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Zinc (Ⅱ) Ions-Mediated Hydrolyzing and Degrading Functions for Bacterial Cell Walls, Viral Protein and RNA, and Cancerous Malignancy and Metastasis

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ABSTRACT

Hydrolysis and degradation activities of Zn^{2+} ions were investigated for bacteriolyses of bacterial cell walls, viral protein and RNA degradations, and regulation of cancer/tumor cell growth. Zn^{2+}ions-mediated hydrolytic and degradative functions for bacteria are due to bacteriolyses and destructions of bacterial cell walls by the inhibitions of PGN elongation owing to activated PGN autolysins.Zn^{2+} ions-mediated degradative function for viruses is viral protein hydrolysis, viral Mrna degradation, and bacteriophage viral-endolysins, by thatZn^{2+}ion inhibits HIV-1 by recruiting the 5' and 3' mRNA degradation, b specifically promotes the degradation of multiply spliced HIV-1 m-RNAs. Zinc selectively and markedly down-regulated nonstructural protein levels by increasing protein degradation.Furthermore,Zn^{2+}-mediated hydrolyzing and degrading function for cancer cell is related to protea some and autophage that leads to cancer and tumor cell death, Zn^{2+}ions inhibit malignant tumor proliferation and metastasis, and zinc complex and zinc chelation that have important roles for anticancer/tumor apoptotic death. Thus, these hydrolysis and degradation methods have being now noteworthy under the hydrolase enzymic development for bactericidal, virucidal, and cancerous cell death .

Keywords: *Hydrolytic and degradative function, Zn^{2+} ions, PGN autolysin, Viral protein and mRNA degradation, Malignant tumor proliferation, Metastasis, Zinc complex and chelation.*

Abbreviation: *APC=activated protein C,APN=aminopeptidaseN, ATP=adenosine triphosphate, E.coli=Escherichia coli, EMT=epithelial to mesenchymal transition, ERAD=endoplasmic reticulum-associated degradation, IFN=inter-feron , HCV=hepatitis Cvirus, HIV=human immunodeficiency virus, MTs=metallothioneins, NC=nucleocapsid protein,NS5A=non-structural 5A,Pol Ⅱ=polymerase Ⅱ, PGN=peptideglycan, PTEN=phosphatase and tensin homologdeleted from chromosome 10, humanairway epithelialcells,S.aureus=Staphylococcusaureus, SINV=Sindbisvirus, SNP=sodium nitroprusside,TAR=transactivating region,TG=glycosylase,TP=transpeptidase,TRIM11=Tripartite motif 11,RBBP9=Retinoblastoma-binding protein 9, ZAP=Zinc-finger antiviral protein, ZnMP=zinc mesoporphyrin,ZIPs=zinc importers, ZNTs=zinc transporters, ZnONPs=zincoxide nanoparticles.*

INTRODUCTION

Zinc is an essential trace element that zinc is applied in several infectious diseases such as acute human immun deficiency virus (HIV) and pneumonia. Zinc homeostasis is crucial for an adequate function of the immune system that zinc deficiency as well as zinc excess result in severe disturbances in immune cell numbers and activities, which can result in increased susceptibility to infections and development of especially inflammatory diseases [1]. The imbalances in Zn homeostasis cause disease states including such as cancer and serious disease. Zinc to be relatively non-toxicto humans, is involved in the regulation of live and death decisions on the cellular level, in which zinc has both roles of regulation of apoptosis and of neuronal death [2]. In the former case accumulation of intracellular zinc, either as a consequence of exogene- ous administration or release from intracellular stores by reactive oxygen species (ROS), activates proapop- totic molecules like p38 and potassium channel, leading to cell death [2].Whereas, in the latter ,intoxication by exposure is rare, zinc deficiency is widespread and has a detrimental impact on growth, neuronal development, and immunity, in severe cases its consequences are lethal [2]. Thus, zinc homeostasis and immunity influence zinc binding states such as zinc ion cancer /tumor cell, zinc ion-viral protein, and zinc ion-

nucleic interactions. In this study, Zn^{2+} ions-mediated hydroly-zing and degrading for bacterial, viral, and cancer cells are investigated using the role of metal in enzyme activity. Zinc complexes as bactericidal, virucidal, and anti-tumoragents are used such as zinc nitrate Zn(NO3)2,zinc sulfate ZnSO4[3], and zinc oxidenano- particles(ZnONPs)[4]. In this review, firstly, Zn^{2+}ions-mediated hydrolyzing and degrading mechanism is considered. Secondly, Zn^{2+}ion-mediated hydrolysis and degradation are discussed for hydrolyses of bacterial cell walls, viral protein and RNA degrading, and regulation of cancer/tumor cell growth. Lastly, highly hydrolytic and degra-dative activity of zinc complexes and zinc chelation has a role of zinc ion-coordinated bonding characteristics for apoptotic death of cancerous cell

Zn^{2+}Ion-Mediated Hydrolyzing And Degrading Mechanism

The accumulation of zinc also inhibits mitochondrial terminal oxidation and respiration. Zn^{2+} ions provide formation of fluorescent product after reaction with -SH groups of thiols [5],

$$Zn^{2+} + 2(-SH) \rightarrow Zn(II)S-S- + 2H^{+}$$

Zinc can inhibit apoptosis induced by both chemical and death-receptor agonists. Apoptotic effects of zinc because zinc is reported to both induce apoptosis in some cancers and to protect other cancer cells against apoptosis induced by other factors. Zinc played a key role in the regulation of epithelial to mesenchymal transition (EMT) and meta-static behaviors that zinc-induced EMT increases the intracellular superoxide anion and induces EMT phenotypes in lung cancer cells by up-regulating of EMT markers and down-regulating of E-cadher in protein.Zn2+ ions promote hydrolysis of RNA and protein. Zinc ion-dependent hydrolysis of RNA cleaves RNA that Zn^{2+}-promoted cleavage was observed to be considerably more sensitive to the secondary structure of the chain [6]. Zn^{2+} ions also were found to efficiently inhibit activated protein C (APC),suggesting a potential regulatory function for such inhibition [7].Zn^{2+}appropriate concentrations may promote the inhibition or regulation of activity of APC for anti-coagulation of blood.Zinc ion-mediated hydrolytic and degradative activity is an essential regulation for bacterial, viral, and cancerous cell growth. The fundamental catalytic hydrolysis, consisting of acylation and diacylation stages similar to those for ester hydrolysis by other serine hydrolases, was proposed based on the simulated various modes of metal-protein interaction include metal-ligand-, and enzyme-bridge complex [8]. Zinc enzymes participate in carbohydrate, lipid protein and nucleic acid synthesis or degradation.

As the molecular mechanism for bacteria, bacterial peptidoglycan (PGN) is a major component of the bacterial cell envelope in both Gram-positive and Gram-negative bacteria that these muropeptides can be produced and modified by the activity of bacterial glycolytic and peptidolytic enzymes referred to as PGN hydrolases and autolysins. Autolysins in bacteria are PGN hydrolases with roles in growth, turnover, and cell lysis that LytM was identified as the only autolysin in an autolysis-deficient strain of S.aureus [9].PGN-hydrolyzing enzymes participate in assembly and disassembly of the bacterial cell wall during the processes of bacterial growth and division. PGN-hydrolyzing enzymes that bind to and degrade intact bacterial cells or PGN of the producing organism are classified as autolysin [10].

For virus, adenosine triphosphate (ATP) hydrolysis results in nonstructural protein 2C auto phosphorylation that the parechovirus 2C protein has enzymatic activities, which may contribute to several functions in the viral replication cycle [11]. As the application of bacterio-phage endolysins, there is hydrolyzing virus of bacterio phage, resulting in cell lysis and release of progeny virion [12]. Endolysins (lysins) are highly evolved enzymes produced by bacterio phage to digest the bacterial cell wall for phage progeny release that viral protein-hydrolyzing and fusion by lysins may be occurred [13].

For cancer and tumor cell, levels of expression of retinoblastoma-binding protein 9 (RBBP9) were equivalent in both normal and cancer tissues, suggesting that enzyme activity drives the functional contribution of this protein to tumor-cell growth [14]. Zinc importers (ZIP) and Zinc transporters (ZNT) mediated tumor degradation and fusion may lead to cancer cell death [15].

Zn^{2+}Ions-Mediated Hydrolysis and Degradation of *S.Aureus* PGN And E.Coli outer me Merane Cell Walls:

Inhibition Of PGN Elongation Due To Activations of PGN Hydrolyses And Autolysins

Bacteriolysis against *S. aureus* peptidoglycan (PGN) cell wall by Zn^{2+}ions is due to inhibition of PGN elongation caused by regulation of PGN synthetic transglycosylase (TG) and transpeptidase (TP), and enhancement of the activation of PGN autolysins of Amidases[16]. On the other hand, bacteriolysis and destruction against E. coli cell wall by Zn^{2+}ions are caused by the destruction of outer membrane structure due to degradative enzymes of lipoproteins at N- and C-terminals, and by the inhibition of PGN elongation owing to inactivation of PGN TP synthetic enzyme endopeptidase and enhancement of the activations of PGN hydrolases and autolysins of Amidase and Carboxypeptidase[16].

Hydrolyzing, Degrading, And Endolysin of Zn^{2+}Ions for Viral Protein Hydrolysis And Viral RNA Degradation

Virus Restriction Factors, Viral Protein Hydrolysis, and Endolysins

Virus restriction factors may be in presence of viral entry, viral DNA synthesis, intracellular movement of viral nucleic acids and viral gene expression. These restriction systems constitute newly appreciated components of an innate immunity that may be important for survival of a host exposed to virus infections [17]. They are cellular proteins that inhibit viral replication and indicate a first line of defense against viral pathogen. As a consequence of virus-host adaptation, restriction factors are usually less effective against viruses in their natural hosts but represent potent barriers against transmissions. Relation of antiviral restriction factor and viral proteinis clarified that the antiviral restriction factor IFN(interferon)-induced transmembrane protein 3 inhibits cell entry of a number of viruses and genetic diversity determines susceptibility to viral disease in humans [18].

Zinc-induced tumor suppressor PTEN (phosphates and tensing homolog deleted from chromosome 10) protein is degraded by the protea some pathway in human airway epithelial cells [19].This phenomenon causes that PTEN protein degradation and loss of function by exposure to Zn^{2+} ions which is mediated by an ubiquitin-associated proteolytic process in the airway epithelium. Tripartite motif 11(TRIM11) protein enhances protein degradation with increasing protea some activity [20].Zinc mesoporphyrin (ZnMP) selectively and markedly down-regulated non-structural 5A(NS5A) protein levels by increasing degradation of NS5A protein that ZnMP may hold promise as a novel agent to treat HCV infection [21]. Zinc binding inhibits formation of the caspase, the activated form of the enzyme that zinc-mediated inhibition is due to regulation of apoptosis by direct inactivation of caspases [22]. For zinc-binding protein [23,24], substituting of the conserved cysteines and the histidine within the motif led to a complete loss of the capacity. For capsid protein-transactivating region (TAR) RNA interactions[25], nucleocapsid protein (NC) variants with mutations in their zinc finger domains have dramatically altered HIV trans-activation response (TAR)RNA binding interactions relative to wild-type NC. Furthermore, zinc-associated hydrolyzing and degrading activities are applied against human cancer-related viruses [26, 27, 28] that it is necessary to develop subunit vaccines consisting of immunogrenic recombinant viral proteins, the current status of immunotherapy for virus-associated malignancies, and aminopeptidase N(APN)-mediated peptide hydrolysis and activation for regulation of several physiological processes such as the control of angiotensins and cell chemotax.

Endolysins (phage lysins) are phage-encoded PGN hydrolases employed by the majority of bacteriophages to enzymatically degrade the PGN layer of the host of bacterium [12]. However, as endolysin as protein and phage as virus both have interaction functions, virus-mediated hydrolyzing and degrading may occur within intracellular cell. This phenomenon remains yet unclear.

Viral RNA Degradation

RNA is degraded at the end of its useful life that it is closely regulated for most mRNA species, in which RNA molecules with defects in processing, folding, or assembly with proteins are identified and rapidly degraded by the surveillance [29]. Ribonucleases (RNase) hydrolyze RNA and cleave the phosphodiester bond between guanosine phosphates and the OH group of the adjacent nucleotide, forming guanosine phosphate in the catalytic cycle [30] that Zn^{2+} ions reduced the amount of cGMP

blocking binase recognition sites of guanine at N7 of nucleophilic purine bases. The metal ions such as Cu^{2+} and Zn^{2+} promote proceeding of cleavage of RNA by an intra molecular transesterification that RNA hydrolysis promoted under the combined catalytic activity of buffer/Mg^{2+} ions with partially degraded RNA [31]. Zinc-finger antiviral protein (ZAP) was originally identified as a host factor that inhibits the replication of many viruses by preventing the accumulation of viral mRNAs in the cytoplasm. ZAP specifically binds to the viral mRNA and recruits the cellular RNA degradation machinery to degrade the RNA [32]. The degradation mediated by the viral RNA polymerase associates with host RNA polymerase Ⅱ (Pol Ⅱ) [33]. ZAP also inhibits HIV-1 infection by promoting the degradation of specific viral mRNAs, whereas reducing in endogenous ZAP enhanced HIV-1 infection [34]. Thus, reduction of each of these mRNA degradation enzymes reduced ZAP's activity and ZAP inhibits HIV-1 by recruiting both the 5' and 3' mRNA degradation machinery to specifically promote the degradation of multiply spliced HIV-1 mRNAs. Tripartite motif 11(TRIM25) also is required for the antiviral activity of ZAP that down-regulation of endogenous TRIM25 abolished ZAP's antiviral activity [35]. ZAP, a type1 interferon (IFN)-inducible gene, plays a critical role in elimination of Sindbis virus (SINV) that ZAP is an RNA-sensing anti-viral effectors molecule which mediates the type-I-IFN-dependent host defense against SINV [36]. Several mammalian viruses encode factors that broadly dampen gene expression by directly targeting mRNA that these factors promote mRNA degradation to globally regulate both host and viral gene expression, in which in some cases, there is a lack of selectively for degradation of host versus viral mRNA [37]. RNA degradation in viral replication and antiviral defense leads to destroy viral RNA and restrict virus [38].

Serine Hydrolyzing And Degrading of Zn^{2+}Ions for Malignant Cell Formation, Tumor Proliferation, And MetAstAsis Autophagy Degradation of Cancer Protein

Autophagy as self-eating is involved in the bulk degradation, in which autophagy is highly conserved homeostatic mechanism for the degradation and recycling of bulk cytoplasm, organelles, and long-lived proteins through the lysosomal machinery. Degradation of the mutant protein by Zn^{2+} ion mediated and induced autophagy lead to cell death in cancer cell line [39,40] and activation of NKG2D ligands in tumor immunity [41].Further, autophagy in tumor immune micro-environment can affect immune responses inside the tumors. The autophagy in tumor cells plays dual roles of immunoglobulin's and immune-related cells in tumor development [42].

Zn^{2+}Mediated Hydrolyzing and Degrading Activity for Malignant Cell Growth, Proliferation, and Metastasis

Lysosomes are membrane-bound organelles containing hydrolyses that function in the degradation of macromolecules of Zn2+ion summation withlysosomal pH by Zn2+ ion solution exposure, and subsequent cellular damage in cancer cells [43].This phenomenon is thought to indicate degradation of extracellular matrix and angiogenesis. New inhibitors of N-acylethanol-amine-hydrolyzing acid amidase have been worthy against bladder cancer [44].Degradation of tumor-associated protein p53 with tumorigenic cell appears to be performed by a nonlysosomal, ATP-dependent proteolytic system that an increased p53 accumulation rate is abnormal feature of transformed tumorigenic cells [45]. Zinc-dependent exopeptidases with a single zinc ion and a pair of zinc ions in the active site, have application in cancer therapy with hydrolyzed and superposed zinc ligand formations of antibody to a tumor-specific antigen [46].Enzyme-mediated hydrolytic activation is important for capecitabine in cancer therapy that plasmin labialized the lysosomes of tumor cells [47].Sodium nitroprusside (SNP) disrupts a critical Zn^{2+}-dependent enzyme activity with metal co-factor of ecto-5-nucleotidase (NT5E) [48] that enzyme activity, membrane-associated enzyme activity, serine hydrolase, invasiveness-associated enzymes, and a secreted serine protease may support the progression of tumors and represent attractive targets for the diagnosis and treatment of cancer [49].In the tumor cells of pancreatic cancer with the most lethal malignancies, anchorage-independent growth as well as pancreatic carcinogenesis is enhanced by elevated activity of the tumor-associated serine hydrolase (retinoblastoma-binding protein 9, RBBP9) that RBBP9-mediated suppression is required that loss of the serine hydrolase activity leads to a reduction in E-cadherin levels and a concomitant decrease in the integrity of tumor

cell-cell junction [50].

The matrix metallo proteinases (MMPs) play roles in breast cancer initiation, invasion, and metastasis, involving in the degradation of the extracellular matrix (ECM)[51]. Zinc inhibits tumor metastasis that Zn^{2+} ions affect the anti-tumor and metastasis blocking and the strong down-regulation effects of Zn^{2+} on plasminogen activator/plasmin system [52].$MgCl^2$ and $ZnCl^2$ promote human umbilical vein endothelial cell migration and invasion and promote epithelial-mesenchymal transition (EMT) through the Wnt/β-catenin pathway [53]. Further studies are essential to observe these cell migrations and invasions.

Cancer Hydrolyzing by Zinc Complexes and Zinc Chelation with Anti-Cancerous High Activity

Metals have unique characteristics that include redox activity, variable coordinated modes, and reactivity towards organic substrates that zinc coordination complexes become attractive probes as potential anticancer agents in which zinc functions as many proteins and enzymes, including transcription factors, cellular signaling proteins, and DNA repair enzymes [54].Zinc compounds have many biological activities, including the ability to induce apoptosis in cancer cells [55]. Zinc oxide nano particles are attributed to vital role in cancer eradiation, that an important advantage of the targeted tumor treatment is lowering the cyto- and genotoxicity of active substance [56]. The new role of MMPs for cancer therapeutics and clinical trials as MMP inhibitors that clioquinol targets NF-kB and lysosome pathways independently, favoring further development of clioquinol as a novel anticancer agent [57]. Zrt-,Irt-like protein(Zip) and zinc transporter (ZnT) or both zinc and metallothioneins(MTs) have important roles for anti-cancer activities of cancer and tumor cells[58]. ZNT, ZIP, and MTs transporters induced hydrolyses of cancer cell may be degraded, subsequent lead to regulate cellular zinc homeostasis and cancer and lead to tumor cell death [15]. Thus, these Zn compounds exert as multipurpose compounds, biological roles in homeostasis, proliferation and roles in immunity and in chronic diseases, such as cancer, brain tumor.

Furthermore, chelation of intracellular Zn^{2+}ions inhibits human neuroblastoma cells by endoplasmic reticulum-associated degradation (ERAD) [59]. Apoptosis-related caspase activation and cellular morphological changes are dependent upon treatment with strong zinc chelators N4Py and BnTPEN, zinc having a full protective effect on the cell [60].Thus, strong zinc-chelating agents may be useful for apoptosis-resistant human cancer Zn^{2+}-mediated hydrolysis of the acetyl groups affords a large, rapid, and zinc-induced fluorescence response that tumorigenic cells are unable to accumulate mobile zinc within their mitochondria [61].This indicate mobile Zn^{2+} ions in mitochondria of cancerous prostate cells. Zn2+ chelator TPEN inducing oxidative stress and reduces tumor growth in a human prostate cancer cell [62].

As described-above, hydrolytic and degradative activities of Zn^{2+} ions for bacterial cell walls, host-viruses, and cancer and tumor cells are widely summarized in Table 1.

Table1. *Hydrolysis and degradation activities of Zn^{2+}ions for bacterial cell walls, host-viruses, and cancer/tumor cells*

Zn^{2+}ions	***Bacterial Cell Walls, Host-Viruses, and Cancer/Tumor Cells***			
	Bacteria Prevention	***Gram-Positive Cell Wall S.Aureus PGN Cell Wall***	***Zn^{2+} ions***	***Gram-Negative Cell Wall E. Coli Outer Membrane, PGN Layer in Periplasmic Space***
Zn^{2+} →	**Zn^{2+}** →	**Zn^{2+}, ROS** ·Teichoic acids are spatial regulators of biosynthesis of PGN cross-linking TP ·Bacteriolysis of PGN cell wall due to inhibition of PGN elongations and PGN autolysin activations. ·ROS productions and the oxidative stress.	**Zn^{2+}** →	**Zn^{2+},ROS** Destruction of outer membrane structure due to degradation of lipoproteins at N- and C-terminals, and bacteriolysis of the inhibition of PGN elongation owing to inactivation of PGN TP synthetic enzyme endopeptidase and enhancement of the activations of PGN auto-lysins of amidaseandcarboxypeptidase.

Zn^{2+}	***Virus Prevention***	***Entry and Uncoating***	***Replication/CapsidProtein/DNA/RNA/mRNA***	***Release and Budding***
	Zn^{2+} ·AZP prevents virus infection ·15mM-$ZnSO_4$ prevent HIV infection	**Zn^{2+}, $\cdot O_2^-$, H_2O_2** ·Zn-metalloprotease inhibits entry and cell-cellfusion ·Zn-binding degradation ·Zn inhibition of virous uncoating	**Zn^{2+},iNOS, NO,$\cdot O_2^-$, H_2O_2** ·AZP**:** inhibitionreplication ·Zn-finger-like motifs**:**nucleic acid damage ·Zinc finger**:**virusDNAdecay ·ROSproductionin viral replicationand organelle ·Oxidative stress in HCV	**Zn^{2+},iNOS, NO** ·A central zinc ion coordinated by histidine**:** inhibits assembly ·Zinc fingers**:** inhibit releaseof non-infectiousviruspar ticles
	Cancer Prevention	***Progression and Malignant cellformation Angiogenesis***	***Proliferation and Invasive growth, Angiogenesis***	***Dissem-Inative Metastasis, Angiogenesis***
Zn^{2+}	**Zn^{2+}** ·Leukotriene A4 hydrolase (LTA4H) withepoxide hydrolase and aminopeptide	**Zn^{2+}, O_2^-,$\cdot$OH, H_2O_2** ·Zn^{2+}inducedautophagy-proteinsdegradation **Zn^{2+}+2(SH)→Zn(Ⅱ)S-S-+2$H^+$$2O_2^-$+2$H^+$ →H_2O_2 + $O_2H_2O_2$+ e^- → HO^-+ $\cdot$OH**	**Zn^{2+}, O_2^-,$\cdot$OH, H_2O_2** ·Zn^{2+}inducedautophagy-proteinsdegradation ·ZnT/ZIPregulate malignanttumor cell ·Anti-angiogenesis	**Zn^{2+}, O_2^-,$\cdot$OH, H_2O_2** ·Zn^{2+}inducedanti-angiogeniceffect throughROS ·MMPs throughZn^{2+}ion inhibittumor metastasis

CONCLUSIONS

Zinc (Ⅱ) ions in intracellular organelle have highly activities for bacteria, viruses, and cancer/tumors. In this mini-review, hydrolysis and degradation functions of Zn2+ ions for bacterial, viral, and cancerous cells were investigated.

For bacteria, bacteriolysis of *S. aureus* PGN cell wall by Zn^{2+} ionsis thought to be due to inhibition of PGN elongation owing to inactivation of PGN synthesis and enhancement of PGN autolysin activities. The other, bacteriolysis and destruction of *E.coli* outer membrane cell wall by Zn^{2+} ions are anticipated to be due to destruction of lipoprotein at N-, C-terminals by degradative enzymes, and to be due to inhibition of PGN elongation depending enhancement of PGN autolysin activations.

For viruses, virus-hydrolyzing activity is chiefly viral protein and viral RNA degradations. Viral protein hydrolytic activity is by loss of function by exposure to Zn^{2+} ions which is mediated by an ubiquity-associated proteolytic process in the airway epithelium, increasing proteasome activity of ZnMP selectively and markedly down-regulated non-structural 5A (NS5A) protein levels by increasing degradation of NS5A protein that ZnMP may hold promise as a novel agent to treat HCV infection. Zinc binding inhibits formation of the caspase-8 dimer, the activated form of the enzyme that zinc-mediated inhibition is due to regulation of apoptosis by direct inactivation of caspases. Viral RNA degradation causes that zinc-finger antiviral protein (ZAP) was originally identified as a host factor that inhibits the replication of many viruses by preventing the accumulation of viral mRNAs in the cytoplasm. Thus, ZAP also inhibits HIV-1 infection by promoting the degradation of specific viral mRNAs, whereas reducing of endogenous ZAP enhanced HIV-1 infection.

For cancer/tumor cells, degradation of tumor-associated protein p53 with tumorigenic cell appear to be performed by a non lysosomal, Enzyme-mediated hydrolytic activation is important for capecitabine in cancer therapy by the increased release of lysosomal enzymes. The matrix metalloproteinase's (MMPs) are involved in the degradation of the extracellular matrix (ECM) for breast cancer initiation, invasion, and metastasis. Zinc inhibits tumor metastasis that Zn^{2+} ions affect the anti-tumor and metastasis blocking and the strong down-regulation effects of Zn^{2+} on plasminogen activator/plasmin system. Chelation of intracellular Zn^{2+} ions inhibits human neuroblastoma cells by endoplasmic reticulum-associated degradation (ERAD). Apoptosis-related caspase activation

and cellular morphological changes are dependent upon treatment with strong zinc chelators. Zinc has a full protective effect on the cell treated with zinc chelators. Thus, strong zinc-chelating agents may be useful for apoptosis-resistant human cancer. As abridgment; Zn^{2+} ions-associated hydrolytic and degradative functions for bacteria are due to bacteriolyses and destructions of bacterial cell walls by the inhibitions of PGN elongation owing to activated PGN autolysins. Hydrolyzing viruses are viral protein hydrolysis, viral mRNA degradation, and bacteriophage viral-endolysins.Furthermore,Zn^{2+}-mediated hydro-lyzing for cancer cell is by proteasome and auto phage that lead to cancer and tumor cell death, Zn^{2+} inducedZIP1 that inhibits malignant tumor and proliferation, and zinc complex and zinc chelation that have important roles for anticancer/tumor apoptotic death. Thus, these hydrolysis and degradation methods are nownotewor-thy under the hydrolase enzymic development for bactericidal, virucidal , and cancerous cell death.

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