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Zinc Immune Anti-Infectious Activities of Bacteriolysis by Zn^{2+}- induced Bacterial PGN Autolysins and ZAP's Viral Destruction by Cell Surface Receptors

Dr. Sci Tsuneo Ishida*

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

Abstract

Bacteriolytic and virucidal anti-infectious activities by bacterial Zn^{2+}-induced PGN autolysins and ZAP's viral destruction of cell surface receptors are discussed and the molecular mechanisms are clarified. Bacteriolyses of Gram-positive cell wall by Zn^{2+} ions-induced activated PGN autolysins of amidases and endopeptidase promote the anti-bacterial activities, and the other, destruction of Gram-negative cell wall by Zn^{2+} ions-induced degrading enzyme of outer membrane lipoprotein and activated PGN autolysins of amidases, endopeptidase, and carboxy-peptides enhance the anti-bacterial activities. Human PGRPs are novel class of recognition and effector molecules with broad Zn^{2+}-dependent bactericidal activity against both Gram-positive and Gram-negative bacteria.

Hence, the zinc-dependent PGN autolysin of amidases is mainly enhanced to the anti-bacterial activities against both Gram-positive and Gram-negative bacteria. Thus, autolysin-mediated bacteriolysis induced bacterial cell death can contribute to the bactericidal activities. Further, autolysin-mediated lysis-induced bacterial cell death may make contribution to the bacteriolytic vaccine activities. ZAP is a host factor that specifically inhibits the replication of certain viruses that on the surfaces of the virion particles are the receptor-binding protein HA which mediates virus entry, and the glycoside hydrolase enzyme NA which is important for mature- virion release. These results have led to NA substrate specificity and different approaches, viral NA inhibitor, relationship with HA, and the receptor binding activities and antibody level of this enzyme. The HA is the most abundant surface glycoprotein of the virus that has the ability to attach the host cell, causing cellular fusion and viral entry, and NA also plays crucial roles in the viral infection with HA-mediated membrane fusion by binding to SA receptors. Infection with influenza viruses usually leads to respiratory involvement and can result in pneumonia and secondary bacterial infections, consisting of point mutations in the HA and NA genes as a result of an error-prone viral polymerase. Thus, newer antiviral agents could be produced by inhibiting the influenza virus NA and HA. The influenza A virus HA/NA receptor balance governs dynamic and motile interaction that is expected to be crucial for penetration of the mucus layer and subsequent infection of cells by IAV but likely also by other enveloped viruses carrying a receptor-destroying enzyme in addition to a receptor-binding protein. ZBTB 25 suppressed interferon production, further enhancing viral replication that ZBTB25-associated functions required an intact zinc finger domain and posttranslational SUMO-1 modification of ZBTB25. Thus, IAV usrups ZBTB25 for IAV RNA synthesis and serves as a novel and potential therapeutic antiviral target

Keywords

Bacteriolysis; PGN Autolysin; Other Membrane Lipoprotein; ZAP; NA and HA; HIV; IAV; Viral Entry; Replication; Spread; Virion Release

Abbreviations

ADP: Adenosine Diphosphate; **Aas:** Autolysin/adhesin of *Staphylococcus Saprophyticus;* **BTB:** Bromothymol Blue; **CMV:** Cucumber Mosaic Virus; **CKD:** Chronic Kidney Disease; ***E. coli:*** *Escherichia coli;* ***Eps:*** *Endopeptidase;* **FnBPs:** Fibronectin- Binding Proteins; **GAS:** Group A *Streptococcus;* **GelE:** Gelatinase; **IAV**: Influenza A Virus; **HA:** Hemagglutin; **HCV:** Hepatitis C Virus; **HD:** Hemodialysis; HA: Hemagglutinin; **HE:** Hemagglutinin Esterase; **HEF:** Hemagglutinin-Esterase-Fusion; **HIV-1:** Human Immunodeficiency Virus type 1; **IAVs:** Influenza A Viruses; **IBVs:** Influenza B Viruses; **IFITMs:** Interferon Induced Transmembrane Proteins; **MCPs:** Metallo-Carboxypeptidases; **NA:** Neuramidase; **NAG:** N-Acetyl Glucosamine; **NAM:** N-Acetylmuramic acid; **NA:** Neuraminidase; **OAS 3:** Oligodenylate Synthetases 3; **PARP: Poly(ADP-ribose) Polymerase; PB2:** Polymerase Basic Protein 2; **PGN:** Peptidoglycan; **PGRPs:** Peptidoglycan Recognition Proteins; **RLR:** RIG-1 Like Receptor; **ROS:** Reactive Oxygen Species; **RNS:** Reactive Nitrogen Species; ***S. aureus:*** *Staphylococcus aureus;* **SA:** Sialic Acid; **SARS:** Severe Acute Respiratory Syndrome; **SUMO-1:** Small Ubiquitin-like Modified 1; **TBVs:** Transmission-Blocking Vaccines; **Tsip1:** Tsi1-Interacting Protein1; **ZAP:**

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***Corresponding author:**

Dr. Sci Tsuneo Ishida
2-3-6, Saido, Midori-Ku, Saitama-Shi, Saitama-Ken, 〒336-0907 Japan.

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Zinc- finger Antiviral Protein; **ZBTB25:** Zinc finger and BTB; **ZNF:** Zinc-finger Proteins; **ZnO-NPs:** Zinc Oxide Nanoparticles

Introduction

Zinc is necessary for the normal function of the immune system. The innate immune system may use zinc as an antimicrobial agent and zinc efflux is an important contributor to group A *Streptococcus* pathogenesis [1]. Zinc is known to be essential for growth and development of all organisms in the human body, especially the immune system depending on the zinc concentration that the human body contains 2-4 g of zinc, but in the plasma, zinc only occurs in a concentration of 12-16 µmol/L [2]. In a concentration of 500 mol/L, zinc suppresses natural killer cell killing and T-cell functions whereas monocytes are activated directly, and in a concentration of 500 µmol/L, zinc evokes a direct chemostatic activation of neutrophil granulocytes [2].

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 [3]. Host zinc homeostasis changes in response to bacterial infections, including production of metal sequestering proteins and bombardment of bacteria with toxic level of zinc at host-pathogen interface [4].

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 endogeneous death in the infected cell, and super antigens [5]. 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.

Zinc deficiency in Chronic Kidney Disease (CKD) 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 [6]. Further, zinc role for patients with severe tinnitus in rhinology & otology may have physical and psychological complaints and their tinnitus can cause deterioration in their quality of life that oral zinc supplementation may be effective in the management of tinnitus, since zinc has a role in cochlear physiology and in the synapses of the auditory system, there is a plausible mechanism of action for this treatment [7]. Zinc serum level in patients with nasal polyposis has been evaluated that the mean of serum zinc level has been 80.94~22.39 mg/dL in patient's wit nasal polyps [8]. In addition, new antiviral proteins that may one day be exploited for drug development have been continued to search, in which these zinc-mediated host cell-infectious protein interactions may be caused by zinc finger antiviral protein due to zinc-immune viral inhibition [9].

In this review, bacteriolytic and virucidal anti-infectious activities by Zn^{2+} ions-induced bacterial peptidoglycan autolysin activation and zinc-finger anti-viral destruction of cell surface receptors are discussed and the molecular mechanisms are clarified.

Zinc and Immune Infectious Function

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 [10]. 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 sighns and reliable biochemical indicators of zinc status. High zinc concentration is that zinc binding to proteins can activate or inactivate their activity, or change characteristics important for substrate binding, whiles, zinc homeostasis is primarily controlled via the expression and action of 14 zinc tranporters that decreasing cytoplasmic zinc can describe export via ZnTs, but also the transport of zinc into one of those organelles [11]. 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 neutrali- zing reactive oxygen species (ROS) and nitrogen species (RNS) [11]. Bacteria have to avoid recognition by the host immune system in order to establish a successful infection which bacterial autolysins enable the bacteriolyses of bacterial cell walls trim cell surface peptidoglycan (PGN) to prevent detection by bacterial innate immune system [12].

Bacterial PGN Autolysins and Action Sites of Autolysins

Bacterial PGN structure of both Gram-positive and Gram-negative bacteria comprises repeating disaccharide backbones of N- Acetylglucosamine (NAG) and β-(1-4)-N-Acetylmuramic Acid (NAM) that are cross linked by peptide stem chains attached to the NAM residues [13]. The PGN growth occurs by balance between PGN synthesis and PGN autolysin. Zn^{2+} ions-induced activated autolysins due to the imbalance in PGN synthesis and autolysin promote the destruction of PGN structutre in bacterial cell walls.

The action sites of bacterial autolysins are comprised that for *Staphylococcus aureus* (*S. aureus)* PGN layer cell wall, there are N-acetylmuramidase-L-alanine amidase and $_{DD}$-endopeptidase. The other, for *Escherichia coli* (*E. coli)* cell wall**,** there are endopeptidase of degrading enzyme at lipoprotein of C- and N-terminals, and amidase, peptidase, and carboxypeptidase at thin PGN layer in periplasmic space [14].

Zn^{2+} Ions Induced Activated PGN Autolysins Promote Anti-Bacterial Activity Against *Gram-Positive* Bacteria

S. aureus amidase AmiA is acted on PGN binding and cleavage. The AmiA distinguishes PGN mostly by the peptide, and the cleavage is facilitated by a zinc-activated water molecule, in order to develop new therapeutics against *MRSA*. The autolytic activity of the recombinant amidase of the Aas (autolysin/adhesin of *Staphylococcus saprophyticus*) is inhibited and is neccesary for the C-terminal GW repeats, not the N-terminal repeats [15].

Lytic amidase autolysin LytA which is released by bacterial lysis, associates with the cell wall via 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 [16]. 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 [17]. The LytB PGN hydrolase responsible for physical separation of daughter cells cleaves the GlcNAc-β-(1,4)-MurNAc glycosidic bond of PGN building units that cell wall digestion products and solubilisation rates might indicate a tight control of LytB activity to prevent unrestrained breakdown of the cell wall [18]. The PGN- remodeling autolysins LytC, LytD, and LytF are expressed in the same subpopulation of cells and complete flagellar synthesis that LytC appears to be important for flagellar function, motility was restored to a LytC mutant by mutation of either

lon A, and LytC, LytD,and LytF autolysins to population heterogeneity in *B. subtilis* [19].

Atl is the major autolysin in *S. aureus* that the bi functional major autolysin plays a key role in staphylococcal cell separation which processing of Atl yield catalytically active amidase and glucosamidase domains [20]. The biochemical and structural staphylococcal Atl have successful cloaning, high level over-expression, and purification Atl proteins [21]. AtlA is the major PGN hydrolases of *Enterrococcus 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 [22]. Major Atl autolysin also have an essential role in the early events of the fibronectin-binding proteins (FnBPs)-dependent *S. aureus* biofilm phenotype [23]. For the contribution of autolysins of PGN hydrolases to bacterial killing, there is N-acetyl-glucosaminidase (AtlA), two N-acetyl-muraminases (AtlB and AtlC) [24].

In addition, endopeptidase of autolysin LytF in *B. subtilis* plays a role in cell separation and hydrolase of the peptide [25].

Zn^{2+} Ions Induced Degrading Enzyme of Outer Membrane Lipoproein and PGN Autolysins Promote Anti-Bacterial Activity Against *Gram-Negative* Bacteria

Amidase gene AmiB catalyzes the degradation of PGN in Gram-negative bacteria that the amiB gene was composed of 1,722 nucleotides and 573 amino acid which is involved in the separation of daughter cells after cell devision and inactivation of the amiB gene, resulting in a marked increases of sensitivity to oxidative stress and organic acids [26]. Amidase activity of amiC controls cell separation and PGN fragments release [27]. Zinc-dependent endopeptidases (Eps) are predicted to hydrolyze PGN to facilitate cell growth that zinc avaliability affects strong activity of cell wall hydrolases, and zur-regulated endopeptidases are present in divergent Gram-negative bacteria [28]. Zinc-regulated peptidase maintains cell wall integrity during immune-mediated nutrient sequestration against *Acinetobacter baumannii* [29].

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 (TBVs) against Malaria eradication [30]. Metallo- carboxypeptidases (MCPs) of the M32 family of peptidases exhibit a significant hydrolytic activity and different hydrolysis patterns against *Trypanosoma brucei* or *cruzi* [31]. Zinc-depedent carboxypeptidase autolysin could adapt to be appreciable the anti-bacterial activities.

Human peptidoglycan recognition proteins (PGRPs) are novel class of recognition and effect or molecules with broad Zn^{2+}-dependent bactericidal activity against both Gram-positive and Gram-negative bacteria [32]. Hence, zinc-dependent PGN autolysin of amidases is enhanced the anti-bacterial activities against both Gram-positive and Gram-negative bacteria. Thus, autolysin-mediated bacteriolysis induced bacterial cell death can contribute to the bactericidal activities. Further, autolysin-mediated lysis-induced bacterial cell death may make contribution to the bacteriolytic vaccine activities (Table 1).

Accordingly, Table 1 represents anti-bacterial activities of bacteriolyses by Zn2+ 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 Immune Function and Membrane-Surface Fusion Glycoprotein

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 HIV, HCV [33]. 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 antigenetic sites as the labile wild-type proteins efficiently elicit potently neutralizing antibodies [34].

Zinc-Finger Proteins (Znfs), Zinc-Finger Antiviral Proteins (Zaps), and Virus Spreading Inhibition

The designed polydactyl zinc finger protein is prepared consisting HIV-1 type integrase fused to the synthetic zinc finger protein (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 [35]. The novel EBV-induced zinc finger gene, ZNF^{EB}, including its intronless locus and human protein variants, controls entry and exit from cell cycling in activated lymphocytes [36]. Artificial zinc finger fusions were targeted to the high affinity Sp1-binding site, and by being fused with TAR-binding mutant (TatdMt), and Pox and Zinc finger (POZ) domain, they strongly block both Sp1-cyclin T1-dependent transcription and Tat-dependent transcription of HIV-1 [37]. ZNF Tsip1 that the candidate genes encoded Tsi1-interacting protein1 (Tsip1), ZNF Tsip1 strongly interacted with CMV 2a protein, controls Cucumber mosaic virus (CMV) RNA replication [38]. The ZFN ZCCHC3 binds RNA and facilitates viral RNA that ZCCHC3 is a co-receptor 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 [39].

Zinc-finger antiviral protein (ZAP) specifically inhibits the replication of certain viruses and promotes viral RNA degradation [40]. ZAP inhibits HIV-1 infection by promoting the degradation of specific viral mRNAs [41] and ZAP also inhibits influenza A virus (IAV) protein that the short form of ZAPS inhibited IAV polymerase basic protein 2 (PB2) expression by reducing the encoding viral mRNA levels and repressing its translation [42]. ZAP-70 kinase regulates HIV cell-to-cell spread [43]. ZAP's stress granule localization due to cytopla-smic structure is correlated with antiviral activities that virus replication processes trigger stress granule formation and ZAP recruit-ment, in which these ZAPs findings provide insight into how antiviral components are regulated upon virus infection to inhibit virus spread [44].

ZAP's Viral Degradation

ZAP is a powerful restriction factor for viruses with elevated CpG (short hand for 5'-C-phosphate-G-3') dinucleotide frequencies. The long isoform ZAPL exerts the antiviral activity via its N-terminal zinc fingers that bind the mRNAs of some viruses, leading to mRNA degradation, in which influenza A virus has partially won the battle against this newly identified ZAPL antiviral activity [45]. Attenuation of CpG- or UpA-high mutants was mediated through either translation inhibition or accelerated RNA degradation that reversal of the attenuation of CpG-high, and UpA-high E7 viruses and replicons was also achieved through knockout of RNAsel and oligodenylate synthetases 3 (OAS3) [46]. The RNA destruction in viral replication is promoted on viral mRNA degradation in several antiviral pathways [47]. ZAP directly binds to its specific target mRNA, depletion of the exosome component hRrp41p or hRrp46p (human homologues

Zn^{2+} Ions	*Gram-Positive* PGN Layer Cell Wall
Zn^{2+}	**Zn^{2+} Ions Induced PGN autolysins** → **Zn^{2+}, O_2^-, H_2O_2, - OH, - NO, $ONOO^-$** **Zn^{2+} Ions Induced PGN autolysins** • *S.aureus* amidase AmiA • Recombinant amidase of the *Aas* • Lytic amidase LytA for *Streptococcus pneumoniae* • *Pneumococcal autolysin* LytA LytC, D, F of PGN remodeling for *Bacillus subtilis* • Endopeptidase LytF for *bacillus subtilis* • AtlA autolysin for GelE against *E. faecalis* • AtlA,AtlB, AtlC autolysins against *enterococcus faecalis* • Fusion protein autolysin, MIBRs against *S. pneumoniae* • Metallocarboxypeptidase M32 against *Trypanosoma brucei* or *cruzi* • PBP2a and autolysin mixture aginst *MRSA* • *ROS* and *RNS* generations *(Zinc homeostasis)* • ZnO-NPs have a very high anti-bacterial activity and ROS • generation gainst *MRSA* (ROS; H_2O_2, OH^-, O_2^{-2}) • ZnO-NPs caused up-regulation of pyrimidine biosynthesis and • degradation agasinst *MRSA*

Zn^{2+} Ions	*Gram-Positive* PGN Layer Cell Wall	
Zn^{2+}	Outer Membrane Lipoprotein at C- and N-terminals	Periplasm Space Thin PGN Layer
	→ **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 N.menigitidis · ETEC subunit vaccine · ZnuB against *P. aeruginosa.* · Preventive vaccine by recombinant flagella against *P.aeruginosa* · *ROS* and *RNS*	· AmiC in PGN fragment release · Carboxypeptidase by transmission- blocking vaccines · PGRPs or PGLYRPs · D-glutamate auxotrophy against *P. aeruginosa* PA14 · ORT in infectious diarrhoea · *ZnuA* against *P. aeruginosa* · Recombinant flagella and pili against *P. aeruginosa* · *ROS* and *RNS*
	· ZnO-NPs disrupt the cell membrane and oxidative stress against *Campylobacter*	

Table 1: Zinc immune bacteriolyses by Zn^{2+} ions-induced bacterial PGN autolysin activation against Gram-positive thick PGN envelope cell wall and Gram negative outer membrane lipoprotein and thin PGN layer cell wall

of yeast) with small interfering RNA significantly reduced ZAP's destabilizing activity, and ZAP is a trans- acting factor that modulates mRNA stability [48]. The longer isoform of ZAP that contains the Poly (ADP ribose) polymerase (PARP) - like domain is a stronger suppressor of murine leukemia virus expression and Semliki forest virus infection [49]. Suppressing Matrin 3 of a nuclear matrix protein powers a heightened and broader ZAP-mediated retroviral restriction of HIV-1 gene expression that this ZAP regulatory mechanism is shared with additional nuclear matrix proteins [50]. Interferon Induced Transmembrane Proteins (IFITMs) can inhibit the cellular entry of a broad range of viruces including IAVs, HCV, Ebola viruses, SARS corona viruses, Dengue virus, Zika virus, and HIV-1. However, a novel role for IFITMs in inhibiting HIV replication at the level of translation is identified, but IFITMs expression reduces HIV-1 viral protein synthesis by preferentially excluding viral mRNA transcripts from translation and thereby restricts viral production, and the effects can be overcome by the lentiviral protein Nef [51]. Zinc oxide nanoparticles (ZnO-NPs) also have high anti-viral activities as such as H1N1 influenza virus and application of nanomedicine [52,53].

ZAP Viral Destruction by Cell Surface Receptors Of Glycoprotein/Enzymes Hemagglutinin and Neuraminidase

Influenza A virus (IAV) that belongs to the Orthomyxoviridae family is a negative-strand segmented RNA vitrus, in which the surface membrane proteins are constituted by three important components; M2 proton channel, hemagglutinin (HA) and Neuraminidase (NA). The M2 proton channel is responsible for proton conductance vitally important to viral replication, HA is responsible for binding to the surface of three infected cell as a trimer leading to the attachment and subsequent penetration by viruses into the target cell, and NA is responsible for cleaving the terminal sialic acid moieties from the receptors to facilitate the elution of the progeny virion from the infected cell [54]. The HA has become one of the main targets for drug design against influenza virus, owing to unique function in assisting viruses to bind the cellular surface with being penetrated into the infected cell [54]. IAV membrane proteins HA and NA are determinants of virus infectivity, transmissibility, pathogenicity, and major antigenicity that virus movement mediated by HA and NA resulted in a three to four-fold increase in virus internalisation by cultutred cells that cooperation of HA moves IAV particles on a cell surface and

enhances virus infection of host cells [55]. The well-documented influenza virus infection cycle starts with the attachment of virus through its HA to sialic acid-containing glycan receptors on the host cell surface, and the potential for NA receptor binding to contribute to influenza virus biology remain yet underappreciated [56]. HA binds to a virus receptor, a sialoglycoprotein or sialoglycolipid on the host cell and mediates virus attachment to the cell surface. The hydrolytic enzyme NA cleaves sialic acid from viral receptors and accelerates the release of progeny virus from host cells. The surface membrane proteins of a negative-strand segmented RNA virus are constituted by three important components of M2 proton channel, and HA, NA [56].

If immunity against NA is desirable in influenza vaccination, selection of vaccine candidate strains must include not only analysis of antigenic changes but also enzymatic studies and determination of the requirement of Zn2+ ions to maintain immunogenicity and activity during production, since Zn2+ had a slight inhibitory effect on the activity of all tested strains [57]. The structures of HA, hemagglutinin-esterase-fusion (HEF) protein, and glycoprotein hemagglutinin esterase (HE) should serve as a basis for furthering our understanding of how viruses recognize their receptors on the cell surface, mediate viral fusion with the cell membrane, and then destroy their receptors that respiratory and enteric viruces have evolved virion-associated receptor-destroying enzymes as viral destruction of cell surface receptors [58]. The structure of the influenza virus neuraminidases, the special organization of their active site, the mechanism of carbohydrate chains desialylation by NA, and its role in the influenza virus function at different stages of the viral infectious cycle has been considered on NA activity to viral attachment, entry and release of virions from infected cells, and surface receptor binding mechanism [59,60]. These results have led to NA substrate specificity and different approaches, viral NA inhibitor, relationship with HA, and the receptor binding activities and antibody level of this enzyme.

ZAP is a host factor that specifically inhibits the replication of certain viruses that on the surfaces of the virion particles are the receptor-binding protein HA which mediates virus entry, and the glycoside hydrolase enzyme NA which is important for mature-virion release [42]. Both IAVs and type B viruses (IBVs) possess a host-derived lipid membrane, referred to as an envelope, which is decorated on the surface with the viral membrane proteins HA, NA, and to a lesser extent the matrix 2 (M2) protein, however, IAVs utilize a combination of viral and cellular mechanisms to coodinate the transport of their proteins and the eight vRNA gene segments in and out of the cell that IAVs facillate cell entry replication, virion assembly, and intercellular movement, in an effort to highlight some of the unanswered questions regarding the coordination of the IAV infection process [61]. The HA is the most abundant surface glycoprotein of the virus that has the ability to attach the host cell, causing cellular fusion and viral entry, and NA also plays crucial roles in the viral infection with HA-mediated membrane fusion by binding to sialic acid (SA) receptors [62]. Zinc finger and BTB (ZBTB 25) suppressed interferon production, further enhancing viral replication that ZBTB25-associated functions required an intact zinc finger domain and posttranslational small ubiquitin-like modified 1 (SUMO-1) modification of ZBTB25 [63]. Thus, IAV usrups ZBTB25 for IAV RNA synthesis and serves as a novel and potential therapeutic antiviral target

The structural features and the fact that the recombinant N10 protein exhibits no, or extremely low, NA activity suggests that it may have a different function than the NA proteins of other influenza viruses. Hence, the N10 protein is termed an NA-like protein until its function is elucidated [64]. Infection with influenza viruses usually leads to respiratory involvement and can result in pneumonia and secondary bacterial infections, consisting of point mutations in the HA and NA genes as a result of an error-prone viral polyme- rase. Hence, the newer antiviral agents could be produced by inhibiting the influenza virus NA and HA [65]. The influenza A virus HA/NA receptor balance governs dynamic and motile interaction that is expected to be crucial for penetration of the mucus layer and subsequent infection of cells by IAV but likely also by other enveloped viruses carrying a receptor-destroying enzyme in addition to a receptor-binding protein [66]. Thus, the anti-viral activities of ZAP's viral destruction for viral entry, replication, and spread by cell surface receptors of glycoproteins HA and NA are summarized in (Table2).

Accordingly, restriction factors of the influenza virus block (A) virus attachment and entry, (B)Transcription and replication, and (C)Virus assembly and budding. However, IAVs reveal chiefly that influenza viral HA attachment to host cell receptors and virus entry by receptor-mediated endocytosis, cleavage of HA by cellular proteases, and that virions then bud from the surface of infected cells and are released by the enzymatic activity of the viral NA [67] (Table 2).

Conclusion

Bacteriolytic and virucidal anti-infectious activities by bacterial autolysins and viral destruction of cell surface receptors are discussed, and the molecular mechanisms are clarified.

For Gram-poisitive bacteria, *S. aureus* amidase AmiA is acted on PGN binding and cleavage, and distinguishes PGN mostly by the peptide, and the cleavage is facilitated by a zinc-activated water molecule, in order to develop new therapeutics against *MRSA*. 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. The LytB PGN hydrolase responsible for physical sep aration of daughter cells cleaves the GlcNAc-β-(1,4)-MurNAc glycosidic bond of PGN building units. The PGN-remodeling autolysins LytC, LytD, and LytF are expressed in the same subpopulation of cells and complete flagellar synthesis that LytC appears to be important for flagellar function, motility was restored to a LytC mutant by mutation of either lon A, and LytC, LytD, and LytF autolysins to population heterogeneity in *B. subtilis*. AtlA is the major PGN hydrolases of *Enterrococcus faecalis* involved in cell division and cellular autolysis and the zinc metalloprotease, GelE of their interplay proposed to regulate AtlA function, Major Atl autolysin also have an essential role in the early events of FnBPs-dependent *S. aureus* biofilm phenotype. For the contribution of autolysins of PGN hydrolases to bacterial killing, there are N-acetyl-glucosaminidase (AtlA), two N-acetyl-muraminases (AtlB and AtlC). In addition, endopeptidase of autolysin LytF in *B. subtilis* plays a role in cell separation and hydrolase of the peptide.

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

Carboxypeptidases are exopeptidases that remove a single amino acid residue from the C terminus of proteins or exopeptidases 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 TBVs against Malaria eradication. MCPs of the M32 family of peptidases exhibit a significant hydrolytic activity and different hydrolysis patterns against *Trypanosoma brucei or cruzi*. Zinc-depedent carboxypeptidase autolysin could adapt to be appreciable the anti-bacterial activities.

PGRPs are novel class of recognition and effector molecules with broad Zn^{2+}-dependent bactericidal activity against both Gram-positive and Gram-negative bacteria. Hence, zinc-dependent PGN

Zn^{2+} Ions	Anti-viral activities of ZAP's viral destruction for virus entry, replication, and spread	
Zn^{2+}	**Adsorption/Entry**	**DNA/RNA Replication, Spread**
	→ Zn^{2+}, O_{2^-}, H_2O_2	→ Zn^{2+}, - O_{2^-}, H_2O_2, NO
	· ZAP inhibits entry of Sindbis virus. HCV · IFTMs as cellular entry inhibitor · EBV-induced zinc 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 · Zinc finger: virus decay · Zinc finger proteinE2C; viral DNA specific sites · Zinc finger protein Tsip1;Cucumber mosaic virus (CMV)RNA replication · Artificial zinc finger fusion; HIV-1 tanscriptions · ZAP inhibits HIV, SINV spread

Table 2: Zinc immune anti-viral activity of ZAP viral destruction by cell surface receptors of glycoprotein/enzymes HA and NA

autolysin of amidases are enhanced the anti-bacterial activities against both Gram-positive and Gram-negative bacteria. Thus, autolysin-mediated bacteriolysis induced bacterial cell death can contribute to the bactericidal activities. Further, autolysin-mediated lysis-induced bacterial cell death may make contribution to the bacteriolytic vaccine activities.

For viruses, ZAP is a powerful restriction factor for viruses with elevated CpG dinucleotide frequencies. The RNA destruction in viral replication is promoted on viral mRNA degradation in several antiviral pathways. ZAP directly binds to its specific target mRNA, depletion of the exosome component hRrp41p or hRrp46p with small interfering RNA significantly reduced ZAP's destabilizing activity, and ZAP is a trans-acting factor that modulates mRNA stability. IFITMs can inhibit the cellular entry of a broad range of viruces including IAVs, HCV, Ebora viruses, SARS coronaviruses, Dengue virus, Zika virus, and HIV-1. However, a novel role for IFITMs in inhibiting HIV replication at the level of translation is identified, but IFITMs expression reduces HIV-1 viral protein synthesis by preferentially excluding viral mRNA transcripts from translation and thereby restricts viral production, and the effects can be overcome by the lentiviral protein Nef. In addition, ZnO-NPs also have high anti-viral activities as such as H1N1 influenza virus and application of nanomedicine.

IAV that belongs to the Orthomyxoviridae family is a negative-strand segmented RNA vitrus, in which the surface membrane proteins are constituted by three important components; M2 proton channel, HA and NA. The HA has become one of the main targets for drug design against influenza virus, owing to unique function in assisting viruses to bind the cellular surface with being penetrated into the infected cell. IAV membrane proteins HA and NA are determinants of virus infectivity, transmissibility, pathogenicity, and major antigenicity that virus movement mediated by HA and NA resulted in a three to four-fold increase in virus internalisation by cultutred cells that cooperation of HA moves IAV particles on a cell surface and enhances virus infection of host cells. HA binds to a virus receptor, a sialoglycoprotein or sialoglycolipid on the host cell and mediates virus attachment to the cell surface. The hydrolytic enzyme NA cleaves sialic acid from viral receptors and accelerates the release of progeny virus from host cells. The surface membrane proteins of a negative-strand segmented RNA virus are constituted by three important components of M2 proton channel, HA, and NA.

The structures of HA, HEF protein, and glycoprotein HE should serve as a basis for furthering our understanding of how viruses recognise their receptors on the cell surface, mediate viral fusion with the cell membrane, and then destroy their receptors that respiratory and enteric viruses have evolved virion-associated receptor-destroying enzymes as viral destruction of cell surface receptors. The structure of the influenza virus neuraminidases, the spacial organization of their active site, the mechanism of carbohydrate chains desialylation by NA, and its role in the influenza virus function at different stages of the viral infectious cycle has been considered on NA activity to viral attachment, entry and release of virions from infected cells, and surface receptor binding mechanism. These results have led to NA substrate specificity and different approaches, viral NA inhibitor, relationship with HA, and the receptor binding activities and antibody level of this enzyme.

ZAP is a host factor that specifically inhibits the replication of certain viruses that on the surfaces of the virion particles are the receptor-binding protein HA which mediates virus entry, and the glycoside hydrolase enzyme NA which is important for mature- virion release. The HA is the most abundant surface glycoprotein of the virus that has the ability to attach the host cell, causing cellular fusion and viral entry, and NA also plays crucial roles in the viral infection with HA-mediated membrane fusion by binding to SA receptors. ZBTB 25 suppressed interferon production, further enhancing viral replication that ZBTB25-associated functions required an intact zinc finger domain and posttranslational small SUMO-1 modification of ZBTB25. Thus, IAV usrups ZBTB25 for IAV RNA synthesis and serves as a novel and potential therapeutic antiviral target

Infection with influenza viruses usually leads to respiratory involvement and can result in pneumo-nia and secondary bacterial infections, consisting of point mutations in the HA and NA genes as a result of an error-prone viral polymerase. Thus, newer antiviral agents could be produced by inhibiting the influenza virus NA and HA. The influenza A virus HA/NA receptor balance governs dynamic and motile interaction that is expected to be crucial for penetration of the mucus layer and subsequent infection of cells by IAV but likely also by other enveloped viruses carrying a receptor-destroying enzyme in addition to a receptor-binding protein.

Accordingly, restriction factors of the influenza virus block (A) Virus attachment and entry, (B) Transcription and replication, and (C) Virus assembly and budding. However, IAVs reveal chiefly that influenza viral HA attachment to host cell receptors and virus entry by receptor-mediated endocytosis, cleavage of HA by cellular proteases, and that virions then bud from the surface of infected cells and are released by the enzymatic activity of the viral NA.

Conflicts of Interest

The author declares there are no conflicts of interest.

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