

Zinc Induced Anti-Angiogenesis for Cancerous Tumor Multi-Steps with Angiogenic Process

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Abbreviation:

AS-ODN: antisense oligodeoxynucleotide; bFGF: basic fibroblast growth factor; CIA: collagen-induced arthritis; CTCF: chromatin insulator-binding factor; Cys: Cystine; EA: ellagic acid; ECM: extracellular matrix; ECs: endothelial cells; Egr3: early growth response 3; FGF: fibroblast growth factor; GATA4: GATA zinc-finger transcription; HIF-1 α : hypoxia inducible factor-1 α ; His: histidine; HS: heparan sulfate; HRGP: histidine-rich glycoprotein; MAZ: Myc-associated zinc finger protein; MMPs: matrix metalloproteinases; THAP1: THAP-zinc finger protein; RA: rheumatoid arthritis; ROS: Reactive oxygen species; VEGF: vascular endothelial growth factor; Vezf1: vascular endothelial zinc finger; ZNF667: Zinc finger protein 667

1. Abstract

Zinc(II) induced anti-angiogenic activities for tumor multi-steps 1~5 on the angiogenesis process are elucidated, and zinc induced anti-angiogenic molecular mechanism is clarified.

At the step 1 of vascular formation, vascular endothelial zinc finger1 (Vezf1) is involved in the regulation of angiogenesis, and Myc-associated zinc finger protein (MAZ) regulates vascular endothelial growth factor (VEGF).

At the step 2, zinc-finger transcription restrains VEGF, zinc finger protein 667 (ZNF 667) transcriptional repression, zinc induces hypoxia inducible factor-1 α (HIF-1 α) proteasomal degradation.

At the Step 3, THAP-zinc finger protein THAP1 regulates endothelial cell (EC) proliferation that the THAP1 is a physiologic regulator of EC proliferation and cell-cycle progression, essential processes for angiogenesis.

At the Step 4, 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 ECs became knocked down due to GATA4 attenuated by collagen-induced arthritis (CIA) and preventing rheumatoid arthritis (RA)-augmented angiogenesis during angiogenic process.

At the Step 5, zinc-chelation inhibits the tube formation and the migration of vascular endothelial cells. In re-organization, the GATA4 also regulates the tube formation of endothelial cells and the Vezf1 also inhibits the tube formation of tumor development in angiogenesis.

ROS generations in zinc(II)-induced angiogenic tumor cells have O₂⁻, •OH, H₂O₂, in which play an important role in tumor anti-angiogenesis.

Therefore, this zinc coordinated molecular anti-angiogenesis mechanism is involved that Zn²⁺ ions having Zn²⁺ ions-centered tetrahedral geometric coordination pattern bind with each multi-steps 1~5 angiogenic tumor proteins, causing Zn²⁺ ions-several protein complex formation, oxidative stress, and angiogenic cells, leading these Zn-CysHis Ligands complexes to molecular anti-angiogenesis activity and cancer angiogenic tumor cells.

2. Introduction

Angiogenesis is the growth of blood vessels from the existing vasculature in cancerous tumor cell that angiogenesis can regulate by the balance production of growth and inhibitory factors in healthy tissues, in which since this balance is disrupted, angiogenesis occurs, resulting in many diseases. Angiogenesis plays an important role in the progression of cancer that angiogenic growth factors such as vascular endothelial growth factor (VEGF) as the ability of a tumor to metastasize seems be related to the quantity of

VEGF produced and that VEGF has been detected in numerous tumor cells having a role in the regulation of inflammatory repair processes [1]. Angiogenic growth factors are so-called because of their varying ability to induce the proliferation of various cells in vitro, which include a diverse range of proteins in addition to VEGF and fibroblast growth factor (FGF): platelet derived growth factor, tumor necrosis factor, insulin like growth factor-1, transforming growth factor, angiogenin, hepatocyte growth factor, and placental growth factor [2].

Angiogenesis has a multi-step process by which new blood capillaries are formed starting from preexisting functional vessels, in which angiogenesis is regulated by the balance of many positive and negative angiogenic modulators within the vascular microenvironment [3].

The other, zinc(II) induced immune anti-angiogenic activities for initial, middle, and final steps during angiogenesis process have been elucidated, resulting extracellular Zn^{2+} ions promoted vascular cell survival/growth through activation of overexpressing of platelet-derived growth factor-receptor, vascular endothelial growth factor, leading enhanced cell adhesion and mobility, endothelial tubule formation, and cytoskeletal reorganization [4].

Zn^{2+} ions regulate angiogenesis and inhibits blood formation that the process of angiogenesis is controlled by proangiogenic chemical signals in the body which stimulate both the formation of new blood vessels and the repair of damaged ones. The chemical signals called angiogenesis inhibitors hinder the blood vessel formation. These pro- and anti-angiogenic chemical signals are normally balanced in a way that blood vessels form only when and where this balance is disrupted in favor of angiogenesis. A blood supply is necessary for tumors to grow and spread to distant sites. Tumor progression is regulated by production of much pro- and anti-angiogenic factors, which are necessary for further outgrowth and metastasis of the tumor [5].

Zinc ions-induced immune anti-angiogenic activities for initial, middle, and final steps during angiogenesis process have been elucidated, resulting extracellular Zn^{2+} ions promoted vascular cell survival/growth through activation of overexpressing of platelet-derived growth factor-receptor, vascular endothelial growth factor, leading enhanced cell adhesion and mobility, endothelial tubule formation, and cytoskeletal reorganization [6].

Zinc could inhibit metastatic angiogenesis that zinc can act as a signaling factor to diminish multiple metastatic characteristics, including migration, invasion, and angiogenesis through metastatic/angiogenic pathways [7].

In this short review article, zinc induced anti-angiogenesis reactions for multi-steps 1~5 during angiogenic process have been investigated, and the molecular mechanism of zinc induced anti-angiogenesis with Zn^{2+} ions-proteins interactions in various multi-steps proteins are elucidated.

3. Angiogenesis has a Multi-Step Process

[1],[8],[9],[10],[11].

Angiogenesis is a complex multi-step process involving extensive interplay between cells, soluble factors, and extracellular matrix (ECM) components that angiogenetic four distinct sequential steps in angiogenesis include: (1) degradation of basement membrane by proteases; (2) migration of endothelial cells (ECs) into the interstitial space and sprouting; (3) ECs proliferation at the migrating tip; (4) lumen formation, generation of new basement membrane with the recruitment of pericyte, formation of anastomoses and finally blood flow.

Angiogenesis also in a multi-step process has New blood vessel capillary formation, Vascular microenvironment, There is accumulating evidence, Angiogenesis-dependent a hallmark of many cancers, diabetic retinopathy, Autoimmune diseases, rheumatoid arthritis, atherosclerosis, cerebral ischemia diseases, and Cardiovascular diseases.

Accordingly, the multi-Step angiogenetic process may be considered as follows:

Step 1; Endothelial cell activation by growth factors including VEGF, bFGF, blood vessel capillary formation, Angiogenic factors (FGF, VEGF) bind to EC receptors. Basement membrane, Angiogenic stimulus, Production of protease.

Step 2; Degradation of the capillary wall by extracellular proteinases (matrix metalloproteinases), vascular microenvironment, MMPs are activated and degrade matrix, EC adhesion and migration,

Step 3; Proliferation and formation of a branch point in the vessel wall, angiogenesis-dependent cancer hallmark.

Step 4; Vascular tube formation; migration of endothelial cells into the extracellular matrix towards the angiogenic stimulus,

Step 5; Blood vessel maturation, Re-organization of endothelial cells to form tubules with a central lumen, cardiovascular disease

4. Zinc(II) induced anti-angiogenesis for multi-Steps 1~5 angiogenic process

(1) Step 1

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 [12].

Myc-associated zinc finger protein (MAZ) regulates vascular endothelial growth factor (VEGF) that the down-regulation of miR-125 was observed on exposure of ECs to glioblastoma-conditioned medium or VEGF [13].

(2) Step 2

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 [14].

Zinc finger transcription restrains VEGF and vascular formation in the chromatin insulator-binding factor (CTCF) binding to the proximal promoter of VEGF against hyperactivation of angiogenesis [15].

Zinc finger protein 667 (ZNF667) facilitates myocardial ischemia-driven angiogenesis through transcriptional repression of VASH1 and regulation of Wnt (waste neutralizer tank), signaling pathway [16].

Zinc downregulates hypoxia inducible factor-1 α (HIF-1 α) levels and suppresses intratumoral VEGF expression for the angiogenic switch during tumor progression that zinc induces HIF-1 α proteasomal degradation [17].

(3) Step 3

THAP-zinc finger protein THAP1 regulates EC proliferation that the THAP1 is a physiologic regulator of EC proliferation and cell-cycle progression, essential processes for angiogenesis [18].

Zinc could regulate proliferation and formation of a branch point in the angiogenesis that zinc and zinc transporters (ZIP10) play an essential role in the migratory activity of highly metastatic breast cancer cells and for the metastatic phenotype [19, 20].

(4) Step 4

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 arthritis (CIA) and preventing rheumatoid arthritis (RA)-augmented angiogenesis during angiogenic process [21].

Zinc deficiency inhibits migration of endothelial cells into the extracellular matrix towards the angiogenic stimulus that zinc deficiency caused by specific zinc chelation promotes HIF-1 translocation to the nucleus, leading to HIF-1-dependent endothelin 1 (ET-1) and endothelial cell migration [22].

(5) Step 5

Zinc-chelation inhibits the tube formation and the migration of vascular endothelial cells that the zinc chelation of ellagic acid (EA) is involved in its anti-angiogenic effects by inhibiting matrix metalloproteinases-2 (MMP-2) activity, tube formation and cell migration of vascular endothelial cells. The MMP-2 inhibition that MMP-2 is a zinc-dependent enzyme, contributes to the anti-angiogenic effect of EA and the effect of EA directly on MMP-2 activity [23].

In re-organization, the GATA4 also regulates the tube formation of endothelial cells [21], and the *VeZF1* also inhibits the tube formation of tumor development in angiogenesis [24].

5. Reactive Oxygen Species in Angiogenesis

Reactive oxygen species (ROS) are a class of molecules derived from the oxygen (O_2) and oxidase, and the other, angiogenesis process of tumor growth, metastasis, arteriosclerosis as well as embryonic development that is dependent on cell proliferation, migration and capillary tube formation in 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 [25].

ROS regulate insulin-induced VEGF and HIF-1 α that p70S6K1 plays an important role in tumor angiogenesis [26].

ROS regulate different steps in vascular development, including smooth muscle cell differentiation and vascular cell migration [27].

6. Zinc(II) Coordinated Angiogenesis Molecular Mechanism in Angiogenic Tumor Cells

Zinc(II) has apoptogenic effects for inflammation, proliferation, invasiveness and migration, metastasis, angiogenesis, and oxidative damage in angiogenic proteins. Zinc(II) (Zn^{2+} ion) is liable to bind with each multi-step angiogenetic proteins that Zn^{2+} ions having Zn^{2+} ions-centered tetrahedral geometric coordination pattern bind with each multi-stage cancer angiogenic tumor proteins. Zinc coordinated molecular apoptosis for zinc-based anticancer drugs with the cellular redox homeostasis and considering chemical properties of the respective anticancer metal complexes currently either in clinical routine in oncology.

Zinc(II) complex has great therapeutic potential and identifies the mechanisms of apoptotic cell death and to reduce the toxicity of $Zn(II)$ complex on control cells that these Zn -CysHis Ligands complexes formations play an important role in anticancer metal-based drugs such as antitumor efficacy, inhibition of migration and invasion activities, and cell senescence [28]. Structural zinc sites typically consist of four Cys and/or His ligands that Zn -CysHis Ligands complexes with tetrahedral geometry are formed by zinc binding of CysHis type Zn -protein [29]. Zinc complexes comprising Nitrogen-donor Ligands in Zn complexes are important as anti-cancer agents that zinc can coordinate various donor atoms and zinc complexes comprising N-donor ligands are very effective as anticancer agents [30].

Therefore, this zinc coordinated molecular anti-angiogenesis mechanism is involved that Zn^{2+} ions having Zn^{2+} ions-centered tetrahedral geometric coordination pattern bind with each multi-steps 1~5 angiogenic tumor proteins, causing Zn^{2+} ions-several protein complex formation, oxidative stress, and angiogenic cells, leading these Zn -CysHis Ligands complexes to molecular anti-angiogenesis activity and cancer angiogenic tumor cells.

Thus, zinc(II) ions induced anti-angiogenesis activities for the multi-Steps 1~5 during angiogenic process, and molecular mechanism of zinc ions-coordinated anti-angiogenesis molecular mechanism are presented in Table 1.

Table 1: Zinc(II) induced anti-angiogenesis activity for multi-Steps 1~5 during angiogenic process, and zinc(II) ions-coordinated anti-angiogenesis molecular mechanism

Zn ²⁺ Ions	Zn ²⁺ ions induced anti-angiogenesis activity during angiogenic process				
	Step 1	Step 2	Step 3	Step 4	Step 5
	Endothelial cell activation by growth factors (including VEGF, bFGF)	Degradation of the capillary wall by extracellular proteinases	Formation of a branch point in the vessel wall and	Migration of endothelial cells to extracellular matrix towards the angiogenic stimulus	Vascular tube formation and maturation Re-organization endothelial cells to form tubules
Zn ²⁺ →	<p>→ Zn²⁺, (O₂⁻, ·OH, H₂O₂)</p> <ul style="list-style-type: none"> ·Vezf1 regulates vascular formation · MAZ regulates VEGF 	<p>→ Zn²⁺, (O₂⁻, ·OH, H₂O₂)</p> <ul style="list-style-type: none"> · Zinc-finger transcription restrains VEGF · ZNF 667 transcriptional repression · Zinc induces HIF-1α proteasomal degradation 	<p>→ Zn²⁺(O₂⁻, ·OH, H₂O₂)</p> <ul style="list-style-type: none"> · THAP-zinc finger protein THAP1 regulates EC proliferation · Zinc and its zinc transporter could proliferation and migration of a branch point 	<p>→ Zn²⁺ (O₂⁻, ·OH, H₂O₂)</p> <ul style="list-style-type: none"> · GATA4 (GATA zinc-finger transcription regulates the tube formation of endothelial cells · Zinc deficiency promotes Ecs formation 	<p>→ Zn²⁺ (O₂⁻, ·OH, H₂O₂)</p> <ul style="list-style-type: none"> · Zinc-chelation inhibits tube formation and migration of vascular endothelial cells · In re-organization, Vezf1 and GATA4 also inhibits the tube formation

Zinc induced anti-angiogenesis molecular mechanism with zinc ions-coordinated tumor anti-angiogenic cells; Zn²⁺ ions that having Zn²⁺ ions-centered tetrahedral geometric coordination pattern, bind with each other multi-Steps 1~5 angiogenic tumor proteins, causing Zn²⁺ ions-several protein complex formations, oxidative stress, and tumor angiogenetic cells, leading the Zn-CysHis Ligands complexes to the anti-angiogenic molecular activities in cancer angiogenetic tumor cells.

6. Conclusions

Zinc(II) induced anti-angiogenic activities for tumor multi-steps 1~5 on the angiogenesis process are elucidated, and zinc induced anti-angiogenetic molecular mechanism is clarified.

At the step 1 of vascular formation, Vezf1 is involved in the regulation of angiogenesis, and MAZ regulates VEGF.

At the step 2, zinc-finger transcription restrains VEGF, ZNF 667 transcriptional repression, zinc induces HIF-1α proteasomal degradation.

At the Step 3, THAP-zinc finger protein THAP1 regulates EC proliferation that the THAP1 is a physiologic regulator of EC proliferation and cell-cycle progression, essential processes for angiogenesis.

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