REVIEW ARTICLE

Zinc-induced Immune Anti-infective Activities of Bacteriolysis by Zn^{2+}-binding Peptidoglycan Autolysins and Virucide by Zinc-finger Antiviral Proteins against Bacterial and Viral Infections

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ABSTRACT

Immune-enhancing zinc induced anti-infective activities of bacteriolysis by Zn^{2+} ions-binding peptidoglycan (PGN) autolysins and virucide by zinc-finger (ZNF) antiviral proteins, respectively, are discussed against bacterial and viral infections. Zn^{2+} ions-induced PGN autolysin AmiA for Staphylococcus aureus amidase is acted on PGN binding and cleavage that AmiA distinguishes PGN mostly by the peptide. The LytB PGN hydrolase responsible for physical separation of daughter cells cleaves the GlcNAc-β-(1,4)-MurNAc glycosidic bond of PGN building units. In these autolysins, zinc-dependent PGN autolysin of amidases may be enhanced and induced antibacterial activities. Lytic amidase autolysin LytA associates with the cell wall through its zinc-binding motif. Enveloped viruses enter cells and initiate disease-causing cycles of replication that in all cases virus-cell fusion is executed by one or more viral surface glycoproteins denoted as the fusion protein, in which the structure and mechanisms on viral membrane fusion protein are important problems. The novel Epstein-Barr Virus (EBV)-induced ZNF gene controls entry, exit, and spread from cell cycling in activated lymphocytes. The designed ZNF protein is prepared consisting human immunodeficiency virus type 1 (HIV-1) type integrase fused to the synthetic ZNF E2C that the integrase-E2C fusion proteins offer an efficient approach and a versatile framework for directing the integration of retroviral DNA into a predetermined DNA site. ZNF Tsi1-interacting protein 1 controls cucumber mosaic virus RNA replication. The ZNF ZCCHC3 binds RNA and facilitates viral RNA that ZCCHC3 is a coreceptor for the retinoic acid-inducible gene-1 and antigen MDA5. ZNF antiviral protein (ZAP) specifically inhibits the replication of certain viruses and promotes viral RNA degradation. ZAPs inhibit HIV-1, influenza virus, and HIV cell-to-cell spread in viral infections. The short form of ZAPs inhibited influenza A virus PB2 protein expression by reducing the encoding viral mRNA levels, in which these ZAPs findings provide insight into how antiviral components are regulated on virus infection to inhibit virus spread. A novel zinc-binding domain (ZBD) is essential for the formation of the functional Junin virus envelope glycoprotein complex. Thus, anti-viral activities of ZAP, ZBD, and membrane fusion protein are recognized by which highly diverse fusion proteins have converged on the same overall strategy to mediate a common pathway of membrane fusion, causing to lead the enhancement of the anti-viral activity.

Key words: Autolysin amidase, bacterial peptidoglycan autolysin, replication, spread, viral entry, zinc-finger antiviral protein, and zinc-binding domain

INTRODUCTION

Zinc plays an important role in human immunity. The importance of zinc in normal immune function has led to increased interest in nutrition and immunity, in which zinc deficiency produces reversible immune dysfunction such as T-cell mediated immunity that experimental high-dose zinc supplementation can produce similar immune dysfunction against viral infection.[1] Immune dysfunction of zinc deficiency against infections is led to a worse outcome in the

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response toward bacterial infection and sepsis inflammation, mainly elevating inflammatory response as well as damage to host tissue.[2] Zinc is an essential trace element, affecting the development and integrity of the immune system that regarding the immunological status of zinc deficiency could lead to public health interventions with nutritional doses of zinc supplements to prevent alteration of the immune system and improve resistance to infections.[3] Zinc is the second most abundant trace metal with human body 2–3 g, 90% in muscle and bone, and 10% other organs include prostate, liver, the gastrointestinal tract, kidney, skin, lung brain, heart, and pancreas in humans that cellular zinc underlies an efficient homeostatic control that avoids accumulation of zinc in excess, in which many organs are affected by zinc deficiency, especially the immune system that is markedly susceptible to changes of zinc levels.

Zinc-altered suitable zinc concentrations are recognized that in a concentration of 100 µmol/L, zinc suppresses natural killer cell killing and T-cell function and in 500 µmol/L, zinc evokes a direct chemotactic activation of neutrophil granulocytes.[4] For the treatment of zinc deficiency, zinc replacement therapy at a daily zinc dose of about 30 mg is considered to be relatively safe.[5] The important roles of zinc for chronic diseases have been become achieved in pulmonary diseases such as pulmonary tuberculosis,[6] chronic obstructive pulmonary diseases,[7-9] pulmonary sepsis,[10] and for respiratory infections such as young children zinc supplement,[11] zinc-mediated antiviral activity on respiratory syncytial virus,[12] zinc-binding system ZevAB against *haemophilus influenza* during lung infection.[13] The role matrix metalloproteinases (MMPs) in progression of chronic lung inflammatory diseases have the effect of MMPs inhibitor on chronic lung disease.[14] The other, zinc deficiency in chronic kidney disease patients may be due to fecal excretion or decrease in its absorption that zinc concentrations were lower in hemodialysis (HD) patients compared to controls and Zn concentration 69.16 µg/dL of blood in HD patients, however, revealed no correlation among serum Zn concentration and anemia, serum parathyroid hormone concentration or pruritus severity in HD patients.[15]

The other, the role of zinc in cell death has apoptosis that the influence of zinc on apoptosis is tissue/cell type, zinc concentration, and expression of zinc transporters, and zinc-binding proteins. Host zinc homeostasis changes in response to bacterial infections, including the production of metal sequestering proteins and bombardment of bacteria with toxic level of zinc at host-pathogen interface.[16] Zinc influences apoptosis by acting on several molecular regulators of programmed cell death and zinc deficiency caused by malnutrition and foods with low bioavailability, aging, and certain diseases, and deregulated homeostasis is a far more common risk to human health without intoxication.[3] Apoptosis is defined as cell death activated by an internally controlled suicide program that bacteria are able to trigger apoptosis, including the secretion of compounds such as protein synthesis inhibitions, pore forming proteins, molecules responsible for the activation of the endogenous death in the infected cell, and super antigens.[17] Regulation of apoptosis is essential for normal embryonic development and for homeostasis in adult tissue.

Zinc has a rather low toxicity and influences apoptosis by acting on several molecular regulators of programmed cell death which can inhibit apoptosis thereby either prolonging the survival of infected cells such that the production of progeny virus is maximized or facilitating the establishment of virus persistence. The influence of zinc on apoptosis is very complex that variables in this complex network are tissue and cell type, zinc concentration, expression of zinc transporters and zinc-binding proteins, oxidative or nitrosative stress, and the improvement of molecular opposing functions.

Zinc ion killing occurs chiefly by bacteriolyses of bacterial cell walls due to activated peptidoglycan (PGN) autolysins such as amidases, endopeptidases (Eps), and carboxypeptidase against bacteria.[18] PGN autolysins induced antibacterial vaccine activity may be enhanced by activation of zinc dependent PGN autolysins. PGN autolysins are bacterial PGN degrading enzymes that these muropeptides can be produced or modified by the activity of bacterial glycolytic and peptidolytic enzymes referred to as PGN hydrolases and autolysins which specific bacterial pathogens use PGN degradation to subvert host innate immunity.[19] Bacteria have to avoid recognition by the host immune system to establish a successful infection which bacterial autolysins enable the bacteriolyses of bacterial cell walls trim cell surface PGN to prevent detection by bacterial innate immune system.[20]

The other, viruses are obligate intracellular parasites that cause infection by invading cells of the body. Their life cycle comprises a short extracellular period and a longer intracellular period during which they undergo replication. The immune system has non-specific and specific mechanism that attack the virus in both phases of its life cycle which specific antibodies protect against viral infections and play an important role in antiviral immunity, mainly during the early stage of the infection.[21]

Zinc homeostasis during acute phase response is the temporal transfer of serum zinc to the tissues, causing transient serum hypozincemia, which is rebalanced during resolution of the inflammatory response that intracellularly increased zinc can intoxicate engulfed pathogens and acts cytoprotective by promotion of neutralizing reactive oxygen species (ROS) and reactive nitrogen species (RNS).[22]

In this review, first, antibacterial activities of bacteriolysis by Zn^{2+} ions induced autolytic PGN activation are debated

against *Staphylococcus aureus* cell wall as Gram-positive bacterium and *Escherichia coli* cell wall as Gram-negative bacterium. Second, the zinc-mediated antiviral immunity, zinc-finger (ZNF) antiviral protein (ZAP) and zinc-binding domain (ZBD), are discussed. Finally, the bacterial and the virucidal mechanisms, respectively, on the zinc-induced activated PGN autolysins and on the ZAP, ZBD become clarified.

ZINC IMMUNITY IN INFECTIONS

The innate immune system represents the defense first line against a pathogen before the adaptive system can develop the appropriate response. Many organs are affected by zinc deficiency, especially the immune system that is markedly susceptible to changes of zinc levels which the immune response involves in the regulation of the innate and adaptive immunity, and this zinc homeostasis is critical for sustaining proper immune function.[22] Thus, inflammation is a natural process required to protect the host from tissue damage and infections, which leads to the resolution of the inflammatory response and the restoration of homeostasis. Despite zinc deficiency can be treated by proper zinc intake, suboptimal zinc status cannot simply diagnosed by reason of the lack of clinical signs and reliable biochemical indicators of zinc status. Zinc homeostasis is primarily controlled thogh the expression and action of 14 zinc transporters that decreasing cytoplasmic zinc can describe export though zinc transporters, but also the transport of zinc into one of those organelles.[23] While, high zinc concentration in zinc binding can change the important characteristics for substrate binding with and without the binding activations.[23] zinc homeostasis during acute phase response is the temporal transfer of serum zinc to the tissues, causing transient serum hypozincemia, which is rebalanced during resolution of the inflammatory response that intracellularly increased zinc can intoxicate engulfed pathogens and acts cytoprotective by the promotion of neutralizing ROS and RNS.[23] Bacteria have to avoid recognition by the host immune system to establish a successful infection in which bacterial autolysins enable the bacteriolysis of bacterial cell walls to trim cell surface PGN to prevent detection by the bacterial innate immune system.[20]

ZN^{2+} IONS-INDUCED PGN AUTOLYSIN ACTIVATION PROMOTES ANTIBACTERIAL ACTIVITY

Molecular structures of *S. aureus* and *E. coli* cell walls and action sites of PGN autolysins

Bacterial PGN structure of both Gram-positive and Gram-negative bacteria comprises repeating disaccharide backbones of N-acetylglucosamine and β-(1-4)-N-acetylmuramic acid (NAM) that are crosslinked by peptide stem chains attached to the NAM residues.[24] The action sites of bacterial autolysins are comprised that for *S. aureus* PGN layer cell wall, there are N-acetylmuramidase-L-alanine amidase and DD-endopeptidase. The other, for *E. coli* cell wall, there is endopeptidase of degrading enzyme at lipoprotein of C- and N-terminals, and amidase, peptidase, and carboxypeptidase at thin PGN layer in periplasmic space.[25] The bacterial cell walls are a strong flexible meshwork of PGN that gives a bacterium structural integrity, in which to accommodate a growing cell, the walls are remodeled by PGN synthesis and PGN autolysin. PGN is the main constituent of bacterial cell walls and must be continuously synthesized and degraded to maintain the integrity and viability of the cells that bacterial cell wall hydrolases of amidase, glycosidase, and peptidase display a modular architecture combining multiple and different catalytic domains, including some lytic transglycosylases as well as cell wall binding domains.[26] In these autolysins, zinc-dependent PGN autolysin of amidases may be enhanced and induced antibacterial vaccine activities.

Zn^{2+} ions-induced activated PGN autolysins promote antibacterial activity against Gram-positive bacteria

S. aureus amidase AmiA is acted on PGN binding and cleavage that AmiA distinguishes PGN mostly by the peptide, and cleavage is facilitated by a zinc-activated water molecule, to develop new therapeutics against methicillin-resistant *S. aureus*.[27]

The autolytic activity of the recombinant amidase of the autolysin/adhesin of *Staphylococcus saprophyticus* (Aas) is inhibited and is necessary for the C-terminal GW repeats, not the N-terminal repeats.[28] Autolysin-mediated lysis-induced bacterial cell death can contribute to bactericidal vaccine activities. Lytic amidase autolysin LytA which is released by bacterial lysis, associates with the cell wall through its zinc-binding motif that the amidase domain comprises a complex substrate-binding crevice and needs to interact with a large motif epitope of PGN for catalysis.[29] Suicidal amidase autolysin LytA having both autolysis and capsule shedding depends on the cell wall hydrolytic activity of LytA that capsule shedding drastically increases invasion of epithelial cells and is the main pathway by which pneumococci reduce surface-bound capsule during early acute lung infection of mice.[30] In the biofilms increase as zinc concentrations increase and biofilm formation effect as a negative regulator of LytA dependent autolysis, zinc availability contributes to the ability of pneumococci to form aggregates and subsequently, biofilms.[31]

Atl is the major autolysin in *S. aureus* that the bifunctional major autolysin plays a key role in staphylococcal cell separation which processing of Atl yield catalytically active amidase and glucosaminidase domains.[32] The biochemical

and structural staphylococcal Atl have successful cloning, high-level over-expression, and purification Atl proteins.[33] Major Atl autolysin also has an essential role in the early events of the fibronectin-binding proteins-dependent *S. aureus* biofilm phenotype.[34] For the contribution of autolysins of PGN hydrolases to bacterial killing, there are N-acetylglucosaminidase (AtlA) and two N-acetyl-muraminases (AtlB and AtlC).[35] AtlA is the major PGN hydrolases of *Enterococcus faecalis* involved in cell division and cellular autolysis and the zinc metalloprotease, gelatinase (GelE) of their interplay proposed to regulate AtlA function, which N-terminal cleavage was required for efficient AtlA-mediated cell division, and AtlA septum localization and subsequent cell separation can be modulated by a single GelE-mediated N-terminal cleavage event.[36]

Zn^{2+} ions-induced degrading enzyme of outer membrane lipoprotein and PGN autolysins promote antibacterial activity against Gram-negative bacteria

Amidase gene (amiB) catalyzes the degradation of PGN in bacteria that the amiB gene was composed of 1722 nucleotides and 573 amino acid which is involved in the separation of daughter cells after cell division and inactivation of the amiB gene, resulting in a marked increase of sensitivity to oxidative stress and organic acids.[37] Zinc-dependent Eps are

Table 1: Zinc immune antibacterial activity against Gram-positive thick PGN envelope cell wall and Gram-negative lipoprotein and thin PGN layer cell wall

Zn^{2+} ions		Gram-positive PGN layer cell wall
		Zn^{2+} ions-induced PGN autolysins
Zn^{2+}		→Zn^{2+}, O_2−, H_2O_2, • OH, • NO, ONOO−
		Zn^{2+} ions-induced activated PGN autolysins
		• *S. aureus* amidase AmiA • Recombinant amidase of the autolysin/adhesin of *Staphylococcus saprophyticus* • Lytic amidase LytA for *Streptococcus pneumoniae* • Endopeptidase LytF for *Bacillus subtilis* • AtlA autolysin for GelE against *Enterococcus faecalis* • Fusion protein autolysin, MIBRs against *Streptococcus pneumoniae* • Carboxypeptidase B1 against *Anopheles stephensi* and for malaria as transmission-blocking • Metallocarboxypeptidase M32 against *Trypanosoma brucei or Trypanosoma cruzi* • PBP2a and autolysin mixture against methicillin-resistant *S. aureus* • ROS and RNS generations (Zn homeostasis)
Zn^{2+} ions	Gram-negative cell wall	
	Outer membrane lipoprotein at C- and N-terminals	Periplasmic space thin PGN layer
Zn^{2+}	→Zn^{2+}, O_2^-, H_2O_2	→Zn^{2+}, O_2^-, H_2O_2, OH^-, • OH
	• Amidase gene amiB/LysM • Endopeptidase regulation of ShyA and ShyB • Outer membrane receptor against *Neisseria meningitidis* • ZnuB against *P. aeruginosa* • Preventive vaccine by recombinant flagella *against P. aeruginosa* • ROS and RNS	• Carboxypeptidase by transmission-blocking vaccines • Metallocarboxypeptidases used • Zn-dependent carboxypeptidase could be appreciable anti-bacterial activities • D-glutamate auxotrophy against *P. aeruginosa* PA14 • ORT in infectious diarrhea • ZnuA against *P. aeruginosa* • Recombinant flagella and pili against *P. aeruginosa*, ROS and RNS

Zn: Zinc, PGN: Peptidoglycan, Zn^{2+}: Zinc ions, *S. aureus*: *Staphylococcus aureus*, MIBRs: Most probable immunoprotective B-cell epitope regions, GelE: Gelatinase, PBP2a: Penicillin-binding protein 2a, ROS: Reactive oxygen species, RNS: Reactive nitrogen species, *P. aeruginosa: Pseudomonas aeruginosa*

predicted to hydrolyze PGN to facilitate cell growth that zinc availability affects the strong activity of cell wall hydrolases, and zur-regulated Eps are present in divergent Gram-negative bacteria.[38] Zinc-regulated peptidase maintains cell wall integrity during immune-mediated nutrient sequestration against *Acinetobacter baumannii*.[39]

Carboxypeptidases are exopeptidases that remove a single amino acid residue from the C terminus of proteins or xopeptidases that remove a single amino acid residue from the C terminus of proteins or peptides that the carboxypeptidase B1 of and its evaluation have been high molecular characterization for transmission-blocking vaccines against malaria eradication.[40] Metallo-carboxypeptidases of the M32 family of peptidases exhibit significant hydrolytic activity and different hydrolysis patterns against *Trypanosoma brucei* or *Trypanosoma cruzi*.[41] Thus, zinc-dependent carboxypeptidase autolysin could adapt to be appreciable the antibacterial activities.

Table 1 represents zinc-homeostatic immune antibacterial activities of bacteriolysis by Zn^{2+} ions-induced activated PGN autolysins against Gram-positive thick PGN layer and Gram-negative outer membrane lipoprotein and thin PGN layer cell walls.

ZINC-INDUCED ANTIVIRAL IMMUNITY AND ANTIVIRAL ACTIVITIES OF ZNF PROTEIN, ZAP, ZBD, AND VIRUS SPREADING INHIBITION

Zinc-induced antiviral immunity

Zinc is an essential trace element that is crucial for growth, development, and the maintenance of immune function which zinc status is a critical factor that can influence antiviral immunity, particularly as zinc-deficient populations are often most at risk of acquiring viral infections such as human immunodeficiency virus type 1 (HIV) and hepatitis C virus.[42] Common features possess that enveloped viruses enter cells by membrane-fusion protein on the surface, fusion glycoprotein on metastable prefusion and interactions with neutralizing antibodies. Implications for immunogen design of next-generation vaccines have been shown from the results that stable immunogens presenting the same anti genetic sites as the labile wild-type proteins efficiently elicit potently neutralizing antibodies.[43]

ZNFs proteins, ZAPs, ZBD, and virus spreading inhibition

The novel Epstein–Barr virus (EBV)-induced ZNF gene, ZNF^{EB}, including its intronless locus and human protein variants, control entry and exit from cell cycling in activated lymphocytes.[44] The designed polydactyl ZNF protein is prepared consisting HIV-1 type integrase fused to the synthetic ZNF protein E2C that the integrase-E2C fusion proteins offer an efficient approach and a versatile framework for directing the integration of retroviral DNA into a predetermined DNA site.[45] Artificial ZNF fusions were targeted to the high-affinity Sp1-binding site, and by being fused with TatdMt and POZ domain, they strongly block both Sp1-cyclin T1-dependent transcription and Tat-dependent transcription of HIV-1.[46] ZNF Tsi1-interacting protein 1(ZNF Tsip1) strongly interacted with cucumber mosaic virus(CMV)2a protein, controls CMV RNA replication.[47] The ZFN ZNF CCHC ZCCHC3 binds RNA and facilitates viral RNA that ZCCHC3 is a coreceptor for the retinoic acid-inducible gene-1 (RIG-1) and antigen MDA5 which is critical for RIG-1 like receptor (RLR)-mediated innate immune response to RNA virus.[48] ZAP specifically inhibits the replication of certain viruses and promotes viral RNA degradation.[49] ZAP inhibits HIV-1 infection by promoting the degradation of specific viral mRNAs[50] and ZAP also inhibits influenza A virus (IAV) protein that the short form of ZAPs inhibited IAV PB2 protein expression by reducing the encoding viral mRNA levels and repressing its translation.[51] ZAP-70 kinase regulates HIV cell-to-cell spread.[52] ZAP's stress granule localization due to cytoplasmic structure is correlated with antiviral activities that virus replication processes trigger

Table 2: Zinc immune antiviral activity of zinc-finger antiviral proteins for virus entry, replication, and spreading

Zn^{2+} ions	Anti-viral activity of Zn^{2+} in entry, replication, spread	
	Adsorption/entry	Replication, DNA/RNA, spread
Zn^{2+}	$\rightarrow Zn^{2+}$, • O_2^-, H_2O_2	$\rightarrow Zn^{2+}$, • O_2^-, H_2O_2, NO
	• EBV-induced Zn finger gene • ZNF^{EB} controls entry and exit • ZBD prevent viral entry and GPC inhibit activate membrane fusion • Zn-metalloprotease inhibits entry and cell-cell fusion	• ZAP inhibits replication of MLV • ZAP-mediated RNA degradation • Zn finger: Virus decay • Zn finger protein E2C; viral DNA specific sites • Zn finger protein Tsip1; cucumber mosaic virus RNA replication • Artificial Zn finger fusion; HIV-1 transcriptions • ZAPs and ZAP-70 kinase inhibit virus spread

Zn^{2+}: Zinc ions, Zinc: Zn, EBV: Epstein–Barr virus, ZBD: Zinc-binding domain, GPC: Glycoprotein complex, ZAP: Zinc-finger antiviral protein, MLV: Murine leukemia virus, Tsip1: Tsi1:interacting protein 1, HIV-1: Human immunodeficiency virus type 1

stress granule formation and ZAP recruitment, in which these ZAPs findings provide insight into how antiviral components are regulated upon virus infection to inhibit virus spread.[53]

A novel ZBD is essential for formation of the functional Junin virus envelope glycoprotein complex (GPC) that the envelope glycoprotein of the Junin arenavirus mediates entry into target cells through a pH-dependent membrane fusion mechanism, in which this unusual motif may act to retain a cleaved 58-amino-acid stable signal peptide (SSP) for its role in modulating membrane fusion activity.[54] Entry of the virus into the host cell is mediated by the viral envelope glycoprotein, GPC that SSP was retained in GPC through interaction with a ZBD in the cytoplasmic tail of transmembrane fusion of G2 subunits that Junin virus ZBD displays a novel fold containing two Zn^{2+}, in which the structural basis for retention of the unique SSP submit suggests a mechanism whereby SSP is positioned in the GPC complex to modulate pH-dependent membrane fusion.[55]

Thus, zinc-homeostatic immune antiviral activity of ZAPs for virus entry, replication, and spreading is represented in Table 2.

CONCLUSIONS

Zinc-induced immune anti-infective activities of bacteriolysis by Zn^{2+} ions-induced activated PGN autolysins and virucides by ZAPs are, respectively, discussed, and the bacteriolytic and the virucidal mechanisms have been partially clarified.

Bacterial PGN autolysin AmiA for *S. aureus* amidase is acted on PGN binding and cleavage that AmiA distinguishes PGN mostly by the peptide and cleavage is facilitated by a zinc-activated molecule. The autolytic activity of the recombinant amidase of the Aas is inhibited and is necessary for the C-terminal GW repeats, not the N-terminal repeats. Lytic amidase autolysin LytA associated with the cell wall through its zinc-binding motif. Human PGN recognition proteins are a novel class of recognition and effector molecules with broad Zn^{2+}-dependent bactericidal activity against both Gram-positive and Gram-negative bacteria. Enterotoxigenic *E. coli* is the most common bacterial cause of children's diarrhea, in which antigen and antitoxin antibodies that neutralized both toxins that are associated with all cases of ETE diarrhea. The autolysin mediated bacteriolysis-induced bacterial cell death can contribute to the bactericidal activities. Bacterial autolysins enable the bacteriolysis of bacterial cell walls to trim cell surface PGN to prevent detection by the bacterial innate immune system. Autolysin mediated bacteriolysis- and zinc-dependent lysis-induced bacterial cell death can contribute to the bactericidal vaccine activities, where PGN autolysins interact with biomolecules causing cell apoptosis leading to cell death. In these autolysins, zinc-dependent PGN autolysin of amidases may be enhanced and induced antibacterial activities.

On the other hand, enveloped viruses enter cells and initiate disease-causing cycles of replication that in all cases virus-cell fusion is executed by one or more viral surface glycoproteins denoted as the fusion protein, in which the structure and mechanisms on viral membrane fusion protein are important problems. The novel EBV-induced ZNF gene, ZNF^{EB}, including its intronless locus and human protein variants, controls entry, and exit from cell cycling in activated lymphocytes. The designed polydactyl ZNF protein is prepared consisting HIV-1 type integrase fused to the synthetic ZNF protein E2C that the integrase-E2C fusion proteins offer an efficient approach and a versatile framework for directing the integration of retroviral DNA into a predetermined DNA site. ZNF Tsip1 controls CMV RNA replication. The ZNF ZCCHC3 binds RNA and facilitates viral RNA that ZCCHC3 is a coreceptor for the RIG-1 and MDA5 which is critical for RLR-mediated innate immune response to RNA virus. ZAP specifically inhibits the replication of certain viruses, and furthermore, an understanding becomes necessary for ZAP-mediated viral RNA degradation. ZAP inhibits HIV-1 infection by promoting the degradation of specific viral mRNAs and ZAP also inhibits IAV protein that the short form of ZAPS inhibited IAV PB2 protein expression by reducing the encoding viral mRNA levels and repressing its translation. ZAP-70 kinase regulates HIV cell-to-cell spread. These ZAPs findings provide insight into how antiviral components are regulated on virus infection to inhibit virus spread. ZAPs, ZBD, and membrane fusion protein specifically inhibit the entry and the replication of many viruses. Thus, the membrane fusion reaction, membrane interaction, conformational changes of specialized virus envelope proteins, and refolding reactions of specific fusion proteins an essential steps entry, replication, and spread of enveloped virus life cycle have been worthy of remark in fascination that these diverse viral fusion protein could be used in next-generation for therapeutic intervention in arenaviral disease.

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