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Anti-Cancer Vaccine Activities of Zinc(Ⅱ) for Cancer Prevention, Malignancy, Angiogenesis, and Metastasis with Cancer Progression

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Abstract: *Anti-cancer vaccine activities of zinc(Ⅱ) for cancer prevention, malignancy, angiogenesis, and metastasis have been investigated. Therapeutic cancer vaccines are designed to generate a targeted, immune-mediated antitumor response. The immunoprevention is a fresh approach to cancer prevention based on the stimulation of the immune system before tumor onset that vaccines made of cells or DNA plasmids combined with appropriate adjuvants completely blocked mammary carcinogenesis. Zinc fingers induced preventive cancer vaccine is capable to induce effective immunity against malignancies, in which the tumor prevention is indicated by anti-tumor of suppressed tumor growth and human clinical trials are evaluated its applications as a vaccine for patients with tumor gene cancers.*

Tumor vaccine for malignant gliomas can react to a variety of tumor-specific antigens that the immunotherapeutic strategy of using tumor vaccines offers a way to harness the activity of the host immune system to potentially control tumor progression.

Angiogenesis, the formation of new blood vessels from pre-existing vasculature, plays a vital role in physiological processes. MMP-2, may play a key role in angiogenesis and tumor growth. Adenovirus-mediated both pro-apoptosis and anti-angiogenesis enhance antitumor efficacy in HCC. Further, as a novel anti-cancer vaccine platform, extending the biomedical application of inorganic ZnO NPs is widely noted.

Tumor metastasis is the main cause for failure of conventional cancer therapy. A vaccine successfully developed for cancer immunoprevention showed a strong therapeutic activity against lung metastasis mediated by protective immune mechanism distinct from those preventing the onset of primary mammary carcinoma. Further, ZnO NPs of nanowires as a novel vaccine platform induce tumor antigen-specific cellular immunity and significantly inhibit tumor growth.

ROS generation is O_2^-, ·OH, H_2O_2 are generated as by-products of aerobic metabolism as well as from a number of other sources. One of the major sources ROS in ECs is NADPH oxide and redox signaling events involved in angiogenesis. Further, zinc ions induced ROS generation is enhanced within cancer tumor cells that the ROS are conventionally thought as cytotoxic and mutagenic, and in high levels they induce apoptosis and cell death.

Keywords: *Zinc(Ⅱ) ions, Therapeutic cancer vaccine, Cancer prevention, Malignant tumor, Angiogenesis, Metastasis, ROS.*

Abbreviations: ***CAMs****=chorioallantoic membranes,* ***DCs****=dendrite cells,* ***ECs=e****ndothelial cells,* ***ER****=endoplasmic reticulum,* ***flk1****=fetal liver kinase,* ***HCC****=hepatocellular carcinoma,* ***HBV****=hepatitis B virus,* ***HPV****=human papilloma virus,* ***MMP****=matrix metalloproteinase,* ***PTGR2****=prostaglandin reductase 2,* ***ROS****=reactive oxygen species,* ***SOD****=superoxide dismutase,* ***Th1****=Treg helper1,* ***TNF****= tumor necrosis factor,* ***TRIL****= TNF-related apoptosis-inducing ligands,* ***WT1****=Wilms' tumor peptide protein 1,* ***ZNF****=zinc-finger protein,* ***ZMCs****=Zinc metallochaperones,* ***ZnT****=zinc transporter,* ***ZnO NPs****= ZnO nanoparticles.*

1. INTRODUCTION

Zinc of an essential trace element plays an important role in regulating carbohydrate metabolism, and acts both structurally and catalytically in metalloenzymes that are Zn metalloenzymes as important hydrolase of catalyzing hydrolysis [1]. Zinc homeostasis is primarily controlled via the expression and action of 14 protein transporters that increase cytoplasmic zinc (Zip1-14) and 10 protein zinc transporters that lower cytoplasmic zinc (ZnT1-10), which zinc deficiency as well as zinc excess can result in increased susceptibility to infections and development of especially inflammatory diseases [2]. Zinc deficiency can also induce apoptosis by disrupting growth

factor signalling molecules that the induction of apoptosis by high levels of intracellular zinc indicates that accumulation of intracellular zinc activates pro-apoptotic molecules like p38 and potassium channels, leading to cell death [3]. Increased intracellular zinc levels may also induce cell death by inhibition of the energy metabolism [3].

Free zinc (Zn^{2+} ions) in immune and tumor cells is regulated by 14 protein distinct zinc importers (ZIP) and transporters (ZNT1-8). Zinc depletion induces cell death via apoptosis and necrosis that cancer cells have upregulated zinc importers, and frequently increased zinc levels, which allow them to survive [4]. Zinc has been ascribed roles in interaction of malignant cells, particularly in apoptosis that zinc is involved in structural stabilization and activity of the p53 that appears to be an important component of the apoptotic process and in activation of proteases, in which zinc deficiency and zinc excess may contribute to the maintenance of DNA and the development of cancer tumor [5]. These zinc-mediated apoptosis and necrosis for cancer tumor cell are anticipated to be applied to anti-cancer vaccine and anti-cancer vaccination. More recently, the concept of vaccination has been developed into a potentially novel strategy to treat and prevent cancer formation, progression, and spread that with more anti-cancer vaccines currently in development, they can eventually become routine tools used in the treatment and prevention of cancer in the future [6]. Next generation cancer vaccines are combining immune check point inhibitors to overcome the immunosuppressive microenvironment and personalized cancer vaccines for directing the host immune system against the chosen antigens [7].

Zn homeostasis impacts maturation of dendritic cells (DCs) that are important in shaping T cell response, in which Zn shapes the tolerogenic potential of DCs and promotes Tregs in regulatory T cell (Treg)-Th (T helper)17 balance during fungal infection [8]. These DCs are required for anti-cancer vaccine with genetic modification and combination with other strategies including adoptive T-cell transfer [9]. Hierarchical Cu- and Zn-buds dressing γ-AlOOH mesostrands, which are oriented in randomly wrinkled matrice, are suitable platforms as novel adjuvants for immunotherapy that alum is only licensed adjuvant by the drug administration used in many human vaccines, and alum hardly induces T helper 1 (Th1) immune responses, being required for anti-tumor immunity [10].

In this review, firstly zinc-mediated tumor cell vaccine development is described, and secondly, cancer preventive vaccine, anti-malignant vaccine, anti-angiogenetic vaccine, and anti-metastatic vaccine are discussed. Finally, reactive oxygen species (ROS) generation in cancer cell and subsequently leading to oxidative stress are discussed, it should help to become apparent that anti-cancer vaccine with Zn^{2+} ion induced ROS generation, and apoptosis, and endoplamic reticulum (ER) stress could be led to tumor cell death.

2. Zinc Mediated Vaccine Development against Tumor Cell

Zinc-finger protein ZNF165 is novel cancer testis antigen capable of eliciting humoral immune response and be involved in tumor biology that ZNF165 induced hepatocellular carcinoma (HCC) vaccine could be achieved [11]. A new class of mutant p53 called Zinc metallochaperones (ZMCs) is developed as the cancer therapeutics and cancer vaccines which ZMCs are small molecular metal ion chelators that bind zinc and other divalent metal ions strong enough to remove zinc from serum albumin, but weak enough to donate it to mutant p53 [12].

Matrix metalloproteinase (MMP) may play a key role in angiogenesis and tumor growth that the vaccine based on chicken homologous MMP-2 as a model antigen could induce both protective and therapeutic antitumor immunity which MMP-2 induced active immunogene therapy with cancer vaccine was apparently inhibited by the vaccination with MMP-2. MMPs11 also as a novel target antigen for cancer immunotherapy are zinc-dependent endopeptidases with matrix degradation, tissue remodeling, inflammation, and tumor metastasis, in which the identification of MMPs11 as a novel broadly expressed tumor associated antigen as target candidate for cancer immunotherapy and cancer vaccine [13]. Thus, these novel targeted cancer therapeutics will be applied to cancer or tumor vaccine in future.

3. Cancer Preventive Vaccine

Cancer vaccine is an emerging therapeutic and prophylactic modality that may play a more important role in cancer prevention and treatment [14], in which therapeutic cancer vaccines are designed to generate a targeted,

immune-mediated antitumor response, but a tough challenge for the majorities of tumor vaccines is the self-nature of tumor antigens that the antigen formulation is essential for a vaccine to be effective [14]. Vaccine against hepatitis B virus (HBV) and human papillomaviruses (HPV) effectively prevents hepato-cellular and cervical carcinoma that the inhibition of immune checkpoints paves the way to application of cancer immune-prevention and the definition of optimal antigen enhances cancer prevention vaccine [15]. The immunoprevention is a fresh approach to cancer prevention based on the stimulation of the immune system before tumor onset that vaccines made of cells or DNA plasmids combined with appropriate adjuvants completely blocked mammary carcinogenesis [16]. Zinc binding cancer vaccine against virus-associated tumor cell has been investigated, in which preventive cancer vaccine that most importantly, the expression of virus-specific antigens by human tumors offers a huge opportunity to develop preventive and therapeutic options. Vaccines for HBV and HPV are available and widely used. The vaccines Cervarix and Gardasil have been developed against HPV, and both vaccines have proven to be almost 100% effective in preventing disease caused by the high-risk HPV types, HPV16 and -18, which together account for 70% of all cervical cancers, as well as other anogenital cancer [17]. Cancer vaccine by using viruses has been noteworthily investigated that preventive and therapeutic vaccines against HPV associated cervical cancers had been established [18]. The prevention of HPV associated malignancies could be accomplished by controlling virus-like particles that HPV vaccines are more affordable, induce wider protective coverage and offer therapeutic coverage against HPV-associated malignancies [19].

Zinc supplements of zinc species such as zinc P. placebo, zinc sulfate have effective for prevention of diseases that the effect of nutritional zinc supplementation on the incidence or severity of a certain disease was clarified [20]. Zinc fingers induced preventive cancer vaccine is capable of inducing effective immunity against malignancies that immunization with tumor gene induces tumor gene-specific cellular and humoral immunity sufficient to protect mice, in which the tumor prevention is indicated by anti-tumor of suppressed tumor growth and human clinical trials are evaluated its applications as a vaccine for patients with tumor gene cancers [21].

4. Cancer Anti-Malignant Vaccine

Cancer vaccine for tumor malignancy appears to find the biological functions of mesothelin in tumor progression that novel functions of mesothelin and new therapeutic vaccine strategy whereby mesothelin are targeted to control pancreatic cancer progression [22]. The vaccine therapy in malignant glioma is widely accepted in clinical neurosurgery as being an extremely lethal diagnosis that the therapeutic potential of vaccine immunotherapy for malignant glioma should not be yet understood [23]. However, as vaccine immunotherapy is unique because it offers the means of delivering treatment that is highly specific to both the patient and the tumor, the clinical benefit and the role of immunotherapy in the management of malignant glioma will become clearer [23]. Tumor vaccine for malignant gliomas can react to a variety of tumor-specific antigens that the immunotherapeutic strategy of using tumor vaccines offers a way to harness the activity of the host immune system to potentially control tumor progression [24]. Wilms' tumor peptide protein 1 (WT1) immune-therapy for gynecological malignancy was safe and produced a clinical response [25], and the other, WT1 cancer vaccine for patients with hematological malignancies and solid tumors revealed an untapped potential for inducing cancer immunity with minimal side effects and hold promise for a new adjuvant treatment against residual disease and against cancer relapse [26]. Thus, zinc-mediated malignant tumor vaccine is still in an early stage, much problems remain unclear.

5. Cancer Anti-Angiogenetic Vaccine

Angiogenesis is essential for the growth and metastasis of solid tumors. Angiogenesis, the formation of new blood vessels from pre-existing vasculature, plays a vital role in physiological processes. Uncontrolled tumor growth, immune evasion, and therapeutic resistance are driven by the dysregulated and constitutive angiogenesis occurring in the vasculature that a placenta-derived endothelial cell (ECs) vaccine, or a polyvalent vaccine that is antigenically similar to proliferating tumor endothelium and is supported by pre-clinical studies to be safe and efficacious against several tumor types [27].

Matrix metalloproteinase (MMP) family, in particular MMP-2, may play a key role in angiogenesis and tumor growth that the elevation of MMP-2 in sera of tumor-bearing mice was abrogated with the vaccination of c-MMP-2, in which transmigration of human endothelial cells and tumor cells through gelatin-coated filter was inhibited with immunoglobulins isolated from mice immunized with c-MMP-2 [28]. And then, the antitumor activity and the inhibition of angiogenesis were acquired by the adoptive transfer of the purified immunoglobulins that angiogenesis was apparently inhibited within tumor, and chick chorioallantoic membranes (CAMs) angiogenesis was also inhibited [28]. Furthermore, Wt1 tumor suppressor has a major regulation of tumor angiogenesis, leading to decreased metastasis, regression of established tumors and enhanced survival [29]. Antitumor efficacy of virus-mediated both anti-angiogenetic vaccine and pro-apoptosis are enhanced that further confirm the enhancement of anti-tumor efficacy through human endostatin and tumor necrosis factor (TNF)-related apoptosis-inducing ligands (TRIL) gene therapy, in which adenovirus-mediated anti-cancer vaccine could provide a promising application prospect by virtue of pro-apoptosis and anti-angiogenesis [30]. In addition, extending the biomedical application of inorganic zinc oxide nanoparticles (ZnO NPs) is widely noted as novel anti-cancer vaccine platform [31].

6. Cancer Anti-Metastatic Vaccine

Tumor metastasis is the main cause for failure of conventional cancer therapy that conventional approaches for cancer immunotherapy usually target antigens expressed by tumor cells, in which receptor fetal liver kinase 1(flk1) inhibits tumor angiogenesis and metastasis [32]. Tumor-associated antigen peptides can be enabled the design of anti-metastatic vaccines against a murine lung carcinoma [33]. A vaccine successfully developed for cancer immunoprevention showed a strong therapeutic activity against lung metastasis mediated by protective immune mechanism distinct from those preventing the onset of primary mammary carcinoma [34]. S100A4 (belong to S100 protein family) calcium binding protein for resistance to anti-cancer therapy and poor patient survival has important functions to increase the tumor progression and metastasis, in which S100A4 in the treatment of human cancers have been evaluated, including RNAi-based knockdown, S100A4 signaling inhibitor, S100A4-specific antibodies, drug/peptide/small molecule-based interference of S100A4-protein interactions, and other inhibitors that their effectiveness on the suppression of S100A4-induced cell motility, invasion, and metastasis remains to be verified [35]. Further, ZnO NPs of nanowires as a novel vaccine platform induce tumor antigen-specific cellular immunity and significantly inhibit tumor growth in vivo [36].

7. Reactive Oxygen Species in Malignancy, Angiogenesis, and Metastasis

High levels of reactive oxygen species (ROS) such as superoxide (O_2^-) and hydrogen peroxide (H_2O_2) are observed in various cancer cells that the reduction of oxygen increases the formation of O_2^-, which can be either dismutated to H_2O_2 spontaneously or in a reaction catalyzed by superoxide dismutase (SOD) [37]. A challenge for novel therapeutic strategies will be the fine tuning of intracellular ROS signaling to effectively deprive cells from ROS-induced tumor promoting events, towards tipping the balance to ROS-induced apoptotic signaling [38].

ROS generation in malignancy occurs accompanying ROS-mediated tumor death that ROS-mediated apoptosis in tumor associates SOD-carrying normal tissue through induction of antibody-dependent cellular cytotoxic effects [39]. The aberrant production of ROS appears in tumor cells for tumor progression [40]. Prostaglandin reductase 2 (PTGR2) modulates ROS-mediated cell death and tumor transformation of gastric cancer cells and suggesting that RTGR2-target based therapy is worth further evaluation [41]. Zn^{2+} ions induce apoptosis of human melanoma cells, while increasing intracellular ROS and modulating p53 and FAS ligand protein [42].

One of the major sources ROS in endothelia cells (ECs) is NADPH oxide and redox signaling events involved in angiogenesis that the accumulating evidence of ROS generation in angiogenesis suggests that ROS function as signaling molecules to mediate various growth-related response including angiogenesis [37]. However, zinc ions induced ROS generation is enhanced within cancer tumor cells that the ROS are conventionally thought as cytotoxic and mutagenic, and in high levels they induce apoptosis and cell death.

Metastasis is a multistep process involving invasion, migration, intravasation into the blood, survival in circulation, extravasation into distant organs, and proliferation that metastasis begins with detachment from local extracellular matrix [43]. ROS generation is O_2^-, hydroxyl radical (·OH), H_2O_2 are generated as by-products of aerobic metabolism as well as from a number of other sources [43]. High level ROS in tumor metastasis can be reached by several anti-cancer treatments, suppresses tumor metastasis by destroying cancer cells because of the oxidative nature of the molecules. On the other hand, sublethal levels of ROS can induce additional changes in DNA of tumor cells to make those cells malignant, stimulate the proliferation of cancer cells, and activate the expression of various molecules, some of which assist cancer cells to form metastatic colonies. Thus, a precise understanding how ROS are generated and involved in tumor metastasis will help us to design better strategies to overcome such life-threating events [38]. Hostile microenvironment within malignant cells of nutrient deprivation, oxygen limitation, high metabolic demand, and oxidative stress disturbs the protein-folding capacity of the ER, provoking cellular state of ER stress, in which ER stress responses enhance the efficacy of standard chemotherapies and evolving cancer immunotherapies in the clinic [44].

Thus, zinc mediated anticancer vaccine with Zn^{2+} ion induced ROS, apoptosis, and oxidative stress in tumor cell could be led to tumor cell death.

Table1 indicates anti-cancer vaccine activities of zinc (Ⅱ) ions for cancer prevention, malignancy, angiogenesis, and metastasis, accompanying with cancer progression. Zinc-mediated cancer vaccine researches have been present in initial step to novel approach for therapeutic vaccine target.

Table1. *Anti-Cancer Vaccine Activities of Zinc (Ⅱ) Ions for Cancer Prevention, Malignancy, Angiogenesis, and Metastasis*

Zn^{2+} Ions	**Zinc Binding Induced Anti-Cancer Vaccines for Cancer Progression Process**			
	Prevention	**Malignancy**	**Angiogenesis**	**Metastasis**
	→ Zn^{2+}	**→ Zn^{2+}, ROS**	**→ Zn^{2+}, O_2^-, H_2O_2**	**→Zn^{2+}, O_2^-, H_2O_2·OH**
Zn^{2+}	·Zinc sulfate and Zn^{2+} ion solution ·Against HPV associated cervical cancer ·Zinc species (zincacetate and zincsulfate) ·Virus-like particles control	·Mesothelin protein ·Zinc oxide-mediated ·ROS-mediated death ·ROS generation within malignant tumor	·MMP-2 ·VEGF-2 Receptor fik1 ·Wt1 peptide protein ·ZnO NPs ·Virus-mediated anti-angiogenic therapy ·ROS production in the process of angiogenesis	·Receptor fik1 ·Antigen peptides ·ZnO NPs ·S100A4 ·ROS production in the process of metastasis

8. CONCLUSIONS

Anti-cancer effects of zinc(Ⅱ) ions for cancer preventative, malignant, angiogenetic, and metastatic tumor vaccines with cancer progression have been investigated. The immunoprevention is a fresh approach to cancer prevention based on the stimulation of the immune system before tumor onset that vaccines made of cells or DNA plasmids combined with appropriate adjuvants completely blocked mammary carcinogenesis. Zinc supplements of zinc species such as zinc P. placebo, zinc sulfate have effective for prevention of diseases that the effect of nutritional zinc supplementation on the incidence or severity of a certain disease was clarified. Zinc fingers induced preventive cancer vaccine is capable to induce effective immunity against malignancies that immunization with tumor gene induces tumor gene-specific cellular and humoral immunity sufficient to protect mice.

Tumor vaccine for malignant gliomas can react to a variety of tumor-specific antigens that the immunotherapeutic strategy of using tumor vaccines offers a way to harness the activity of the host immune system to potentially control tumor progression. WT1 cancer vaccine for patients with hematological malignancies and solid tumors revealed an untapped potential for inducing cancer immunity with minimal side effects and hold promise for a new adjuvant

treatment against residual disease and against cancer relapse. Thus, zinc-mediated malignant tumor vaccine is still in an early stage, much problems remain unclear.

Angiogenesis, the formation of new blood vessels from pre-existing vasculature, plays a vital role in physiological processes. MMP-2, may play a key role in angiogenesis and tumor growth that the elevation of MMP-2 in sera of tumor-bearing mice was abrogated with the vaccination of c-MMP-2. Wt1 tumor suppressor has a major regulation of tumor angiogenesis, leading to decreased metastasis, regression of established tumors and enhanced survival. As a novel anti-cancer vaccine platform, extending the biomedical application of inorganic ZnO NPs is widely noted.

Metastasis is a multistep process involving invasion, migration, intravasation into the blood, survival in circulation, extravasation into distant organs, and proliferation that metastasis begins with detachment from local extracellular matrix. Tumor metastasis is the main cause for failure of conventional cancer therapy. Tumor-associated antigen peptides can be enabled the design of anti-metastatic vaccines against a murine lung carcinoma. A vaccine successfully developed for cancer immunoprevention showed a strong therapeutic activity against lung metastasis mediated by protective immune mechanism distinct from those preventing the onset of primary mammary carcinoma. Further, ZnO NPs of nanowires as a novel vaccine platform induce tumor antigen-specific cellular immunity and significantly inhibit tumor growth in vivo.

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