SEMI-REVIEW ARTICLE

Elucidation of Zinc-Induced Antiangiogenic Molecular Mechanism as "Therapy Treatment of CANCER and TUMOR Disease"

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ABSTRACT

Antiangiogenic features of Zn^{2+} ions during angiogenic process are that zinc finger protein restricts vascular endothelial growth factor (VEGF) at the initial step in angiogenesis, vascular endothelial zinc finger 1 (Vezf1) regulates VEGF-induced inflammatory angiogenesis at the middle step in angiogenesis, and Vezf1 regulates vascular tube formation and vessel maturation at the final step in angiogenesis. Initial step molecular mechanism seems that Zn^{2+}-binding VEGF protein molecule may be bound by the coordination for triad of cysteine (Cys), histidine (His), and asparagine (Asp) residues around a zinc ion, leading to typical Zn^{2+} interacting ligands, Asp, Cys, and His. Middle step molecular mechanism suggests that Zn^{2+}-binding inflammatory angiogenic proteins may be bound by zinc ions induced inflammatory VEGF proteins as three molecules with typical Zn^{2+} interacting ligands, Cys, His, and Asp. Final step molecular mechanism is assumed that Vezf1 regulates vascular tube formation and vessel maturation, in which Zn^{2+} ions facilitate diverse protein functions in Zn^{2+}-binding vessel maturation proteins that common Zn^{2+} ligands found within proteins include cysteine (S), histidine (N), aspartate (O), and glutamate (O) residues that Zn^{2+}-cysteine complexes may regulate protein activities. As overall steps molecular mechanism, Zn^{2+} ions inhibit angiogenesis growth process, in which zinc-binding proteins resulting from the interaction of zinc ions and angiogenesis proteins such as VEGF protein, inflammatory molecule, vessel growth formation, and vessel maturation are formed by zinc coordinated binding. Thus, zinc ions induced immune antiangiogenesis molecular mechanism may be caused that Zn^{2+} ions are bound with each angiogenic protein molecules, such as VEGF protein, inflammatory molecule, vessel growth formation, and vessel maturation proteins by zinc ion coordinated tetrahedrally or zinc ion triad binding structure formation, leading to formation of zinc coordinated binding proteins molecules.

Key words: Angiogenesis process, inflammatory angiogenesis, vascular endothelial growth factor, vascular tube formation and vessel maturation, vascular endothelial zinc finger 1, zinc coordinated triad Cys, His, and Asp, zinc-binding protein

ABBREVIATIONS

Ang=Angiopoietin, **ANGPTL**=Angiopoietin-like, **bFGF**=basic fibroblast growth factor, **EA**=ellagic acid, **ECM**=extracellular matrix, **ECs**=endothelial cells, **FGF2**=fibroblast growth factor receptor2, **FGFR**=fibroblast growth factor receptor, **GPR39**=G protein-coupled receptor39, **Gq**=G protein, **HGF**=hepatocyte growth factor, **MAZ**=Myc-associated zinc finger protein, **MMP**=Matrix metalloproteinase. **NF-κB**=nuclear factor kappa-B, **NRP1**=neuropilin 1, **OP18**=oncoprotein18, **PDGF-BB**=platelet-derived growth factor-BB, **PLC**=phospholipase C, **Tie2**=**TEK**=tunica interna endothelial cell kinase, **TGF-β1**= transforming growth factor-β1, **TGF-β1**=transforming growth factorβ1, **VEGF**=vascular endothelial growth factor, **Vezf1**=vascular endothelial zinc finger 1, **ZNFs**=Zinc finger proteins, **ZnR**=zinc oxide non-linear resistor.

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INTRODUCTION

Vasculogenesis and angiogenesis are the fundamental processes by which new blood vessels are formed, in the embryo, blood vessels form through both vasculogenesis and angiogenesis. Vasculogenesis is defined as the differentiation of precursor cells (angioblasts) into endothelial cells (ECs) and the *de novo* formation of a primitive vascular network. Vasculogenesis occurs during both embryonic development and adult vascular growth by angioblast mobilization, whereas sprouting angiogenesis entails two successive phases: Neovessel growth and neovessel stabilization, and intussusceptive angiogenesis is caused by the insertion of interstitial cellular columns into the lumen of preexisting vessels. Subsequent growth of these columns and their stabilization results in partitioning of the vessel and remodeling of the local vascular network.[1]

Angiogenesis is defined as the formation of new blood vessel growth from pre-existing blood vessels and involves several processes, including proliferation of ECs, proteolytic degradation of the extracellular matrix (ECM), and migration of endothelial cells, leading to the organization of endothelial cells. These new blood vessels grow into the tumor and provide the necessary oxygen, nutrients, and growth factors for tumor progression that inhibition of angiogenesis is explored as therapeutic prospect to treat cancer. There are many steps which are critical for angiogenesis and blood capillary formation including endothelial cell survival, proliferation, migration, organization, and remodeling into capillary structure.[2] Whereas, angiogenesis is a complex multistep process that involves degradation of the ECM, endothelial cell migration and proliferation, tube formation, and vessel maturation with tumor angiogenesis during embryogenesis or in response to a specific stimulus such as specific growth factor or cytokine.[3] An understanding of the transcriptional hierarchy and network is critical to gaining a more complete understanding of how specific factors regulate the complex angiogenic process and vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) are particularly important to tumor angiogenesis.[4]

Vascular cells, the ECM, and angiogenic factors are indispensable in the promotion of lumen formation and vascular maturation to support blood flow. However, the addition of growth factors or proteins involved in pro-angiogenic effects is not effective for regulating angiogenesis in different microenvironments. The angiogenesis is regulated by the activity of vascular endothelial zinc finger 1 (Vezf1) protein. The discovery of Vezf1 as an endothelial transcription factor and its role in angiogenesis is relatively new, however, the mechanism by which Vezf1 regulates gene expression and angiogenesis during development and disease is unknown. The structure of Zif268 was used to model the structure of Vezf1 given the high sequence similarity between the zinc fingers of Vezf1 and Zif268. The Zif268 structure was determined in complex with DNA and demonstrates detailed molecular interactions between zinc fingers and DNA backbone. Discovery of a small molecular inhibitor against Vezf1 will not only have therapeutic use but can also be employed to understand its mechanism in development and disease. Tumor cells treated with these inhibitors can be tested for proliferation, migration, and tube formation.[5] On zinc immune angiogenesis, zinc (Ⅱ) ions (Zn^{2+}) have strongest effect on the immune system through Th lymphocytes that zinc supplementation in the amount of 20 mg/day zinc for 5 weeks or 5 mg/kg for 4 weeks promotes anticancer activity, in which these zinc ions may be indicated for effective antiangiogenic effect.[6]

Antiangiogenetic activities of Zn^{2+} ions during angiogenesis process have been reported previously that zinc finger protein (ZNF) restricts VEGF in angiogenesis at the initial step, Vezf1 regulates VEGF-induced inflammatory angiogenesis at the middle step, and Vezf1 regulates vascular tube formation and vessel maturation at the final step.[7] However, zinc ions molecular antiangiogenesis mechanism for these three steps during angiogenesis process could be not shed light and remained unclear.

In this mini-review, Zn^{2+} ions induced antiangiogenesis for the initial step, the middle step, and the final step in angiogenesis process has become apparent, and molecular mechanisms of the zinc-binding proteins at each initial, middle, and final steps may be anticipated to be clarified, by which Zn^{2+} ion is bound in a tetrahedral site through such as a triad binding of cysteine, histidine, and glutamine.

ANTIANGIOGENESIS FEATURES OF ZN^{2+} IONS DURING ANGIOGENIC PROCESS

Initial step in angiogenic process

Antiangiogenesis activities of Zn^{2+} ions during angiogenic process have been reported previously that decrease of Vezf to G2/M population of endothelial cells (ECs), degrading of ECM, regulation of Myc-associated ZNF (MAZ) to VEGF, zinc suppression of intratumoral VEGF expression, and zinc finger transcription restraining of VEGF in angiogenesis at the first step.[5] The VEGF plays an important role in the initiation of angiogenesis with lymphoma progression (ZNF restricts VEGF in angiogenesis).

VEGF plays an important role in the initiation of angiogenesis that lymphoma progression may be enhanced by angiogenesis. VEGF promotes tumor angiogenesis through several mechanisms including enhanced endothelial cell proliferation and survival, increased migration and invasion of endothelial cells, increased permeability of existing vessels forming a

lattice network for endothelial cell migration, and enhanced chemotaxis and homing of bone marrow derived vascular precursor cells. In addition to having pro-angiogenic effects, VEGF has several important functions that are independent of vascular processes including autocrine effects on tumor cell function (survival, migration, and invasion), immune suppression, and homing of bone marrow progenitors to prepare an organ for subsequent metastasis.[8]

Zinc ions inhibit new blood vessel growth that the zinc chelation of EA is involved in its antiangiogenic effects by inhibiting matrix metalloproteinase-2 (MMP-2) activity, tube formation, and cell migration of vascular endothelial cells. The role of zinc was confirmed to be important in the process of angiogenesis[9] and extracellular Zn^{2+} regulates endothelial cell activity in zinc oxide non-linear resistor/G protein-coupled receptor 39 (ZnR/GPR39)-dependent manner and through the downstream Gq-phospholipase C pathways. Thus, ZnR/GPR39 may be a therapeutic target for regulating endothelial activity.[10] The findings herein provide evidence for a specific Zn^{2+} sensing mechanism involving cellular Ca_2 and PI3 signaling and, hence, controlling key vascular cellular processes.[10]

Middle step in angiogenic process

Zinc-induced antiangiogenic 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 downregulated in glioblastoma-associated endothelial cells, attenuated primary human brain endothelial cell migration and tubule formation. 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.[3]

Angiogenesis can stimulate and intensify the inflammatory response by providing nutrients and oxygen in inflammatory sites, and some angiogenic factors exert pro-inflammatory activity. Conversely, in chronic inflammation, inflammatory cells produce cytokines and growth factors that may affect endothelial cell functions. Angiogenesis and inflammation are associated with nuclear factor kappa-B and angiopoietin- (Ang-) tyrosine kinase endothelial (Tie2) signaling pathways. Inflammatory cells release MMPs involved in the release of angiogenic factors, such as VEGF and FGF-2, and cryptic antiangiogenic factors. VEGF derived from matrix stores, as a result of MMP-9, is implicated in the angiogenic switch and tumor growth.[11]

VEGF is a key tumor-derived angiogenic factor that exerts multiple functions including stimulation of angiogenesis, vasculogenesis, inflammation, and vascular permeability. In inflammatory angiogenesis, the association of chronic inflammation and angiogenesis occurs in inflammatory bowel disease where continuous ulceration and regeneration lead to the development of chronic inflammation and pathological angiogenesis that all inflammatory processes are estimated to lead to tumor development. The established tumor can initiate the metastatic process, in which vasculogenic mimicry and cooption contribute to mechanisms of invasion and the migration of tumor cells. A recent therapeutic option includes the combination of antiangiogenic therapy with inhibitors of various immunological checkpoints. Sustained angiogenesis and cancer-related inflammation share important signaling pathways and molecules. These hallmarks ultimately serve to support tumor development. Therefore, 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.[12]

Vezf1 was expressed in ECs at the site of angiogenesis. Moreover, the specific elimination of Vezf1 expression abrogated proliferation, migration, and network formation by cultured ECs as well as angiogenesis *in vivo*. Thus, Vezf1 is involved in the regulation of angiogenesis. As Vezf1 is a transcription factor, Vezf1 should regulate angiogenesis by modulating downstream target genes. Although endothelin-1 is reported to be the candidate target of Vezf1 in ECs, stathmin/oncoprotein 18 (OP18) gene and metallothionein gene were downregulated to less than one-half of basal levels. Vezf1 exhibited the abnormality in cell cycle progression and apoptosis, which was characteristic to stathmin/OP18 inhibition. Thus, Vezf1 and stathmin/OP18 are functionally related in the regulation of angiogenesis.[13]

Vezf1 regulates VEGF-induced inflammatory angiogenesis that Zn^{2+} regulates cell viability, proliferation, motility, angiogenesis, vascular tone, and inflammation through ZnR/GPR39 in endothelial cells, in which the role of ZnR/GPR39 in Zn^{2+} regulated endothelial activity related to angiogenesis contributes endothelial permeability, vascular tone, and inflammation. They are endothelial cell viability, proliferation, mobility, and tubule formation as related to angiogenesis and regulation of key molecules involved in vasoconstriction and vasodilation as related to vascular tone, as well as expression and secretion of key molecules involved in inflammation.

ZNFs also inhibit inflammatory angiogenesis that ZNF354C is a repressive transcription factor which acts through a KRAB domain to inhibit endothelial angiogenic sprouting.

Final step in angiogenetic process

The zinc-induced antiangiogenic activity at the final stage of angiogenesis process is involved that the Vezf1 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 ECs to investigate the functions in angiogenesis. Vascular tube formation and vessel maturation have been regulated. Further, pericyte-expressed Tie2 controls sprouting angiogenesis and vessel maturation.[6] This vascular development process is the differentiation of pluripotent stem cells into endothelial cells, following by endothelial proliferation, migration, and eventual formation of endothelial tubes that maturation of these primitive tubes into fully developed blood vessels requires the recruitment of surrounding pericytes and their differentiation into vascular smooth muscle cells.[14]

Vezf1 regulates vascular tube formation that Vezf1-mediated regulation of Cited2 expression is potentially relevant during adult angiogenesis and wound healing where Vezf1 could downregulate or maintain low Cited2 expression in the ECs and that loss of Vezf1 causes inhibition of blood vessel formation.[15]

The current concepts of vascular Ang/Tie signaling by establishing the contribution of pericyte Tie2 signaling are expanded to vascular maturation. Consequently, the classical endotheliocentric view of Tie2 signaling with Ang1 acting in a paracrine manner and Ang2 through an autocrine loop needs to be revised in favor of a bidirectional reciprocal model in which the EC signaling is complemented reciprocally by an autocrine Ang 1/Tie 2 (Ang1/Tie2) loop in pericytes and paracrine acting. Thus, pericyte-expressed Tie2 controls vascular tube formation and vessel maturation in angiogenesis.[16]

Zinc ions dependent ectoprptidase-Tie2 may control vessel maturation that CD13 is identical with a predominant metalloproteinase (MMP), a Zn^{2+}-dependent ectopeptidase that activates or inactivates bioactive peptides on the cell surface by preferential cleaving of proteins with NH2-terminal neutral amino acids and that regulates the availability of peptides to adjacent cells.[17]

THE MOLECULAR MECHANISMS OF ZINC IONS BINDING ANGIOGENIC PROTEINS

During angiogenesis process, many molecules are essentially involved, such as VEGF, FGF, hepatocyte growth factor, platelet-derived growth factor-BB (PDGF-BB), Ang/Tie, and transforming growth factor β1 (TGF-β1), which are responsible for inducing and stabilizing the formation of blood vessel networks. Each angiogenic protein molecule binds to specific receptors on the cells to elicit the necessary biological response. VEGF binds to receptors VEGFR-1 and VEGFR-2, while bFGF binds to receptors FGFR1b/c, FGFR2b/c, FGFR3b/c, and FGFR4. Further, PDGF binds to receptors PDGFRα and β, Ang-1 to Tie-2 receptor, and Ephrin to Ephrin receptor tyrosine kinase.[18]

First step molecular mechanism

ZNF restricts VEGF in angiogenesis. The zinc-dependent VEGF of angiogenesis protein is that zinc-dependent protein like TGF-β1 may be regulated by 4HR and induce VEGF and angiogenesis. The Zn^{2+}-binding VEGF protein molecule is formed, by which the coordination for triad of cysteine (Cys), histidine (His), and asparagine (Asp) residues around a zinc ion may be formed an independent domain, in which sticks as a finger-like projection that three molecules were chosen in the side chains of typical Zn^{2+} interacting ligands, Asp, Cys, and His.[19]

Thus, zinc ions are bound with angiogenic VEGF protein molecule, leading to be formed zinc coordinated binding proteins molecules, in which Zn^{2+}-binding VEGF proteins molecule may be bound with the zinc ion coordinated triad of Zn^{2+} interacting ligands, Asp, Cys, and His.

Middle step molecular mechanism

Interaction of zinc ions with inflammatory angiogenic protein is that interaction of zinc ions with inflammatory angiogenic protein seems that Zn suppresses the activation of STAT3, which is an important step in Th17 development, there is a great deal of data supporting the anticancer effect of lymphocytes. It seems to be largely dependent on the advancement of the disease (having a different role in the early and late stages), as well as the origin of the cancer and the role of inflammatory processes and angiogenesis in its pathogenesis.[20]

Ang-like (ANGPTL) protein family plays role in angiogenesis, inflammation, and in the regulation of different steps of carcinogenesis and metastasis development, including that ANGPTL1, 2, 3, 4, and 6 likely regulate angiogenesis.[21] Zn^{2+}-binding ANGPTL proteins may be bound with inflammatory angiogenic protein that zinc ions induced inflammatory VEGF proteins may stick as a finger-like projection that three molecules are chosen in the side chains of typical Zn^{2+} interacting angiogenic ligands of inflammatory triad of Cys, His, and Asp. Thus, zinc ions are bound with angiogenic inflammatory protein molecule, leading to be formed zinc coordinated binding protein molecules.

Final step molecular mechanism

Ang1 expressed by pericytes (and likely other cells) activates pericyte Tie2 and contributes thereby to vascular maturation.

Table 1: Zn^{2+}-induced chief antiangiogenic activities and these molecular mechanisms for the initial step, the middle step, and the final step in the angiogenesis process

Zn^{2+} ions	Zn^{2+}-induced chief antiangiogenic activities and these molecular mechanisms for the initial step, the middle step, and the final step in the angiogenesis process		
Zn^{2+}→	Zn^{2+}-induced antiangiogenic activity at the initial step	Zn^{2+}-induced antiangiogenic activity at the middle step	Zn^{2+}-induced antiangiogenic activity at the final step
	• Vezf1 restricts vascular formation and VEGF • MAZ regulates VEGF • Zn^{2+} ions inhibit new blood vessel	• Vezf1 inhibits proliferation, migration, network formation • Vezf1 regulates VEGF-induced inflammatory angiogenesis • ZNFs also inhibit inflammatory angiogenesis	• Vezf1 inhibition of tube formation • Vezf1 regulates vascular tube formation • Zinc finger restricts vascular smooth muscle differentiation and endothelial differentiation • Tie2 controls vessel maturation
	The molecular mechanism at the initial step	The molecular mechanism at the middle step	The molecular mechanism at the final step
Zn^{2+}→	Zn^{2+}-binding VEGF proteins molecule may be bound with the zinc ion coordinated triad of Zn^{2+} interacting ligands, Asp, Cys, and His	Zinc ions induced inflammatory VEGF proteins with typical Zn^{2+} interacting ligands of triad inflammatory Cys, His, and Asp	Zn^{2+}-binding vessel maturation proteins with common Zn^{2+} ligands within proteins include cysteine (S), histidine (N), aspartate (O), and glutamate (O) residues

Ang2 is produced by EC and acts paracrine on pericytes, thereby contributing to vascular destabilization through direct pericyte effects.[17]

Vezf1 regulates vascular tube formation and vessel maturation that zinc ions (Zn^{2+}) are known to facilitate diverse protein functions in Zn^{2+}-binding vessel maturation proteins that are essential for life. Common Zn^{2+} ligands found within proteins include cysteine (S), histidine (N), aspartate (O), and glutamate (O) residues that Zn^{2+}-cysteine complexes may regulate protein activities through sophisticated mechanisms, including inhibition, redox switching, and protein interface stabilization and new modes of Zn^{2+}-based regulation are constantly being unveiled.[22]

Thus, zinc ions are bound with angiogenic protein of vessel growth formation and vessel maturation, leading to be formed zinc coordinated binding proteins molecules.

Overall steps molecular mechanism

Molecular mechanism that Zn^{2+} ions inhibit angiogenesis growth process, has become apparent that zinc-binding proteins molecules of Zinc ions-angiogenic proteins, such as VEGF protein, inflammatory molecule, vessel growth formation, and vessel maturation may be formed by zinc ions-coordinated binding. Thus, antiangiogenesis molecular mechanism may be caused by zinc ion coordinated tetrahedrally or by zinc ion triad binding structure formation. Zinc ions are bound with each angiogenic protein molecules, such as VEGF protein, inflammatory molecule, and vessel growth formation and vessel maturation, leading to be formed zinc coordinated binding proteins molecules.

As above mentioned, Zn^{2+}-induced chief antiangiogenic activities and these molecular mechanisms for the initial step, the middle step, and the final step in the angiogenesis process are represented in Table 1.

CONCLUSIONS

Antiangiogenesis features of Zn^{2+} ions during angiogenic process are that ZNF restricts VEGF at the initial step in angiogenesis, Vezf1 regulates VEGF-induced inflammatory angiogenesis at the middle step in angiogenesis, and Vezf1 regulates vascular tube formation and vessel maturation at the final step in angiogenesis.

At the initial step of angiogenesis process, VEGF plays an important role in the initiation of angiogenesis with lymphoma progression, promotes tumor angiogenesis through several mechanisms including enhanced endothelial cell proliferation and survival, increased migration and invasion of endothelial cells, increased permeability of existing vessels forming a lattice network for endothelial cell migration, and enhanced chemotaxis and homing of bone marrow-derived vascular precursor cells. Zinc chelation of EA is involved in its antiangiogenic effects by inhibiting MMP-2 activity, tube formation, and cell migration of vascular endothelial cells.

At the middle step of angiogenesis process, Vezf1 regulates proliferation, migration, and network formation in angiogenesis, MAZ mediates VEGF-induced angiogenesis in glioblastoma, attenuated primary human brain endothelial cell migration and tubule formation. Vezf1 regulates VEGF-induced inflammatory angiogenesis that Zn^{2+} regulates cell viability, proliferation, motility, angiogenesis, vascular tone,

and inflammation through ZnR/GPR39 in endothelial cells, in which the role of ZnR/GPR39 in Zn^{2+} regulated endothelial activity related to angiogenesis contribute endothelial permeability, vascular tone, and inflammation. They are endothelial cell viability, proliferation, mobility, and tubule formation as related to angiogenesis and regulation of key molecules involved in vasoconstriction and vasodilation as related to vascular tone, as well as expression and secretion of key molecules involved in inflammation.

At the final step of angiogenesis process, Vezf1 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 NRP1 is closely associated with angiogenesis in tumor progression which gain- and loss-of-function experiments of NRP1 were performed in vascular ECs to investigate the functions in angiogenesis. Vascular tube formation and vessel maturation have been regulated. Further, pericyte-expressed Tie2 controls sprouting angiogenesis and vessel maturation.

Initial step molecular mechanism seems that Zn^{2+}-binding VEGF proteins molecule that the coordination for triad of cysteine (Cys), histidine (His), and asparagine (Asp) residues around a zinc ion may form an independent domain, in which sticks as a finger-like projection that three molecules were chosen in the side chains of typical Zn^{2+} interacting ligands, Asp, Cys, and His.

Middle step molecular mechanism suggests that Zn^{2+}-binding ANGPTL proteins may be formed inflammatory angiogenesis that zinc ions induced inflammatory VEGF proteins may stick as a finger-like projection that three molecules are chosen in the side chains of typical Zn^{2+} interacting angiogenic ligands of inflammatory triad of Cys, His, and Asp.

Final step molecular mechanism is assumed that Vezf1 regulates vascular tube formation and vessel maturation that Zn^{2+} ions are known to facilitate diverse protein functions in Zn^{2+}-binding vessel maturation proteins that are essential for life. Common Zn^{2+} ligands found within proteins include cysteine (S), histidine (N), aspartate (O), and glutamate (O) residues that Zn^{2+}-cysteine complexes may regulate protein activities through sophisticated mechanisms, including inhibition, redox switching, and protein interface stabilization and new modes of Zn^{2+}-based regulation are constantly being unveiled.

Overall steps molecular mechanism seems that Zn^{2+} ions inhibit angiogenesis growth process, in which zinc-binding protein of zinc ions angiogenesis proteins, such as VEGF protein, inflammatory molecule, vessel growth formation, and vessel maturation is formed by zinc coordinated binding.

Thus, zinc ions induced immune antiangiogenesis molecular mechanism may be caused that Zn^{2+} ions are bound with each angiogenic protein molecules, such as VEGF protein, inflammatory molecule, and vessel growth formation and vessel maturation proteins by zinc ion coordinated tetrahedrally or zinc ion triad binding structure formation, leading to be formed by zinc coordinated binding proteins molecules.

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