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Zinc(II)-Induced Immune Anti-Angiogenic Activity during Angiogenesis Process

Dr. Sci. Tsuneo Ishida*

2-3-6, Saido, Midori-Ku, Saitama-Shi, Saitama-Ken, 〒336-0907, Japan

***Corresponding Author:** ***Dr. Sci. Tsuneo Ishida**, 2-3-6, Saido, Midori-Ku, Saitama-Shi, Saitama-Ken, 〒336-0907, Japan **Email:** ts-ishida@ac.auone-net.jp*

Abstract: *Zinc ions-induced immune anti-angiogenic activities for initial, middle, and final steps during angiogenesis process have been revealed, and the molecular mechanism has been clarified. Steps toward angiogenesis process include (1) protease production, (2) endothelial cell migration and (3)proliferation, (4)vascular tube formation, (5)anastomosis of newly formed tubes, (6)synthesis of a new basement membrane, and incorporation of pericytes and smooth muscle cells.*

Zinc induced anti-angiogenic activity at the initial stage of angiogenesis process is involved that Vezf1 antisense oligodeoxynucleo-tide (AS-ODN) decreased endothelial cells (ECs) and increased apoptosis, degrading of extracellular matrix (ECM) as antiangiogenic activity, MAZ regulates vascular endothelial growth factor (VEGF), Zinc downregurates HIF-1α levels and suppresses intratumoral VEGF expression for the angiogenic tumor progression that zinc induces HIF-1α proteasomal degradation, and Zinc finger transcription restrains VEGF in angiogenesis that vascular formation in the chromatin insulator-binding factor (CTCF) binds to the proximal promoter of VEGF.

Zinc induced anti-angiogenic activity at the middle stage of angiogenesis process is involved that Vezf1 regulates proliferation, migration, and network formation, inhibition of MAZ accumulation is down-regulated in glioblastoma-associated ECs, attenuated primary human brain EC migration and tubule formation in angiogenesis. THAP1 is a physiologic regulator of EC proliferation and cell-cycle progression, and the GATA4 regulates VEGF secretion for the first time. but afterwards cell migration and angiogenic tube formation of ECs became knocked down due to GATA4 attenuated by collagen-induced arthris (CIA) and preventing rhematoid arthris (RA)-augmented angiogenesis during angiogenic process. Further, during acute inflammation, vascular hyperpermeability allows inflammatory mediators and immune response cells with sustained angiogenesis and cancer-related inflammation share.

Zinc induced anti-angiogenic activity at the final stage of angiogenesis process is required that the zinc-chelation inhibits the tube formation and the vascular ECs migration, and the GATA4 also regurates the tube formation of endothelial cells. Vezf1 also inhibits the tube formation of tumor development in angiogenesis with an innovative avenue of angiogenesis regulation regarding tubulin turnover in ECs. Vascular maturation plays important roles in tumorigenesis and tumor development that neuropilin 1 (NRP1) is closely associated with angiogenesis in tumor progression which NRP1 was performed in vascular ECs to investigate the functions in angiogenesis. Kruppel-like transcription factor 2 (KLF2) modulates blood vessel maturation that is required for smooth muscle cell migration and involved with the communication between KLF2 and platelet derived growth factor (PDGF) in vascular maturation. Further, pericyte-expressed Tie2 controls sprouting angiogenesis and vessel maturation

Zn2+ homeostasis takes place, enables extracellular Zn2+ to trigger intracellular signaling pathways regulating key cell functions in vascular cells that how extracellular Zn2+ regulates cell viability, proliferation, motility, angiogenesis, vascular tone, and inflammation in endothelial cells, in which extracellular Zn2+ promoted vascular cell survival/growth through activation of overexpressing of platelet-derived growth factor-receptor, vascular endothelial growth factor, enhanced cell adhesion and mobility, endothelial tubule formation, and cytoskeletal reorganization. In addition, ROS regulate different steps in vascular development, including an important role in tumor angiogenesis with smooth muscle cell differentiation and vascular cell migration.

Keywords: *Angiogenesis process, Endothelial cell migration, Vascular tube formation, EC proliferation, Blood vessel and vascular maturation.*

Abbreviations: ***AS-ODN**=antisense oligodeoxynucleotide, **bFGF**=basic fibroblast growth factor, **CKD**=chronic kidney disease, **CIA**=collagen-induced arthris, **CTCF**=chromatin insulator-binding factor, **ECM**=extracellular matrix, **ECs**=endothelial cells, **Egr3**=early growth response 3, **GATA4**=transcripion factor zinc finger protein, **GPR39**=G protein-coupled receptor 39, **HIF-1α**=hypoxia inducible factor-1α, **HRGP**=histidine-rich glycoprotein, **KLF2**= Kruppel-like transcription factor 2, **MAZ**=Myc-associated zinc finger protein, **MCL-1**=myeloid cell leukemia sequence-1, **PDGF**=platelet derived growth factor, **THAP1**= THAP-zinc finger protein1, **VEGF**=Vascular endothelial growth factor, **Vezf1**=Vascular endothelial zinc finger 1, **RA**=rhematoid arthris, **ROS**=reactive oxygen species, **ZnR**=Zinc-sensing receptor.*

1. INTRODUCTION

Zinc ions-induced immune promotion accelerates anti-bacterial, anti-viral, anti-cancerous, and anti-angiogenic activity effects. The angiogenesis in cancer is the development of new blood vessels from the exisisting vasculature that the formatiom of new blood vessels contributes to tumor growth and metastasis, malignant proliferation, inflammatory, infectious and immune disorders **[1].**

Angiogenic balance is controlled between pro-angiogenic and anti-angeogenic factors that a large number of anti-angiogenesis inhibitors have been discovered ranging from endogenous angiogenesis inhibitors to monoclonal antibodies for cancer agents **[2].**

In cancer progression, the angiogenesis is a critical factor in the development of tumors and metastases in numerous cancers that the transcription factors, such as Hypoxia-Inducible Factors (HIFs) act as angiogenic regulators, have been considered potential treatment options for several types of cancers **[3].** Angiogenesis-related factors in the progression of chronic kidney disease (CKD) are essential for potential therapeutic effect on CKD, vascular endothelial growth factor (VEGF)-A with a potent pro-angiogenic factor, angiopoietin induced maturation of newly formed blood vessels, therapeutic effects of angiogenesis inhibitors, and pro-or anti-angiogenic strategies for patients with CKD **[4].** Relation of tumor angiogenesis and anti-angiogenesis drug has tumor-host interaction, tumor microenvironment with respect to tumor development, disease progression, and response to therapy, in which zinc ions-induced anti-angiogenesis drug may be considered to one of anti-angiogenesis inhibitors **[5].**

Vascular endothelial zinc finger 1 (Vezf1) contains six C2H2 zinc fingers, is expressed at sites of postnatal angiogenesis, and can regulate endothelial gene products such as endothelin-1. Downregulation of Vezf1 expression in endothelial cells impairs proliferation, migration, and network formation. Vezf1 may normally function to promote aspects of angiogenesis. Strategies to induce and inhibit angiogenesis are of considarable therapeutic interest that zinc-finger proteins (ZnF) regulate transcriptional angiogenesis **[6].** Extracellular Zn^{2+} ions regulate cell viability, proliferation, motility, angiogenesis, vascular tone, and inflammation through zinc-sensing receptor (ZnR)/G protein-coupled receptor 39 (GPR39) in endothelial cells that ZnR/GPR39 may be a therapeutic target for regulating endothelial activity **[7].** Zinc ions-induced cancer and tumor cells cause tumor immunity, anti-angeogenic effect, and oxidative stress due to reactive oxygen species (ROS) generation **[8]**.

In addition, aniogenesis involves multiple pathways that are dependent on the homeostatic balance between the growth factors (stimulators and inhibitors). Although no angiogenesis inhibitors have been approved for patients with metastatic prostate cancer, therapies that target new blood vessel formation are still an emerging and promising area of prostate cancer research **[9].**

In this semi-review, zinc-induced immune anti-angiogenic activity with cancerous cell proceeding is discussed, and the molecular mechanism has been considered.

2. ZINC-ENHANCED IMMUNE ANTI-ANGIOGENESIS

Zn^{2+} ions promote the multiplication of pathogens in addition to the positive effect of zinc on human immune cells, in which this immunosuppressive effect of zinc may have a new therapeutic application in autoimmune diseases, the selective suppression of lymphocyte function is beneficial, and zinc finger structures play an important role in the regulation of DNA replication and repair, transcription and translation, cell proliferation and maturation, and apoptosis **[10].** Zinc is critical for normal immune cell function, whereby zinc depletion causes immune cell dysfunction, and zinc supplementation can either restore function in the setting of dysfunction or improve normal immune cell function. Specifically, zinc deficiency depresses expression of myeloid cell leukemia sequence-1 (MCL1), the longer product enhancing cell survival while the alternatively spliced (shorter) form promoting apoptosis. zinc supplementation suppresses the development of Th17 cells **[11].** Zinc supplement 50 mg/day for three month with each treatment for cancer patients becomes efficient, in order to strengthen the immune system to prevent the serious effects of COVID-19 infection **[12].**

3. Processes in Angiogenesis Have Involved with the Various Steps in New Blood Vessel Formation

Angiogenesis process is known to play an important role in cancer development for oxygen nutrient supply. Steps toward angiogenesis process include (1) protease production, (2) endothelial cell migration and (3) proliferation, (4) vascular tube formation, (5) anastomosis of newly formed tubes, (6) synthesis of a new basement membrane, and incorporation of pericytes and smooth muscle cells **[13, 14, 15].** The angiogenesis process has involved of the various steps in new blood vessel formation: the first step, the middle step, and the final step**.**

3.1. The First Stage in the Angiogenic Process is the Degradation of Subendothelial Basement Membrane and Surrounding Extracellular Matrix[13]

Production of protease and Migration; Endothelial cell activation by growth factors (including VEGF, bFGF), Degradation of the capillary wall by extracellular proteinases (matrix metalloproteinases).

Cell behaviors and dynamics during angiogenesis have a key step during angiogenic sprouting and anastomosis, forming an interconnected luminal space and allowing the subsequent circulation of blood that ECs exhibit numerous, sometimes unique, cellular behaviors during sprouting angiogenesis with ECs behaviors and their coordination in angiogenesis **[16].**

The induction of angiogenesis was by the expression of key pro-angiogenic factors, fibroblast growth factor (FGF) and vascular endothelial growth factor (VEGF), upregulated due to the presence of zinc ions released from ZnO nanoparticles **[17].**

Alleviating numerous cancer indications may be the strengthening application of notable antiangiogenic therapies to inhibit metastasis-related tumor growth that pathogenic factors contribute to the accumulation of angiogenic activators such as the vascular endothelial growth factor (VEGF) family and basic fibroblast growth factor (bFGF). Thus, circumstantial clarification of Traditional Chinese Medicines (TCMs)-driven therapeutic actions suppress tumor angiogenesis by targeting VEGF/VEGFRs pathway thar TCMs may provide permanent and attractive effects on inhibiting tumor angiogenesis as underlying chemopreventive agents in the treatment of diversified cancers **[18].**

3.2. The Middle Stage; Proliferation, Branch Formation, Migration of Endothelial Cells; Formation of a Branch Point in the Vessel Wall, Migration of Endothelial Cells Into the Extracellular Matrix Towards the Angiogenic Stimulus

The ability of ECs to assemble into vascular networks in a dynamic fashion is remarkable that sustained angiogenesis and cancer-related inflammation share important signaling pathways and molecules. These hallmarks ultimately serve to support tumor development with chronic inflammation and angiogenesis during carcinogenesis and the participation of endothelial cells in the inflammatory process **[19].**

3.3. The Final Stage in Angiogenesis Process ;Vascular Tube Formation and Blood Vessel Maturation

Re-organisation of endothelial cells to form tubules with a central lumen, Interconnection of the new tubules to form a branched network (anastomosis).

Though Tie2 exerts its functions through its supposed endothelial-specific expression, the pericyte-expressed Tie2 controls sprouting angiogenesis and vessel maturation that the endotheliocentric view of Tie2 signalling with Angiopoietin1 acting in a paracrine manner and Angiopoietin2 through an autocrine loop needs to be revised in favour of a bidirectional reciprocal model in which the EC signalling is complemented reciprocally by an autocrine Ang1/Tie2 loop in pericytes and paracrine acting Ang2 **[20].**

4. Zinc(II) Ions-Induced Anti-Angiogenic Activity for the Angiogenesis Process

4.1. The Early Step in the Angiogenic Process: Vezf1 of Angiogenesis Regulation, Degradation of ECM, Regulation of VEGF

At the first step of vascular formation, vascular endothelial zinc finger (Vezf1) is involved in the

regulation of angiogenesis that Vezf1 antisense oligodeoxynucleotide(AS-ODN) decreased G2/M population of Ecs and increased apoptosis **[21].** Degradation of extracellular matrix (ECM) occurring in response to an angiogenic stimulus, leads to degradation, release of soluble factors, and exposure of cryptic sites with pro-and/ or antiangiogenic activity **[22].** The plasma protein histidine-rich glycoprotein (HRGP), which has been identified as an angiogenesis inhibitor, binds to heparan sulfate (HS) in a Zn^{2+}-dependent manner that saturation of the HS binding sites in HRGP 330 by pre-incubation with heparin abrogates the HRGP330-induced rearrangement of endothelial cell focal adhesions, suggesting that interaction ith cell surface HS is needed for HRGP330 to_exert its anti-angiogenesis effect **[23].**

Myc-associated zinc finger protein (MAZ) regulates vascular endothelial growth factor (VEGF) that the down-regulation of miR-125 was observed on exposure of endothelial cells to glioblastoma-conditioned medium or VEGF **[24].** Zinc downregurates HIF-1α levels and suppresses intratumoral VEGF expression for the angiogenic swich during tumor progression that zinc induces HIF-1α proteasomal degradation **[25].** Zinc finger transcription restrains VEGF in angiogenesis that vascular formation in the chromatin insulator-binding factor (CTCF) binds to the proximal promoter of VEGF against hyperactivation of angiogenesis **[26].**

4.2. The Middle Step in the Angiogenic Process: Inhibition of VEGF-Mediated Endothelial Cell Proliferation

Vascular endothelial zinc finger 1(Vezf1) is an identified zinc finger transcription factor that is expressed in endothelial cells (ECs) during vascular development in mouse embryo, in which Vezf1 regulates proliferation, migration, and network formation in angiogenesis **[21].** The zinc-finger transcription factor, early growth response 3 (Egr3) inhibits VEGF-mediated endothelial cell proliferation, migration and tubulogenesis that Egr3 has an essential downstream role in VEGF-mediated endothelial functions leading to angiogenesis and may have relevance for adult angiogenic processes with vascular repair and neovascular disease **[27].**

The MAZ mediates VEGF-induced angiogenesis in glioblastoma that inhibition of MAZ accumulation by miR-125b that is down-regulated in glioblastoma-associated endothelial cells, attenuated primary human brain endothelial cell migration and tubule formation **[28].** THAP-zinc finger protein THAP1 regulates EC proliferation that the THAP1 is a physiologic regulator of EC proliferation and cell-cycle progression, 2 essential processes for angiogenesis **[29].** Zinc-chelation of ellagic acid (EA) is involved in its antiangiogenic effects by inhibiting MMP-2 activity, tube formation and cell migration of vascular endothelial cells **[30].**

GATA4 that belongs a member of GATA zinc-finger transcription factor family, has been shown to regulate differentiation, growth, and survival of a wide range of cell types that the GATA4 regulates VEGF secretion for the first time, but afterwards cell migration and angiogenic tube formation of endothelial cells became knocked down due to GATA4 attenuated by collagen-induced arthris (CIA) and preventing rhematoid arthris (RA)-augmented angiogenesis during angiogenic process **[31].**

During acute inflammation, vascular hyperpermeability allows inflammatory mediators and immune response cells, including leukocytes and monocytes/macrophages, to infiltrate the site of damage, in which sustained angiogenesis and cancer-related inflammation share important signaling pathways and molecules, whereas improving the combination of therapies that inhibit pathological angiogenesis and stimulate the antitumor response may prove to be a successful strategy for the treatment of patients with cancer **[32].**

4.3. The Final Step in the Angiogenic Process

The zinc-chelation inhibits the tube formation and the migration of vascular endothelial cells **[30] and** The GATA4 also regurates the tube formation of endothelial cells **[31].** Vezf1 also inhibits the tube formation of tumor development in angiogenesis with an innovative avenue of angiogenesis regulation regarding tubulin turnover in ECs **[33].** Vascular maturation plays important roles in tumorigenesis and tumor development that neuropilin 1 (NRP1) is closely associated with angiogenesis in tumor progression which gain- and loss-of-function experiments of NRP1 were performed in vascular endothelial cells (ECs) to investigate the functions in angiogenesis **[34].** KLF2 (Kruppel-like transcription factor 2) that

constitutes a subfamily of zinc finger proteins, modulates blood vessel maturation, in which KLF2 is required for smooth muscle cell migration and involved with the communication between KLF2 and platelet derived growth factor (PDGF) in vascular maturation **[35].** Zinc inhibits re-organization of endothelial cells to form tubules with a central lumen that Vascular tube formation and vessel maturation have been regulated **[13]**

Zn^{2+} homeostasis takes place, enables extracellular Zn^{2+} to trigger intracellular signaling pathways regulating key cell functions in vascular cells that how extracellular Zn^{2+} regulates cell viability, proliferation, motility, angiogenesis, vascular tone, and inflammation in endothelial cells, in which extracellular Zn^{2+} promoted vascular cell survival/growth through activation of overexpressing of platelet-derived growth factor-receptor, vascular endothelial growth factor, enhanced cell adhesion and mobility, endothelial tubule formation, and cytoskeletal reorganization **[36].**

5. Reactive Oxygen Species in Angiogenesis Process

Reactive oxygen species (ROS) genertion begins in VEGF of the first step and VEGFR2 autophosphorylation occurs at the middle step, leading ROS migration at the final step that ROS plays an inportant role in neobascularization during tumor growth. ROS are a class of molecules derived from the oxygen (O_2) and oxidase, and the other, angiogenesis process of tomor growth, metastasis, arteriosclerosis as well as embryonic development that is dependent on cell proliferation, migration and capillary tube formation in endothelial cells ECs, and high levels of ROS such as superoxide and H_2O_2 are observed in various cancer cells and major source of ROS in ECs is a NADPH oxidase **[37].** ROS regulate insulin-induced VEGF and HIF-1α that p70S6K1 plays an important role in tumor angiogenesis **[38].** ROS also regulate different steps in vascular development, including smooth muscle cell differentiation and vascular cell migration **[39].**

As mentioned above, anti-angiogenesis activities of zinc(II) ions for the first step, the middle step, and the final step during angiogenesis process are presented in ***Table 1.***

Thus, molecular mechanism of Zn^{2+} ions-induced immune anti-angiogenesis is considered that numerous molecule of extracellular Zn^{2+} promoted vascular cell survival/growth through activation of over expressing of platelet-derived growth factor-receptor, vascular endothelial growth factor, enhanced cell adhesion and mobility, endothelial tubule formation, and cytoskeletal reorganization.

Table1. *Anti-angiogenic activities of zinc(II) ions for the first step, the middle step, and the final step during angiogenesis process*

Zn^{2+} ions	**Anti-angiogenetic activities of Zn^{2+} ions during angiogenesis process**		
	The first step	**The middle step**	**The final step**
Zn^{2+}	**→ Zn^{2+},O_2^-,·OH, H_2O_2** ·Vezf1 regulates vascular formation ·ECM modulates degradation ·Endothelial cell inactivation by HRGP ·MAZ regulates VEGF ·Zinc-finger trancription restrains VEGF	**→ Zn^{2+}, O_2^-,·OH, H_2O_2** ·Vezf1 inhibits proliferation, migration, network formation ·Egr3 inhibits proliferation, migration, tubulogenesis ·MAZ inhibits endothelial cell migration and tubule formation ·THAP1 regulates EC proliferation ·GATA4 inhibits cellular Migration	**→ Zn^{2+}, O_2^-,·OH, H_2O_2** ·Vezf1 inhibition of tube formation ·Zinc-chelation of EA inhibits tube formation ·GATA4 regulates tube formation of EC ·KLF2 modulates blood vessel maturation ·Tie2 controls vessel maturation

6. Conclusions

Zinc ions-induced immune anti-angiogenic activities for initial, middle, and final steps during angiogenesis process have been revealed, and the molecular mechanism is clarified. Steps toward angiogenesis process include (1) protease production, (2) endothelial cell migration and (3) proliferation, (4) vascular tube

formation, (5) anastomosis of newly formed tubes, (6) synthesis of a new basement membrane, and incorporation of pericytes and smooth muscle cells.

Zinc induced anti-angiogenic activity at the initial stage of angiogenesis process is involved that Vezf1 antisense oligodeoxynucleo-tide (AS-ODN) decreased G2/M population of Ecs and increased apoptosis, Degradation of extracellular matrix (ECM) as antiangiogenic activity , MAZ regulates vascular endothelial growth factor (VEGF) , Zinc downregurates HIF-1α levels and suppresses intratumoral VEGF expression for the angiogenic swich during tumor progression that zinc induces HIF-1α proteasomal degradation, and Zinc finger transcription restrains VEGF in angiogenesis that vascular formation in the chromatin insulator-binding factor (CTCF) binds to the proximal promoter of VEGF

Zinc induced anti-angiogenic activity at the middle stage of angiogenesis process is involved that Vezf1 regulates proliferation, migration, and network formation in angiogenesis, MAZ mediates VEGF-induced angiogenesis in glioblastoma that inhibition of MAZ accumulation by miR-125b that is down-regulated in glioblastoma-associated endothelial cells, attenuated primary human brain endothelial cell migration and tubule formation, THAP1 is a physiologic regulator of EC proliferation and cell-cycle progression, 2 essential processes for angiogenesis, the GATA4 regulates VEGF secretion for the first time, but afterwards cell migration and angiogenic tube formation of endothelial cells became knocked down due to GATA4 attenuated by collagen-induced arthris (CIA) and preventing rhematoid arthris (RA)-augmented angiogenesis during angiogenic process, During acute inflammation, vascular hyperpermeability allows inflammatory mediators and immune response cells, including leukocytes and monocytes/ macrophages, to infiltrate the site of damage, in which sustained angiogenesis and cancer-related inflammation share important signaling pathways and molecules,

Zinc induced anti-angiogenic activity at the final stage of angiogenesis process is involved that the zinc-chelation inhibits the tube formation and the migration of vascular endothelial cells and the GATA4 also regurates the tube formation of endothelial cells. Vezf1 also inhibits the tube formation of tumor development in angiogenesis with an innovative avenue of angiogenesis regulation regarding tubulin turnover in ECs. Vascular maturation plays important roles in tumorigenesis and tumor development that neuropilin 1 (NRP1) is closely associated with angiogenesis in tumor progression which gain- and loss-of-function experiments of NRP1 were performed in vascular endothelial cells (ECs) to investigate the functions in angiogenesis. KLF2 (Kruppel-like transcription factor 2) that constitutes a subfamily of zinc finger proteins, modulates blood vessel maturation, in which KLF2 is required for smooth muscle cell migration and involved with the communication between KLF2 and platelet derived growth factor (PDGF) in vascular maturation. Vascular tube formation and vessel maturation have been regulated. Further, pericyte-expressed Tie2 controls sprouting angiogenesis and vessel maturation.

Zn^{2+} homeostasis takes place, enables extracellular Zn^{2+} to trigger intracellular signaling pathways regulating key cell functions in vascular cells that how extracellular Zn^{2+} regulates cell viability, proliferation, motility, angiogenesis, vascular tone, and inflammation in endothelial cells, in which extracellular Zn^{2+} promoted vascular cell survival/growth through activation of overexpressing of platelet-derived growth factor-receptor, vascular endothelial growth factor, enhanced cell adhesion and mobility, endothelial tubule formation, and cytoskeletal reorganization.

ROS regulate insulin-induced VEGF and HIF-1α that p70S6K1 plays an important role in tumor angiogenesis that the ROS regulate different steps in vascular development, including smooth muscle cell differentiation and vascular cell migration**.**

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