liwei Cui,[b] Hongzhe Sun,[c,*] Yuxi Gao,[a,b] Bai Li,[a] and Yu-Feng Li [a,b,*]

[a] CAS-HKU Joint Laboratory of Metallomics on Health and Environment, & CAS Key Laboratory for Biomedical Effects of Nanomaterials and Nanosafety, & Beijing Metallomics Facility, & National Consortium for Excellence in Metallomics, Institute of High Energy Physics, Chinese Academy of Sciences, Beijing 100049, P.R. China

[b] University of Chinese Academy of Sciences, Beijing 100049, P.R. China

[c] Department of Chemistry, & State Key Laboratory of Synthetic Chemistry, & CAS-HKU Joint Laboratory of Metallomics on Health and Environment, The University of Hong Kong, Pokfulam, Hong Kong, P. R. China

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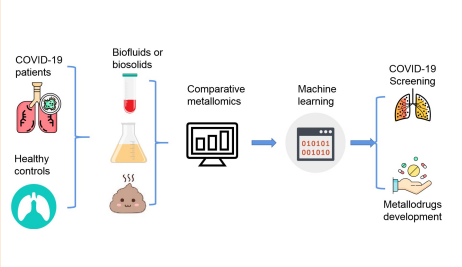
ABSTRACT: The COVID-19 pandemic has led to severe threat globally. As a result, scientists are increasing their efforts in developing testing methods, antiviral drugs, and vaccines, to diagnose, treat, and defend against COVID-19 respectively. Although RT-PCR and antigen tests are used for the screening of COVID-19, there are many disadvantages including high cost, long processing time, and false-negative results. With the exception of supportive care, no specific treatment for COVID-19 has been established. Metallomics focuses on the systematic study of the interactions and functional connections of metallic/metalloid ions and their species with genes, proteins, metabolites, and other biomolecules within organisms and ecosystems. It has been applied in the screening of various cancers, neurodegenerative diseases, and viral infections and metallodrug development with the advantages of high throughput, low risk of cross-infection, low cost, and ready availability. Therefore, we proposed the use of metallomics for the screening and metallodrug development of COVID-19. An operational work scheme is also presented.



INTRODUCTION

The ongoing coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has presented a severe global health crisis.[1] Governments have implemented measures including self-isolation, social distancing, and the use of personal protective equipment, to prevent the transmission of the virus. Substantial research on the development of testing methods, antiviral drugs, and vaccines, to diagnose, treat, and defend against COVID-19 have also been reported.[2]

Timely and reliable diagnosis is one of the foremost priorities for COVID-19 prevention and control. Reverse transcription polymerase chain reaction (RT-PCR) is the gold standard for the diagnosis of COVID-19 through the detection of SARS-CoV-2 using samples from respiratory secretions.[3] However, a single negative PCR result does not rule out the infection, since false-negative results have been reported.[4] In addition, RT-PCR-based detection methods require high manpower and long processing time, which may lead to delayed reporting, potentially increasing further transmission of the virus. Antigen tests detect certain proteins in SARS-CoV-2 which can provide results in minutes and are less expensive than RT-PCR tests. A positive antigen test result is considered very accurate, but there are increased chances of false-negative results, which require confirmation from a RT-PCR test.[5] Therefore, more timely and reliable diagnostic methods are required to combat COVID-19.

There are no established specific treatment for COVID-19 infections, with the exception of supportive care.[6] The efficacy of some promising antivirals,[7,8] convalescent plasma transfusion,[9,10] neutralizing antibodies,[11-13] immunotherapeutics,[14,15] and traditional Chinese medicine,[16-18] still require further validation.[1,5] Therefore, new treatments for COVID-19 are still highly desirable.

Elements, including metals and metalloids, play a vital role in life processes. For example, selenium plays a key role in host oxidative defense through selenoenzymes and selenoproteins, while copper serves as a cofactor in many redox enzymes including cytochrome c oxidase, which influences the respiratory electron transport chain of mitochondria.[19] To address the vital role of metals/metalloids, a new research field, metallomics, was developed. This focused on the systematic study of the interactions and functional connections of metallic/metalloid ions and their species, with genes, proteins, metabolites, and other biomolecules within various organisms and ecosystems.[20,21] Metallomics has been applied to various sciences including medical, environmental, biological, agricultural, nano, geological, archaeological, radiological, and material science.[19,22-26] The application of metallomics on dyshomeostasis in the host, which occurs after invasion of SARS-CoV-2, may offer insight into the screening of COVID-19 Moreover, the restoration of elemental homeostasis in the host using metallodrugs may also shed light on the development of novel treatment methods for COVID-19.

In this paper, we discussed the contributions of metallomics to the screening of different diseases including cancer, neurodegenerative diseases, and viral diseases. We also highlighted the contribution of metallomics to the development of metallodrugs to treat different diseases, particularly viral infections. A proposal for the use of metallomics as a tool for the screening of COVID-19 and the development of metallodrugs as a treatment is also presented.

METALLOMICS FOR DISEASE SCREENING AND METALLODRUG DEVELOPMENT

An excess or deficiency in elements can lead to elemental dyshomeostasis, resulting in diseases including cancers.[27] Comparative metallomics can provide hints on the prediction of diseases, comparing the difference in metallome between the normal and pathological groups.[21,28-30]

The screening of cancer. Cancer is the leading cause of death before the age of 70 in many countries.[31] Early detection and timely treatment is the most effective method for managing cancer.[32] Comparative metallomics plays a unique role in the screening and diagnosing of various cancers including prostate, lung, and breast cancer.

Prostate cancer is the second most prevalent cancer in men after lung cancer.[31] A comparative metallomics study on samples of human prostate tissues with cancer and benign prostate hyperplasia, as well as normal tissues, showed a reduction in the concentrations of S, K, Ca, Fe, Zn, and Rb in the two pathological tissues (cancer and benign prostate hyperplasia) compared with the concentrations in normal tissues. This revealed an association between these elements and carcinogenesis. Furthermore, a 61% reduction of Zn in prostate cancer samples was observed when compared with normal tissues, indicating the potential of Zn as a biomarker for prostate cancer.[33]

Lung cancer is the most prevalent cancer, and has the highest mortality rate of all the cancers.[31] A cross-sectional study was conducted on 48 lung cancer patients and 39 controls, and 11 elements (V, Cr, Mn, Fe, Co, Cu, Zn, Se, Mo, Cd, and Pb) in serum, urine, and bronchoalveolar lavage fluid (BALF).[34] Elemental ratios (in serum: V/Mn, V/Pb, V/Zn, Cr/Pb, urine: Cr/Cd, Mn/Cd, V/Cd, Co/Cd, Cd/Pb, and BALF: V/Cu) were found to be important biomarkers for lung cancer. Additionally, the presence of V and Cr in high molecular mass species and Cu in low molecular mass species in serum, urine, and BALF could be used to distinguish healthy people from lung cancer patients. The study revealed that in addition to elemental concentration, elemental species could also be used for cancer screening. This broadened the concepts of comparative metallomics.

In women, breast cancer is the most common cause of cancer-related deaths.[31] A comparative metallomics study in different human breast tissues (normal, normal adjacent to the tumor, benign, and malignant) found that the concentrations of Ca, Cu, and Zn were lower in malignant tissues than in normal and normal adjacent tissues.[35] It was also observed that malignant tissues had a higher concentration of Fe than benign neoplastic tissues.[35] More importantly, a further multivariate discriminant analysis identified the elemental differences between normal and malignant tissues with an overall accuracy of 80% and 87% for benign and malignant tissues, respectively. The high predictive accuracy indicated that comparative metallomics could be used for the rapid diagnosis or prognosis of patients with breast cancer.

The screening of neurodegenerative diseases. Neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), and Huntington's disease (HD) are progressive and fatal brain diseases characterized by the progressive degeneration of the structure and function of the central or peripheral nervous system.[36]

AD is characterized by the presence of amyloid-beta-containing plaques and hyperphosphorylated tau-containing neurofibrillary tangles in the pathological brain.[37] In addition, mitochondrial function impairment,[36] insulin resistance[38] and metal dyshomeostasis[39,40] were also found to be involved in the pathogenesis of AD. Zheng *et al.*[41] studied 15 elements in the cerebrum of Se-treated AD mice, AD mice, and wild-type (WT) mice. Differentially changed elements were identified between the groups at specific time points. Elevated concentrations of Fe, Zn, Cu, Cd, Hg, and Bi were observed, while concentrations of Mn and Se decreased in AD mice compared to WT mice. There was an increase in the concentrations of Se, As, Cr, and Mg in AD mice treated with Se, whereas a decrease in levels of Fe, Zn, Mn, Cd, V,

and Bi was reported. It was also found that the largest numbers of differentially changed elements were observed at the time point of 8 months.

PD is the second most prevalent neurodegenerative disorder after AD. Exposure to metals has been implicated in the pathogenesis of PD.[42] Examination of the levels of heavy metals in the blood and urine of PD patients revealed that whole-blood Mn, serum Fe levels, and urine Fe and Cu levels were significantly higher than that of non-PD patients.[43,44] This indicated that excessive intake of Fe and Cu as well as the accumulation of Mn might be involved in the etiology of PD[44]. A significant correlation between serum and urinary Fe was also observed in PD patients. In addition, ferroptosis was believed to elicit apoptosis in cell death caused by iron overload in PD.[45] Another study investigated the levels of Pb in the bone and blood of PD patients and found that the risk of PD was elevated by over 2-fold for individuals with a longer lifetime of Pb exposure.[46]

The screening of viral diseases. Infectious viral diseases including acquired immune deficiency syndrome (AIDS), severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS), viral hepatitis, and avian influenza all have the potential for rapid, global transmission with high morbidity and mortality.[47]

In 2019, it was reported that there were approximately 38 million people living with HIV and about 0.69 million people who died from AIDS-related complications (https://www.unaids.org/en/resources/fact-sheet). Comparative metallomics was applied to determine the role of trace elements in HIV infection, and its progression to AIDS.[48] Serum Cu levels increased considerably in HIV infections, which subsequently led to the development of anemia due to chronic HIV infections. In addition, low serum Fe and transferrin levels, as well as an increase in serum ferritin levels were observed. Se deficiency in HIV-infected subjects was also associated with a more rapid disease progression and an increase in the rate of mortality. A correlation between declining serum Zn levels and the progression of AIDS was also reported.[48,49]

Viral hepatitis is a major global concern, accounting for 1.34 million deaths in 2015.[50] Many of these deaths were due to long-term complications of the hepatitis B virus (HBV) and hepatitis C virus (HCV) infections. An increase in the levels of Cu, Fe, Mn, and Cd, and a decrease in the levels of Zn, Ni, and Co, were reported in patients with hepatitis B and C.[51] In addition, viral load and serum levels of Cu, Mn, Fe, and Cd showed a positive correlation, while viral load and serum metal levels of Zn, Ni, and Co showed a negative correlation.

The H1N1 virus is a subtype of the influenza A virus and was responsible for a pandemic in 2009 to 2010. Plasma and erythrocyte Se levels, selenoenzyme activities, and other oxidant/antioxidant parameters in H1N1-infected children were evaluated. Marked decreases in both plasma and erythrocyte Se levels (11%, both) were reported. Decreases in the activities of Glutathione peroxidase 1(GPx1) (45%), GPx3 (16%), and TrxR (30%) in H1N1-infected children compared to the control group were also observed.[52]

Hemorrhagic fever with renal syndrome (HFRS) caused by hantaviruses and transmitted by rodents is a significant public health issue.[53] It was found that the incidence of HFRS in humans was approximately 6 folds and 2 folds in severely Se-deficient and moderately Se-deficient areas respectively, compared to non-deficient areas in China.[54] This revealed the potential role of Se deficiency in the increased incidences of hantavirus infections in both humans and rodents, which may be used for the screening of HFRS.

Metallodrugs for the treatment of human viral diseases. A comparative metallomics study on the differences in metallome in diseases can result in the development of the corresponding metallodrug. Metallodrugs such as cisplatin, arsenite, silver, gold complexes, sodium vanadate, and lithium carbonate have been approved for the medical treatment of various diseases such as cancers, leukemia, rheumatoid arthritis, diabetes, cardiovascular disorders, and gastrointestinal disorders.[21,55-57]

Metallodrugs are also used for the treatment of human viral diseases. Rozenbaum *et al.* showed that HPA-23 (ammonium-21-tungsto-9-antimonate) could decrease the levels of HIV in AIDS patients.[58] The introduction of various transition metals (V, W, Mo, and Nb) into polyoxometalates, resulted in a reduction in the activities of SARS coronavirus (SCV), influenza virus, herpes simplex virus, and HBV in vivo.[59] The cobalt chelate complex, bis (2-methylimidazole)[(bis(acetylacetone)(ethylenediimine)]cobalt(III), completed phase II clinical trials for the treatment of herpes simplex labialis and phase I clinical trials for the treatment of ophthalmic herpetic keratitis and adenoviral conjunctivitis.[60]

Al and Hg compounds have been used as adjuvants in vaccines. $Al(OH)_3$, $AlPO_4$, and potassium alum ($KAl(SO_4)_2 \cdot 12H_2O$), stimulated the immune response while displaying an excellent safety profile.[61,62] Sodium-2-ethylmercurithio-benzoate has been used as a preservative in several vaccines.[63] The ethylmercurithio cation of thiomersal binds readily to thiol groups in protein structures, blocking enzymatic activity. However, the toxicity of Hg compounds raised concerns regarding the safety of these vaccines.

SARS, a life-threatening viral pneumonia first recognized in late 2002, was reported as the cause of SCV. Metallodrugs have been proposed for the treatment of SARS. For example, Bi and related compounds exhibited excellent antiviral activity against SCV through the inhibition of SCV helicase.[64,65] Zn compounds such as zinc pyrithione and $ZnOAc_2$, inhibited SCV replication in Vero E6 cells by targeting the RNA-dependent RNA polymerase (Nsp 12).[66,67]

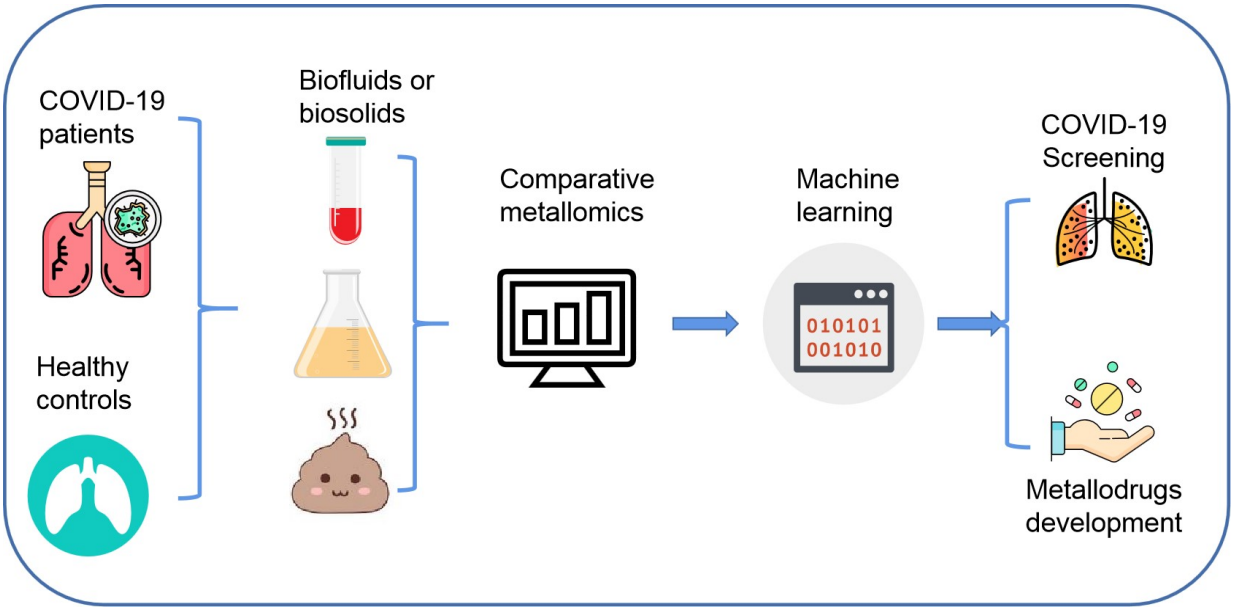


Fig. 1 Working scheme for the screening of COVID-19 and the development of metallodrugs using comparative metallomics

Metallodrugs also showed excellent antiviral activity against COVID-19. A recent study found that ranitidine bismuth citrate (RBC), suppressed SARS-CoV-2 replication in Syrian hamsters by disrupting the functions of helicase and other essential enzymes.[68] Since RBC is a commonly used drug with a safe and comprehensive pharmacological profile, its clinical use against COVID-19 can be facilitated. Zinc supplementation in combination with hydroxychloroquine (HCQ) in hospitalized COVID-19 patients resulted in higher rates of hospital discharge, and a reduction in the rate of mortality or hospice transfers.[69-71] Other minerals such as selenium have been found to have antiviral effects against COVID-19.[72,73]

USING METALLOMICS TO SCREEN COVID-19 AND DEVELOP NEW METALLODRUGS?

Despite the application of comparative metallomics to various diseases, no comparative metallomics studies of COVID-19 patients have been reported. As such, a proposal to conduct a comparative metallomics study on COVID-19 patients to establish a new method of screening, and to provide insight into the development of new metallodrugs is presented. The working scheme is illustrated in Fig. 1.

According to our proposed working scheme, blood, urine, or feces would be collected from the COVID-19 patients and the healthy controls. A comparative metallomics study would then be performed to identify the differences of the metallome (metallome signature) between COVID-19 patients and the controls. Subsequently, a machine learning-based method would be used for model construction and data mining, to screen for COVID-19 in the blind samples. These identified metallome differences between COVID-19 patients and healthy controls could also contribute to the development of new metallodrugs COVID-19 patients.

Compared to RT-PCR and antigen tests in the screening of COVID-19, our proposed protocol has the following merits. First, metallomics methods have high throughput,[74,75] which can be used for a highly efficient screening of potential COVID-19 infections. Second, metallomics methods have a lower risk of SARS-CoV-2 infection for the laboratory clinicians and related medical workers who are performing the laboratory tests. All the collected biofluids and/or biosolid samples may be completely disinfected through acid digestion or other harsh pretreatment measures before being sent to clinical laboratories. Third, metallomics methods are less expensive since they do not require specific test kits. This is important since the production capacity of specific test kits may be the limiting factor, as observed in the COVID-19 pandemic. Fourth, metallomics methods are more readily available in different clinical laboratories globally, while many regions may have limited resources for RT-PCR and antigen testing for SARS-CoV-2.

As for the development of metallodrugs, comparative metallomics can reveal elemental dyshomeostasis in COVID-19 patients. This will, in turn, provide insight into the development of metallodrugs against COVID-19.

Considering the advantages and successful application of metallomics in disease screening and drug development, we propose the use of metallomics for the screening of COVID-19 and metallodrug development.

AUTHOR INFORMATION

Corresponding Authors

* H. Z. Sun

Email address: hsun@hku.hk

* Y. -F. Li

Email address: liyf@ihep.ac.cn

Notes

The authors declare no competing financial interest.

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