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REVIEW ARTICLE

Nanometallo-Immunotherapy: Targeting Ion Channels and Innate Immunity for Precision Cancer Treatment

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Abstract

Ion channels play a central role in regulating inflammation and immune responses, making them increasingly attractive targets for tumor immunotherapy. In recent years, the integration of metallic nanoparticles into immunotherapeutic strategies has opened new avenues for enhancing treatment efficacy while reducing immune-related adverse effects. These engineered nanomaterials are not merely passive carriers; they actively participate in immune modulation by triggering key pathways, such as cyclic GMP-AMP synthase (cGAS)–STING, inducing immunogenic cell death, and reshaping the tumor microenvironment through the activation of innate immune responses. As a result, they contribute to a more robust and sustained antitumor immune response. This review provides a comprehensive and updated overview of the role of biologically relevant metal ions – including zinc (Zn^{2+}), magnesium, manganese (Mn^{2+}), and calcium – in modulating ion channel activity and regulating innate immune signaling pathways. It further examines how these ions, in combination with metallic nanoparticles, such as gold nanoparticles (AuNPs), Mn^{2+} dioxide, silver nanoparticles, and Zn^{2+} oxide, influence tumor immune phenotypes beyond the classical cGAS–STING axis. Special attention is given to recent advances in biosynthetic and green fabrication strategies for nanoparticle development, along with critical considerations related to biocompatibility, toxicity, and clinical safety. Moreover, the review highlights the synergistic potential of combining metal-based nanomedicines with existing immunotherapeutic approaches to overcome present limitations in cancer treatment. Finally, it outlines emerging targeted delivery strategies and key translational challenges, emphasizing the promise of nanometallo-immunotherapy as a next-generation platform for precision oncology.

Key words: Cyclic GMP-AMP synthase–STING pathway, ion channels, metallic nanoparticles, nanometallo-immunotherapy, technology

INTRODUCTION

Inflammation is a crucial physiological defense mechanism that protects the body from infections and tissue damage by removing a harmful stimulus and initiating tissue repair. It can be classified into two types: Acute inflammation, which is a short-term process lasting about a few days, and chronic inflammation, which indicates a prolonged and persistent response. Since inflammation and immunity are closely associated with cancer progression, in standard cancer therapies, the clinical practices used to kill tumor cells, such as hormone therapy, immunotherapy, chemotherapy, and radiotherapy (RT), cause the primary tumor to become less intense.[1-3] The deeper understanding of the standard cancer treatment and biology of tumors and its effect in human immunity and immunotherapy has rapidly grown, which helps in the development of modern and new generations of cancer treatment for clinical practices.[4,5] However, the need for new drugs with highly

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advanced technology is being developed by the widening condition of tumors. This promotes new ideas for the development of metal-based nanoparticles with more high-level designing of molecular mechanisms, especially in tumors, and is also used to treat various other diseases. Therefore, the Nanoparticles which act as a powerful tool for the achievement of tumor immunotherapy.[6,7] Those of particularly inorganic metal organic nanomaterials, which are more explored for cancer immunotherapy. For example, nanomaterials in cancer are AuNPs, which act as a photo-thermal therapy, and silver nanoparticles (AgNPs) used as an anticancer effect, triggering the oxidative stress and apoptosis of the tumor cell.[8,9] Metallic elements, for example, sodium (Na^+), potassium (k^+), magnesium (Mg^{2+}), calcium (Ca^{2+}), and so on, which are naturally produced by our body and play an important role in the immune system also responsible for the functions of T cells and natural killer cells and the recognition of active pattern of recognition receptor (PRRs).[10-17]

HOT AND COLD TUMORS

Tumor scan be classified into three immune phenotypes according to the special spatial arrangement of the cytotoxic T cells within the tumor microenvironment (TME) also known as Transfer Multisort Elektronik those are; immune inflamed, immune desert, and immune excluded. In this immune inflamed tumor is known as "Hot tumor" characterized by the more infiltration of the immune cell that is T cell, a sturdy immune response will occur and are also responsible of the immunotherapy. Then, the immune desert and immune excluded is called as a "as cold tumor," the infiltration of immune cell (T cell) is generally completely lacking of the immune cell, which is an immunosuppressive cancer that leads to the resist state of present immunotherapies and develops a favorable environmental condition known as immunosuppressive TMV.[18-22]

METALLIC NANOPARTICLES FOR CANCER IMMUNOTHERAPY

Nanoparticles are a classical cancer immunotherapy, which is an effective way to fight against cancer, and the carriers of nanoparticles have a size of <300 nm. They improve the cellular uptake of the chemotherapy, which is the portion of the main functional part of the molecules into the cancer cells, but it lowers the targeted toxicological effect.

However, metallic materials are broadly divided into two primary categories-Ferrous and non-ferrous based on their appearance and physical properties. Ferrous metals include iron, manganese (Mn^{2+}), chromium, and various alloys of these elements. They are classified as ferrous because steel surfaces commonly form a dark Fe_3O_4 layer, while Mn^{2+} and chromium are often alloyed with iron to produce different types of steel. These three metals are the core raw materials in steel manufacturing, accounting for roughly 95% of global metal output and also playing a vital role in both industrial and medical fields.[23]

CYCLIC GMP-AMP SYNTHASE (CGAS)-STING PATHWAY ACTIVATION BY METAL IONS

The innate immune system acts as the body's first defense mechanism by detecting foreign substances through PRRs [Figure 1]. In that system, the cytosolic DNA sensor plays an important role. One such sensor, Cyclic GMP-AMP synthase cGAS, combines with adaptor protein STING (also known as MYPS or TMEM173), located on the endoplasmic reticulum (ER). This communication triggers the production of type 1 interferons (IFNs),[24-29] which begins the canonical cGAS-STING signaling cascade. Across this pathway, the identification of cytosolic DNA makes a strong innate immune response.[30] The nanoparticles are well developed in the cancer treatment, which is an ideal platform of the innate immune system, the important metal ion activating cGAS-STING pathway nowadays, considering the zinc (Zn^{2+}) and Zn^{2+}-based biodegradable biomaterials that are inorganic non-metallic nanomaterials for immunotherapy.[31-36] Mn^{2+}, Ca^{2+}, Mg^{2+}, and Na^+ are the various other metals used for cancer immunotherapy. Below is a list of examples and mechanisms describing how nanoparticles, specifically the cGAS-STING pathway, are activated by metal-based nano substances.[15]

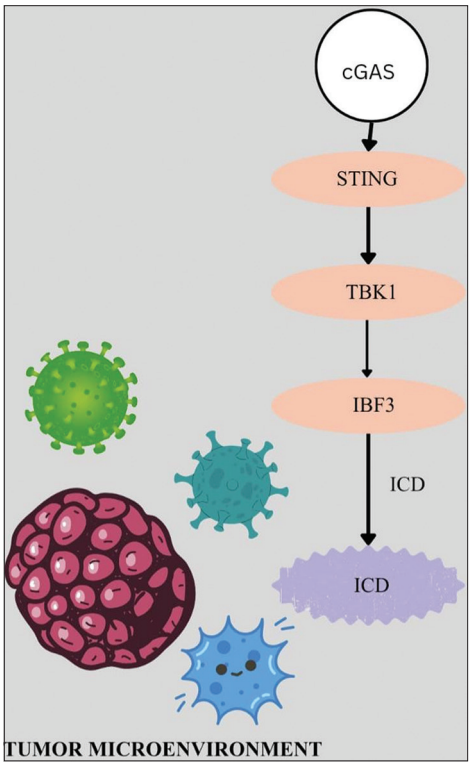


Figure 1: Activation of cyclic GMP-AMP synthase-STING axis in the tumor-microenvironment

ZN^{2+}

Zn^{2+} is a kind of metal ion that serves a significant role in the activation of the cGAS-STING pathway and the activation of other innate immune system. Which is more important in the process of DNA amplifying effect of cGAS-STING separation and powering up the activity of other cGAS enzymes, followed by the activation of STING.[37] Hence, the deficiency of Zn^{2+} can affect both the innate and adaptive immune system. Not only this, but also affects the quantity of CD8+ cytotoxic T cells and at the same time affects the function of CD4+ T cells.[38,39] Hence, the Zn^{2+} based cGAS-STING pathway and the therapeutic effect in cancer are discussed below.

ZN^{2+} CGAS-STING ACTIVATION PATHWAY

Zn^{2+} is essential for maintaining immune function and plays a significant role in activating the T cell receptor due to the Zn^{2+} being used for the identification of cancer cells by signaling the T cell pathway, and acts as an antigen-recognizing receptor.[37] Zn^{2+}, combined with cGAS ribbon, is essential for proper activation of cGAS enzyme and cGAS-STING signaling pathway, promotes the formation of cGAS-DNA phase, and cGAMP response.[40,41] In addition to the Zn^{2+} ionic particles, Zn^{2+} oxide nanoparticles are also most useful, particularly in the immune cell, because they are mostly engulfed by phagocytes. Zn^{2+} functioned as a cofactor that significantly boosted the catalytic activity of DNAzymes, promoting the degradation of Programmed cell death-ligand 1 messenger RNA and thereby facilitating gene silencing and regulation of the tumor's immunosuppressive microenvironment.[42]

MN^{2+}

Mn^{2+} is a broadly distributed element in the Earth's crust and functions as a redox-active metal, which is essential for all living organisms.[43] It contributes to multiple physiological processes, particularly the nervous and immune system, when it acts as a secondary messenger in innate immune signaling.[44,45] Mn^{2+} contributes to the regulation of metabolic pathways and the maintenance of homeostasis, along with the activation of specific enzymes through tissue-specific mechanisms.[43] Enzymes, such as glutamine synthetase, pyruvate carboxylase, and arginase depend on Mn^{2+} for their proper function.[46]

MN^{2+} CGAS-STING ACTIVATION PATHWAY

Mn^{2+} based nanoparticles have attracted significant attention due to their particular physicochemical properties. Mn^{2+} ions are capable of activating the cGAS-STING signaling pathway, leading to the secretion of IFNs and pro-inflammatory cytokines, which later increase antitumor immune responses. These nanoparticles have been investigated for their potential as effective sonosensitizers, catalytic nanozymes, and STING-targeted nano agonists. However, to date, no studies have reported the introduction of immunogenic cell death (ICD) through reactive oxygen species (ROS) combined with Mn^{2+} ions, which promote cGAS-STING activation to synergistically increase dendritic cell activation.[47] Mn^{2+} dioxide (MnO_2), a Mn^{2+}-based nanomaterial, has gained considerable attention in biomedical research due to its responsiveness to glutathione, relatively narrow bandgap, and versatile enzyme-like catalytic capabilities. Although MnO_2 shows potential as an effective nanozyme and sonosensitizer, its sonodynamic performance and multi-enzyme catalytic efficiency remain constrained, leading to insufficient production of ROS necessary to make strong ICD.[17,42,48,49]

CA^{2+}

The Ca^{2+} involves both the stimulatory and inhibitory mechanisms in the triggering of the STING complex. In cGAS-STING signaling, Ca^{2+} acts as an emergency role in the signaling of innate immunity and autoimmunity. In eukaryotic cells, they regulate the movement of Ca^{2+} into and out of the different organelles to control many essential functions, such as exocytosis, cell movement, programmed cell death, and neural communication. Together, these processes are referred to as intracellular Ca^{2+} signaling.[50]

CA^{2+} CGAS-STING ACTIVATION PATHWAY

Stromal interaction molecule 1 (STIM1) regulates the STING position and function indirectly by detecting fluctuations in Ca^{2+} levels within the ER.[51] Furthermore, mechanical stress can cause mitochondrial Ca^{2+} overfilled, resulting in the release of mitochondrial DNA, that afterward activate the STING signaling pathway.[52] In addition, a lack of STIM1 clearly increased type 1 IFN production following viral infection and protected against final outcomes from a DNA virus *in vivo*. These findings focus the regulatory STIM1-STING axis that preserves the STING pathway in its inactive state under normal conditions. In the loss of Ca^{2+} sensor STIM1 was found to trigger spontaneous activation of STING, resulting in the increased production of type1 IFN even without external stimulation by combined immunodeficiency as observed in mice and a patient.[53] Ca^{2+} signaling seems to act a essential role in triggering STING and IRF3 after human cytomegalovirus particles enter the cells, indicating that this pathway helps cells become more responsive to detecting the viral genome contained in invading particles. Replicate viruses activates IRF3 by generate and accumulating viral pathogen-associated molecular patterns, a process that was extensively studied. It was depicted in Table 1.

Table 1: Immunomodulatory roles of metallic ions

Metal ion	Targeted pathway	Immune/inflammatory response	Mechanism
Zn^{2+}	cGAS-STING activation pathway	Which increases the immunity of antiviral and anticancer	Promotes type-1 interferon response
Mn^{2+}	cGAS-STING activation pathway	It triggers dendritic cell maturation and results in IFN-β production	Enhances cytosolic DNA sensing
Ca^{2+}	TRP, ORA11 signaling ion channel	The release of cytokines and the stimulation of T cells are regulated	Controls NFATmedicated transcription
Fe^{2+}	Generating ROS pathway	Which induce oxidative stress and inflammation	Fenton reaction will occur due to medicated immune signaling

cGAS: Cyclic GMP-AMP synthase, IFN-β: interferons-β, TRP: Transient receptor potential, NFAT: Nuclear factor of activated T-cells, ROS: Reactive oxygen species, Zn^{2+}: Zinc, Mn^{2+}: Manganese, Ca^{2+}: Calcium, Fe^{2+}: Iron

OTHER METALLIC NANOPARTICLES IN CANCER IMMUNOTHERAPY

The other metallic nanoparticles, such as Gold, Silver, and Iron oxide are useful for treating the cancer immunotherapy. Gold nanoparticles (AuNPs) and other nanoparticles have been widely explored not only as direct anticancer agents but also act as carriers for delivering chemotherapeutic drugs or supporting combination therapies and also function as multi-functional therapeutic interactions [Figure 2].

BIOGENIC SYNTHESIS OF GOLD NANOPARTICLE

Gold ions are used for synthesizing stable gold nanoparticle (AuNPs). Unlike bulk gold, nanoscale AuNPs exhibit distinctive physical, chemical, electrical, mechanical, magnetic, optical, and biological characteristics due to their size and morphology. Their excellent compatibility with biological stability, strong chemical stability, and unique physical characteristics make them highly attractive for medical uses, especially in targeted drug delivery.[54-56] The microbial synthesis of AuNPs using various bacteria, such as *Pseudomonas aeruginosa* and *Rhodopseudomonas* capsulate, is gaining attention as a sustainable, efficient, and eco-friendly method. Among the factors influencing nanoparticle formation, the pH is a particularly fundamental one as it affects both the size and shape of the AuNPs.[57]

GOLD NANOPARTICLE AND ITS ACTION ON IMMUNOTHERAPY

At present, more research is moving toward the use of AuNPs to power up the effectiveness of cancer immunotherapy and increases the immune response. Immunotherapy provides unique benefits over conventional treatments, such as chemotherapy, RT, and surgery. It has the ability to develop a lasting immune memory, reduce the chance of cancer recurrence, and help manage the spread of tumors.[58,59] Thus,

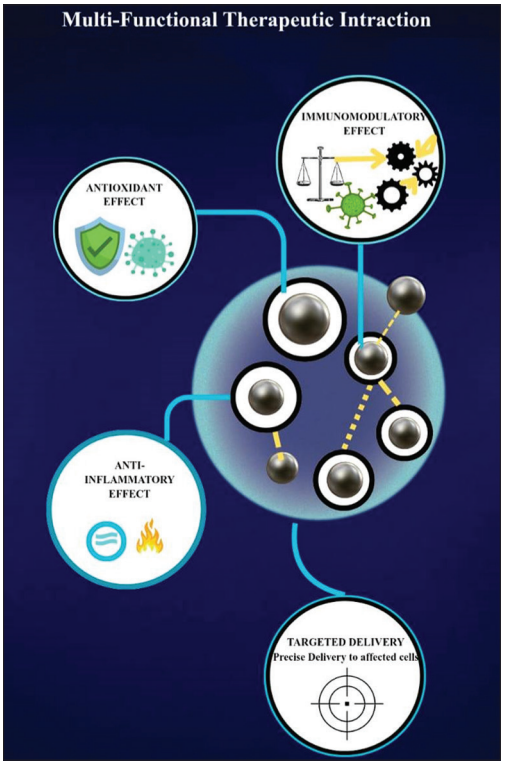


Figure 2: Interaction of metallic nanoparticles with ion channels in immune cells

the gold nanoparticles (AuNPs) have been widely explored across nearly every field of modern biomedicine, finding valuable roles in diagnostics, therapy, disease prevention, and even hygiene applications.[60-63]

AuNPs, known for their excellent biocompatibility, can be administered intravenously and through the increased permeability and retention mechanism in tumor tissues. Different nanostructures, such as nanosphere, nanorods, nanostars, nanoshells, and nanocages, have been researched as platforms for efficient photothermal therapy against a range of cancers. In addition, AuNPs have a major role in immunotherapy by enabling the delivery of cancer antigens and immune adjuvants, and they are also employed in combined approaches that integrate immunotherapy with

photothermal therapy.[64] Research indicates that AuNPs can generate ER stress and ROS, which in turn activate danger signaling pathways in the cancer cells. This process encourages the release of damage-associated molecular patterns, also known as "danger signals," such as calreticulin, adenosine triphosphate, heat shock proteins, and high mobility group box 1.[65-67] Gold nanoparticles are widely explored in cancer immunotherapy and in developing advanced cancer treatment approaches because they can target tumor cells, induce ICD, and further strengthen the body's defense mechanisms by generating heat for photothermal therapy and activating immune pathways. It is under the process for further strategies in the future for large-scale use by improving their design and combining it with other immune strategies, such as cGAS-STING activation. Table 2 shows the role of metallic nanoparticles in cancer.

BIOGENIC SYNTHESIS OF AGNP

AgNPs display scale and configuration influenced by spectroscopic characteristics, with their absorption maxima in solution shifting according to particle diameter. Studies indicate that particles within 40–100 nm range provide the greatest enhancement.[68] Moreover, AgNPs aggregation can reduce dye photobleaching, which is especially advantageous for live cell visualization use.[68] These nanocarriers can be engineered in a range of morphologies, such as spheres, rods, cubes, plates, and disks.[69,70] One widely adopted and adoptable method for generating such structures is the polyol process, in which ethylene glycol act as the reductant during polyvinylpyrrolidone (PVP) acts as a surfactant and capping agent.[71] In this synthesis route, Ag+ ions are reduced to metallic Ag° by ethylene glycol, initiating nucleation, and PVP directs particle growth and prevents aggregation. AgNPs are well known for their strong antimicrobial properties. They include various customer products, such as textiles, house hold items, and also in children's toy. In medical applications, AgNPs are used in burn and wound dressings, to promotes the healing process effectively.[72]

AGNP AND ITS ACTION ON IMMUNOTHERAPY

AgNP has gained considerable focus in the study of autoimmune and auto inflammatory disorders due to their excellent role on biochemical attributions, such as antioxidant, anti-inflammatory and immunoregulatory actions. Nanoparticles have the ability to regulate overactive immune cell activity and help in reestablishing equilibrium in inflammatory signaling pathways influenced by ion channels. Their capacity to neutralize ROS and adjust cytokine secretion positions them as a promising compound for managing chronic inflammation. Moreover, AgNPs can affect Ca^{2+} and k^{+} ion movements in immune cells, thereby modulating immune reactions and maintaining tissue injury in autoimmune disorders.[73]

AgNPs are used in multiple fields, but their effects on neutrophiles remains controversial, particularly regarding their potential induce harmful inflammation. Exposure to AgNPs markedly elevated interleukin-8 levels without increasing the secretion of conventional pro-inflammatory cytokines, indicating that AgNPs initiate neutrophils without provoking strong inflammatory responses or causing necrotic cell damage.[74] In addition, AgNPs can also alter the movement of ions, particularly Ca^{2+}, across the cell membranes, which acts as a major factor in controlling the

Table 2: Metallic nanoparticles in cancer immunotherapy

Types of nanoparticles	Ion released	Mechanism	Immunological effect	Applications	References
AuNPs	Gold	It acts as an immune adjuvant by activating the macrophages	It will improve the presentation of antigen	Gold and its nanoparticles are widely used in cancer immunotherapy	[135]
AgNPs	Silver	Regulates the neutrophil and its subtype	Which induces immunogenic cell death	Silver is useful for tumor suppression	[136]
MnO_2NPs	Manganese oxide	cGAS-STING pathway was activated by the releases of Mn^{2+}	It further promotes tumor-specific immunity	It has immuno-oncological effects	[137]
ZnONPs	Zinc oxide	It strengthening the interferon response	Induces apoptosis in tumor cells	Zinc oxide is particularly useful for nanomedicine and vaccines	[138]

AgNP: Silver nanoparticles, MnO_2NPs: Manganese dioxide, ZnONPs: Zinc oxide nanoparticles

intensity of immune cell responses and determining the specific types of cytokines they release.

CONCLUSION

Metallic ions and their nanoscale derivatives act as powerful regulators of immune and inflammatory signaling by influencing ion-channel dynamics and activating the cGAS-STING pathway. Elements, such as Zn^{2+}, Ca^{2+}, and Mn^{2+} function as both catalytic cofactors and as adaptive immunoregulatory species that are involved in tumor-associated immune activity. When integrated into nanomedicine formulations, these ions enable precise drug delivery, which promotes ICD, and strengthen antitumor defense mechanisms. Recent progress in metal-based nanomaterials, such as AuNPs, AgNPs, and MnO_2 nanostructures has revealed their synergistic capacity to enhance their existing immunotherapies, including immune checkpoint blockade and photothermal treatment. Remaining issues involving cytotoxicity, biocompatibility, *in vivo* compatibility, and controlled ion release highlight the importance of standardized evaluation methods. Combining the advances from nanotechnology, immunology, and ion-channel biology opens a pathway for next-generation cancer immunotherapies. Further, it aimed at refining targeted delivery systems, ensuring safety, and developing multimodal therapeutic strategies to firmly establish the gap bridge between experimental findings and clinical applications, thereby locating the nanometallo-immunotherapy as a strong and accurate cancer treatment method.

CREDIT AUTHORSHIP CONTRIBUTION STATEMENT

All authors contributed to the review. Sambasivam Gopinath: Conceptualization, supervision, writing-review and editing, Data curation, data analysis. Sabrin S: writing-review and editing. Pratheesha Vijaya Kumar Rajathi: writing-review and editing. Sankar Jeeva: Data curation, data analysis. Devan Pandu: writing-review and editing. Siva Shankar Gunasekaran: writing-review and editing, Ahamad Badhurudeen: writing-review and editing, Gopika Kannan: Writing original draft and editing, Data curation, Literature search, data analysis. All authors read and approved the final manuscript.

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