https//doi.org/10.33805/2690-2613.109
Volume 2 Issue 1 | PDF 109 | Pages 5

EDELWEISS PUBLICATIONS
OPEN ACCESS

Edelweiss Journal of Biomedical Research and Review

Review Article ISSN 2690-2613

Virucidal Activities of Zinc-Finger Antiviral Proteins and Zinc-Binding Domains for Virus Entry, DNA/RNA Replication and Spread

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Citation: Ishida T. Virucidal activities of zinc-finger antiviral proteins and zinc-binding domains for virus entry, DNA/RNA replication and spread (2020) Edel J Biomed Res Rev 2: 9-13.

Received: Feb 17, 2020

Accepted: Mar 02, 2020

Published: Mar 08, 2020

Abstract

The novel EBV (Epstein-Barr virus)-induced ZNFEB including its intronless locus and human protein variants, controls virus entry and exit from cell cycling in activated lymphocytes. ZNF ZCCHC3 binds RNA and facilitates viral RNA that is critical for RLR-mediated innate immune response to RNA virus. ZAP (Zinc-Finger Antiviral Protein) inhibits entry, replication and spread of certain viruses and promotes viral RNA degradation. ZAP may regulate DNA and RNA virus replication that ZAP inhibits Retroviral RNA production and HIV-1(Human Immuno-Deficiency Virus Type 1) infection by promoting the degradation of specific viral mRNAs. Futhermore, ZAP could regulate RNA virus degradation of SARS-CoV's (SARS Corona Virus) and MERS-CoV's (MERS Corona Virus) RNA virus. Replication of SARS-CoV requires proteolytic processing of the replicase polyprotein by a PLpro (Papain-Like Protease) that zinc conjugate inhibits SARSCoV PLpro protease activity. Zinc conjugated complexes as SARS-CoV 3C-like protease inhibitors play important role for this Zn^{2+}-centered coordination pattern that the zinc-coordinating inhibitor is tetrahedrally coordinated. ZBD (Zinc-Binding Domain) is essential for formation of the functional Junin virus envelope glycoprotein complex. Complex ZBD regulates replicative arterivirus helicase and controls mRNA decay helicase. Viral inhibitor p53 down-regulates SARS-CoV replications that p53 inhibits replication of infectious SARS-CoV as well as of replicons and HCoV-NL63 (Human Coronavirus NL63). ZAP-70 kinase regulates HIV cell-to-cell spread that HIV usurps components of the immunological synapse machinery to ensure its own spread through cell-to-cell contacts. 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. Virucidal activities of ZNF, ZAP and ZBD are recognised by which Zn^{2+} ions bind RNA and facilitates viral RNA that is critical for RLR (RIG-1 Like Receptor)-mediated innate immune response to RNA virus and highly diverse fusion proteins have converged on the same overall strategy to mediate a common pathway of membrane fusion, causing to lead enhancement of the anti-viral activity. Zinc ions become used as Zn-coordinated inhibitors for viral regulation of virucidal activities.

Keywords: Zinc-finger antiviral protein, Virus entry, Replication and spread, RNA degradation, SARS-CoV, PLpro, Zn^{2+} ion-coordination pattern

Introduction

Zinc homeostasis is a key factor in maintaining a healthy immune system. Zinc ions are involved in regulating intracellular signaling pathways in innate and adaptive immune cells that the influences of zinc status on the overall immune function are present in zinc deficiency as overproduction of pro-inflammatory cytokines and reactive mediators, zinc homeostasis as balanced immune cell functions and zinc excess as suppression of T and B cell functions [1]. Zinc is known to be essential for highly growth and development of all organisms in the human body, especially the immune system. A variety of effects of zinc on immune cells depend on the zinc concentration that in a concentration of 100 μmol/L, zinc suppresses natural killer cell killing and T-cell function whereas monocytes are activated directly and in a concentration of 500 μmol/L, zinc evokes a direct chemotactic activation of neutrophil granulocytes [2]. Zinc is a fundamental trace element in human body that the recommended daily intake of zinc depends on several factors. Average values of recommended intake may be 7～11 mg/day for adults. Zinc is the second abundant trace metal with human body 2～3 g and a plasma concentration of 12-16 μM, 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. Zinc status play an important role in antiviral immunity, mainly during the early stage of the infection that the most effective antiviral antibodies are neutralizing antibodies which bind to the viral envelope or capsid proteins and regulate the virus entering into host cell [3]. Zinc deficiency accounts currently for approximately 16% of lower respiratory tract infections, 18% of malaria and 10% of diarrheal diseases, while severe zinc deficiency is rare, mild to moderate deficiency is more common worldwide [4]. The zinc deficiency leads to cell-mediated immune dysfunctions among other manifestations which such dysfunctions lead to a worse outcome in the response

towards virus infection [4]. Zinc homeostasis during acute phase response is the temporal transfer of serum zinc to the tissues, causing transient serum hypozincemia.

Zinc homeostasis 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) [4]. The other, 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 [5]. 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 viral infections, including production of metal sequestering proteins and bombardment with toxic level of zinc at host-pathogen interface [6]. Zinc influences apoptosis by acting on several molecular regulators of programmed cell death and zinc deficiency caused by malnutrition and foods with low bio-availability, aging, certain diseases and deregulated homeostasis is a far more common risk to human health without intoxication [7]. 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 [8].

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. 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. 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 [9]. Human coronaviruses (HCoVs) are known as respiratory pathogens that HCoVs play only a minor role in causing gastrointestinal illness in children<6 year old which interest in coronaviruses in relation to enteric diseases in humans increased with the emergence of Severe Acute Respiratory Syndrome (SARS) and identification of SARS Coronavirus in 2003 [10]. The emergent development of antiviral drugs for new type-coronavirus (2019-novel CoV) respiratory infection is nowadays desired to be due to the employment. In this review, the zinc-mediated antiviral immunity and the virucidal activities of zinc-finger protein, zinc-finger antiviral protein and zinc-binding domain are discussed against many infectious viruses. Thereby, the virucidal mechanisms by zinc ions-binding formation, RNA virus degradation and Zn^{2+}-centered coordination via the zinc-finger antiviral proteins, zinc-binding domain and zinc-conjugated complexes may be clarified.

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 HIV, HCV [3]. In immune cells, HIV infection is sensed by several Pattern Recognition Receptors (PRRs), leading to Type 1 Interferon (IFN-1) and inflammatory cytokines production that up regulate antiviral Interferon-Stimulated Genes (ISGs) [11]. Tripartite Motif (TRIM) 25 enabled to regulate antiviral innate immunity can bind to RNA, leading to uncover new mechanism by which this molecule regulates intracellular signaling and/or RNA virus replication [12]. 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 [13].

Zinc-Finger Protein

Interferon Induced Transmembrane Proteins (IFITMs) inhibit the cellular entry of a broad range of viruses that IFITM-mediated restriction requires recognition of viral RNA elements, in which the IFITMs can inhibit the viral entry of IAV (Influenza A Virus), HCV, Ebora virus, SARS Coronavirus, Dengue virus, Zika virus and HIV-1 [14]. In addition, interferon-stimulated genes serve as enhancers of antiviral innate immunity [15]. The novel EBV-induced Zinc Finger Gene (ZNFEB) including its intronless locus and human protein variants, controls entry and exit from cell cycling in activated lymphocytes [16].

The designed polydactyl Zinc-Finger Protein (ZNF) is prepared consisting HIV-1 type integrase fused to the synthetic zinc finger 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 [17]. The ZNF 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 [18]. Artificial ZFNs strongly block both Sp1-cyclin T1-dependent transcription and Tat-dependent transcription of HIV-1 [19]. ZNF Tsip1 that the candidate genes encoded Tsi1-interacting protein 1 (Tsip1), a ZNF Tsip1 strongly interacted with CMV 2a protein, controls Cucumber Mosaic Virus (CMV) RNA replication [20].

Zinc-Finger Antiviral Protein

Zinc-Finger Antiviral Protein **(**ZAP) controls virus entry, DNA/RNA replication and spreading against viral infection. ZAP specifically inhibits the replication of certain viruses and promotes viral RNA degradation [21]. ZAP may regulate DNA and RNA virus replication. Inhibition of bacterial DNA replication during nitrosative stress is accompanied by zinc mobilization [22]. ZAP inhibits Retroviral RNA production [23] and ZAP inhibits HIV-1 infection by promoting the degradation of specific viral mRNAs [24]. The ZAP in first steps of HCV infection may be used as entry inhibitor [25]. ZAP inhibits alpha virus replication that elucidation of the antiviral mechanism by which ZAP inhibits Sindbis Virus (SINV) translation may lead to the development of agents with broad activity against alpha viruses [26]. The ZAP also inhibits IAV protein expression, in which suggests an important role of ZAP in the host effort to control IAV infection and the importance of the threat of ZAP to the virus [27]. The host cell restriction factors that limit IAV have been investigated [28].

Hence, ZAPs inhibit viral entry, DNA/RNA replication and spreading that ZAP regulates virus infection with degradation of specific viral mRNA. Furthermore, this ZAP could probably inhibit the HCoVs that to date, the six known HCoVs have been identified, namely HCoV-229E, HcoV-NL63, HCoV-OC43, HCoV-HKU1, SARS-CoV and Middle East respiratory syndrome corona-virus (MERS-CoV), subsequent phylogenetic studies pointed to the bat origin of SARS-CoV based on sequences of SARS-like virus found in bats [29]. Replication of SARS-CoV requires proteolytic processing of the

replicase polyprotein by two viral cystein proteases, a chymotrypsin-like protease (3CLpro) and a Papain-Like Protease (PLpro).

This PLpro is important for development of antviral drug that would inhibit viral replication and reduce mortality associated with outbreaks of SARS-CoV that a model of PLpro in complex with ubiquitin aldehyde reveals well defined sites within the catalytic cleft that help to account for strict substrate-recognition motifs [30]. The MERS-CoV PLpro Blocking Loop 2 (BL2) structure differs from that of SARS-CoV PLpro, where it has been proven to play a crucial role in SARS-CoV PLpro inhibitor binding that inhibitor recognition specificity of MERS-CoV PLpro may differ from that of SARS-CoV PLpro. In addition, inhibitory activity, of this compound was selective for SARS-CoV and MERS-CoV PLpro enzymes over two human homologues and the ubiquitin C-terminal hydrolases [31]. The papain-like protease 1 (PL1pro) domain is present in nonstructural protein 3 (nsp3) of alphacoronaviruses and subgroup 2a beta coronaviruses and the papain-like protease 2 (PL2pro) is present in SARS-CoV.

In combination with the prior characterization of PL2pro from other alpha corona-viruses of human coronaviruses 229E, NL63, these viruses employ two PLpros with overlapping specificities toward both viral and cellular substrates [32]. The ZAP could regulate RNA virus degradation of SARS-CoV's and MERS-CoV's RNA virus. Zn^{2+} ions are capable of inhibiting PLpro activity and the zinc conjugates to inhibit SARS-CoV PLpro activity that targeting PLpro with antiviral drug may have an advantage in not only inhibiting viral replication but also inhibiting the dysregulation of signaling cascades infected cells, leading to cell death [33]. Zn^{2+} inhibits coronavirus and arterivirus RNA polymelase activity and zinc ionophores block the virus replication that the combination of Zn^{2+} and pyrithione at low concentrations inhibits the replication of SARS-CoV and arterivirus RNA [34].

High zinc ion concentration and the addition of compounds that stimulate cellular import of zinc ions were found to inhibit the replication of various RNA virus, influenza viruses, respiratory syncytial virus and coronaviruses [34]. Further, zinc conjugated complexes as SARS-CoV 3C-like protease inhibitors play important role for this Zn^{2+}-centered coordination pattern that the zinc-coordinating inhibitor is tetrahedrally coordinated to the His40-Cys147 catalytic dyad of CVB3 3Cpro [35,36]. ZAP' stress with antiviral activity and induced virus replication are regulated upon virus infection to inhibit virus spread [37]. ZAP-70 kinase regulates HIV cell-to-cell spread that HIV usurps components of the immunological synapse machinery to ensure its own spread through cell-to-cell contacts [38]. An understanding of viral cell-to-cell transmission spreading will enhance our ability to intervene in the efficient spreading of viral infection [39].

Zinc-Binding Domain

A novel Zinc-Binding Domain (ZBD) is essential for formation of the functional Junin virus envelope glycoprotein complex that the envelope glycoprotein of the Junin arenavirus (GP-C) 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 [40]. 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 zinc ions, 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 [41]. Complex ZBD regulates replicative alterivirus helicase and controls mRNA decay helicase [42]. Viral inhibitor p53 down-regulates SARS-CoV replications that p53 inhibits replication of infectious SARS-CoV as well as of replicons and human coronavirus NL63. Hence, HCoVs antagonize the viral inhibitor p53 via stabilizing RCHY1 and promoting RCHY1-mediated p53 degradation [43]. Zinc-binding status having Zn^{2+} ions-centered coordination structure could serve as the development of potential drugs for SARS therapies. A complex zinc finger ZBD modulates the enzymatic activities of coronaviridae-Nidovirus helicases, leading that the ZBD is critically involved in nidovirus replication and transcription [44].

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 [45]. The membrane fusion reaction, membrane interaction, conformational changes of specialized virus envelope proteins and refolding reactions of specific fusion proteins can mediate both virus-cell fusion leading to infection and pathological cell-cell fusion, in which they are increasingly viewed as targets for antiviral intervention [45]. Thus, the virucidal activities of zinc-finger antiviral proteins for virus entry, replication and spread are represented in **Table 1.**

Zn^{2+} ions	**Anti-viral activity of ZAP in entry, replication and spread**	
Zn^{2+}	Adsorption/Entry	DNA/RNA Replication, Spread
	→ Zn^{2+}, ·O^{2-}, H_2O_2 ·EBV-induced zinc finger gene ZNFEB controls entry and exit ·ZBD prevent viral entry and GPC inhibit activate membrane fusion ·Zn-metalloprotease inhibits entry and cell-cell fusion	→ Zn^{2+}, ·O^{2-}, H_2O_2, NO ·ZAP inhibits entry of Sindbis virus, HCV ·IFTMs as cellular entry inhibitor ·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 transcriptions ·Zinc-conjugated complexes as SARS- CoV 3C-like protease inhibitors ·Combination of Zn2+ and pyrithione against SARS-CoV ·Zinc-coordinatng inhibitor as SARS- CoV ·ZAP inhibits HIV, SINV spread

Table 1: Virucidal activity of zinc-finger antiviral proteins for virus entry, replication and spread.

Accordingly, anti-viral activities of ZNF, ZAP and ZBD are recognized by which Zn^{2+} ions bind RNA and facilitates viral RNA that is critical for RIG-1 like receptor (RLR)-mediated innate immune response to RNA virus and highly diverse fusion proteins have converged on the same overall strategy to mediate a common pathway of membrane fusion, causing to lead enhancement of the anti-viral activity.

Conclusion

The ZNFEB controls entry and exit from cell cycling in activated lymphocytes. The designed polydactyl ZNF is prepared consisting HIV-1 type integrase fused to the synthetic zinc finger protein E2C. ZAP inhibits virus entry, replication and spread of certain viruses and an understanding becomes necessary for ZAP-mediated viral RNA degradation. ZAP inhibits the replication of certain viruses, regulates DNA and RNA virus replication and promotes viral RNA degradation. The ZAP also inhibits IAV protein expression, Retroviral RNA

production and HIV-1 infection by promoting the degradation of specific viral mRNAs. Further, the ZAP may regulate RNA virus degradations of HCoV, SARS-CoV's and MERS-CoV's RNA virus. HCoVs are known as respiratory pathogens that HCoVs play only a minor role in causing gastrointestinal illness in children year old.

The six known HCoVs have been identified, namely HCoV-229E, HCoV-NL63, HCoV-OC43, HCoV-HKU1, SARS-CoV and MERS-CoV. Zn^{2+} ions are capable of inhibiting PLpro activity and the zinc conjugates to inhibit SARSCoV PLpro activity that targeting PLpro with antiviral drug may have an advantage in not only inhibiting viral replication but also inhibiting the dysregulation of signaling cascades infected cells, leading to cell death. Zn^{2+} inhibits coronavirus and arterivirus RNA polymelase activity and zinc ionophores block the virus replication. That the combination of Zn^{2+} and pyrithione at low concentrations inhibits the replication of SARS-CoV and arterivirus RNA. Zinc-conjugated complexes as SARS-CoV 3C-like protease inhibitors play important role for this Zn^{2+}-centered coordination pattern that the zinc-coordinating inhibitor is tetrahedrally coordinated to the His40-Cys147 catalytic dyad of CVB3 3Cpro.

ZAP's stress with antiviral activity and induced virus replication are regulated upon virus infection to inhibit virus spread. ZAP-70 kinase regulates HIV cell-to-cell spread that HIV usurps the immunological components to ensure its own spread through cell-to-cell contacts. A novel ZBD is essential for formation of the functional Junin virus envelope glycoprotein complex. 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 zinc ions, 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.

Complex ZBD regulates replicative arterivirus helicase and controls mRNA decay helicase. Thus, ZNF, ZAP and ZBD specifically inhibit virus entry, replication and spread of many viruses. The host-virus interaction, conformational changes of specialized virus envelope proteins and refolding reactions of specific fusion proteins in 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. Complex ZBD regulates replicative alterivirus helicase and controls mRNA decay helicase. Viral inhibitor p53 down-regulates SARS-CoV replications that p53 inhibits replication of infectious SARS-CoV as well as of replicons and human coronavirus NL63.

Hence, HCoVs antagonize the viral inhibitor p53 via stabilizing RCHY1 and promoting RCHY1-mediated p53 degradation. 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. Accordingly, virucidal activities of ZNF, ZAP and ZBD are recognized by which Zn^{2+} ions bind RNA and facilitate viral RNA that is critical for RLR-mediated innate immune response to RNA virus and highly diverse fusion proteins have converged on the same overall strategy to mediate a common pathway of membrane fusion, causing to lead enhancement of the anti-viral activity.

References

1. Wessels I, Maywald M and Rink L. Zinc as gatekeeper of immune function (2017) Nutrients 9: 1-44.
2. Ibs KH and Rink L. Immunity enhanced by trace elements (2003) J Nutr 133: 1452S-1456S.
3. Read SA, Obeid S, Ahlenatiel C and Ahlenstiel G. The role of zinc in antiviral immunity (2019) Adv Nutr 10: 696-710. https://doi.org/10.1093/advances/nmz013
4. Gammoh NZ and Rink L. Zinc in infection and inflammation (2017) Nutrients 9: 1-25.
5. Dashti-Khavidaki S, Khalili H, Vahedi SM and Lessan-Pezeshki M. Serum zinc concentrations in patients on maintenance hemodialysis and its relationship with anemia, parathyroid hormone concentrations and pruritus severity (2019) Saudi J Kidney Dis Trans 21: 641-645.
6. Ishida T. Review on the role of Zn^{2+} ions in viral pathogenesis and the effect of Zn^{2+} ions for host cell-virus growth inhibition (2019) American J Biomed Scie Res 2: 28-37. https://doi.org/10.34297/ajbsr.2019.02.000566
7. Pium LM, Rink L and Haase H. The essential toxin: impact of zinc on human health (2010) Int J envir res public health 7: 1342-1365. https://doi.org/10.3390/ijerph7041342
8. Lancellotti M, Pereira RFC, Cury GG and Hollanda LM. Pathogenic and opportunistic respiratory bacteria-induced apoptosis (2009) Brazilian J Infec Dis 13: 226-231. https://doi.org/10.1590/s1413-86702009000300014
9. Navarro JM and Perez-Ruiz M. Antiviral immunity (2011) Curr Immuun Rev 7: 19-24. https://doi.org/10.2174/157339511794474244
10. Jevsnik M, Steyer A, Zrim T, Pokorn M, Mrvič T, etal. Detection of human coronaviruses in simultaneously collected stool samples andnasopharyngeal swabs from hospitalized children with acute gastroenteritis (2013) Virol J 10: 1-7. https://doi.org/10.1186/1743-422x-10-46
11. Bergantz L, Subra F, Deprez E, Delelis O and Richetta C. Interplay between intrinsic and innate immunity during HIV infection (2019) Cells 8: 922. https://doi.org/10.3390/cells8080922
12. Martin-Vicente M, Medrano L, Resino S, García-Sastre A and Martínez I. TRIM25 in the regulation of the antiviral innate immunity (2017) Front immunol 8: 1-9. https://doi.org/10.3389/fimmu.2017.01187
13. Rey FA and Lok SM. Common features of enveloped viruses and implications for immunogen design for next-generation vaccines (2018) Cell 172: 1319-1334. https://doi.org/10.1016/j.cell.2018.02.054
14. Lee WYJ, Menhua R, Liang C and Sloan RD. IFITM proteins inhibit HIV-1 protein synthesis (2018) Sci Rep 8: 1-15. https://doi.org/10.1038/s41598-018-32785-5
15. Crosse KM, Monson E, Beard MR and Helbig KJ. Interferon-simulated genes as enhancers of antiviral innate immunesignaling (2018) J Innate Immun 10: 85-93. https://doi.org/10.1159/000484258
16. Tune CE, Pilon M, Saiki Y and Dosch HM. Sustained expression of the novel EBV-induced zinc finger gene, $ZNF^{EB,}$ is critical for the transition of B lymphocyte activation to oncogenic growth transformation (2002) J immunol 168: 680-688. https://doi.org/10.4049/jimmunol.168.2.680
17. Tan W, Zhu K, Segal DJ, Barbas CF and Chow SA. Fusion protein consisting of HIV type 1 integrase and the designed polydactyl zinc finger protein E2C firect integration of viral DNA into specific sites (2004) J Virol 78: 1301-1313. https://doi.org/10.1128/jvi.78.3.1301-1313.2004
18. Lian H, Zang R, Wei J, Ye W, Hu MM, et al. The zinc-finger protein ZCCHC3 binds RNA and facilitates viral RNA sensing and activation of the RIG-I-like receptors (2018) Immun 49: 438-448. https://doi.org/10.1016/j.immuni.2018.08.014
19. Kim YS, Kim JM, Jung DL, Kang JE, Lee S, et al. Artificial zinc finger fusions targeting Sp1-binding sites and the trans-activator-responsive element potently repress transcription and replication of HIV-1 (2005) J Bio Chem 280: 21545-21552. https://doi.org/10.1074/jbc.m414136200
20. Hur SU, Kim MJ, Kook B, Ham BK and Paek KH. A zinc finger protein Tsip1 controls cucumber mosaic virus infection by

interacting with the replication complex on vacuolar membranes of the tobacco plant (2011) New Phytol 191: 746-762. https://doi.org/10.1111/j.1469-8137.2011.03717.x

21. Wang X, Lv F and Gao G. Mutagenesis analysis of the zinc-finger antiviral protein (2010) Retrovirol 7: 1-9. https://doi.org/10.1186/1742-4690-7-19
22. Schapiro JM, Libby SJ and Fang F. Inhibition of bacterial DNA replication by zinc mobilization during nitrosative stress (2003) PNAS 100: 8496-8501. https://doi.org/10.1073/pnas.1033133100
23. Gao G, Guo X and Goff SP Inhibition of retroviral RNA production by ZAP, a CCCH-type zinc finger protein (2002) SCIE 297: 1703-1706. https://doi.org/10.1126/science.1074276
24. Zhu V, Chen G, Lv F, Wang X, Ji X, et al. Zinc-finger antiviral protein inhibits HIV-1 infection by selectively targeting multiply spliced viral mRNA for degradation (2011) PNAS 108: 215834-215839. https://doi.org/10.1073/pnas.1101676108
25. The Rockefeller University. Virus entry and virus-host interactions (2019) Lab Virol Infec Dis 15: 1.
26. Bick MJ, Carroll JWN, Gao G, GoffS P, Rice CM, etal. Expression the zinc-finger antiviral protein inhibits alpha virus replication (2003) J Virol 77: 11555-11562. https://doi.org/10.1128/jvi.77.21.11555-11562.2003
27. Tang Q, Wang X and Gao G. The short form of the zinc finger antiviral protein inhibits influenza A virus protein expression and is antagonized by the virus-encoded NS1 (2017) J Virol 91: 1-14. https://doi.org/10.1128/jvi.01909-16
28. Villalon-Letelier F, Brooks A. Saunders P, Londrigan S and Reading P. Host cell restriction factors that limit influenza A infection (2017) Viruses 9: 376. https://doi.org/10.3390/v9120376
29. Lim YX, Ng YL, Tam JP and Liu DX. Human coronaviruses:A review of virus-host interactions (2016) Diseases 4: 1-28. https://doi.org/10.3390/diseases4030026
30. Ratia K, Singh K, Saikatendu KS, Santarsiero BD, Barretto N, et al. Severe acute respiratory syndrome coronavirus papain-like protease: Structure of a viral deubiquitinating enzyme (2006) PNAS 103: 58717-5722. https://doi.org/10.1073/pnas.0510851103
31. Lee H, Lei H, Santarsiero BD, Gatuz JL, Cao S, et al. Inhibitor recognition specificity of MERS-CoV papain-like protease differs from that of SARS-CoV (2015) ACS Chem Biol 10: 1456-1465. https://doi.org/10.1021/cb500917m
32. Wojdyla JA, Manolaridis I, Kasteren PB, Kikkert M, Snijder E, et al. Papain-like protease 1 from transmissible gastroenteritis virus: crystal structure and enzymatic activity toward viral and cellular substrates (2020) J Virol 84: 10063-10073. https://doi.org/10.1128/jvi.00898-10
33. Baez-Santos YM, John SE and Mesecar AD. The SARS-coronavirus papain-like protease: structure, function and inhibition by designed antiviral compounds (2015) Antiviral Res 115: 21-38. https://doi.org/10.1016/j.antiviral.2014.12.015
34. Velthuis JW, van den Worm SHE, Sims AC, Baric RS, Snijder EJ, et al. Zn^{2+} inhibits coronavirus and arterivirus RNA polymerase activity in vitro and zinc ionophores block the replication of these viruses in cell culture (2010) PLOS Patho 6: 1-10. https://doi.org/10.1371/journal.ppat.1001176
35. Lee CC, Kuo CJ, Hsu MF, Liang PH, Fang JM, et al. Structural basis of mercury- and zinc-conjugated complexes as SARS-CoV 3C-like protease inhibitors (2007) FEBS Letters 581: 5454-5458. https://doi.org/10.1016/j.febslet.2007.10.048
36. Lee CC, Kuo CJ, Ko TP, Hsu MF, Tsui YC, et al. Structural basis of inhibition specificities of 3C and 3C-like proteases by zinc-coordinating and peptidomimetic compounds (2009) J Bio Chem 284: 7646-7655. https://doi.org/10.1074/jbc.m807947200
37. Law LMJ, Razooky BS, Li MMH, You S, Jurado A, et al. ZAP's stress granule localization is correlated with its antiviral activity and induced by virus replication (2019) PLOS Patho 15: 1-22. https://doi.org/10.1371/journal.ppat.1007798
38. Sol-Foulon N, Sourisseau M, Porrot F, Thoulouze MI, Trouillet C, et al. ZAP-70 kinase regulates HIV cell-to-cell spread and virological synapse formation (2007) The EMBO J 26: 516-526. https://doi.org/10.1038/sj.emboj.7601509
39. Mothes W, Sherer NM, Jin J and Zhong P. Virus cell-to-cell transmission (2010) J Virol 84: 8360-8368. https://doi.org/10.1128/jvi.00443-10
40. York J and Nunberg H. A novel zinc-binding domain is essential for formation of the functional Junin-virus envelope glycoprotein complex (2007) J Virol 81: 13385-13391. https://doi.org/10.1128/jvi.01785-07
41. Briknarova K, Thomas CJ, York J and Nunberg H. Structure of a zinc-binding domain in the junin virus envelope glycoprotein (2012) J Bio Chem 286: 1528-1536. https://doi.org/10.2210/pdb2l0z/pdb
42. Deng Z, Lehmann KC, Li X, Feng C, Wang G, et al. Structural basis for the regulatory function of a complex zinc-binding domain in a replicative arterivirus helicase resembling a nonsense-mediated mRNA decay helicase (2014) Nucleic Acids Res 42: 3464-3477. https://doi.org/10.1093/nar/gkt1310
43. Ma-Lauer Y, Carbajo-Lozoya J, Hein MY, Müller MA, Deng W, et al. p53 down-regulates SARS coronavirus replication and is targeted by the SARS-unique domain and PLpro via E3 ubiquitin ligase RCHY1 (2016) PNAS 113: E5192-E5201. https://doi.org/10.1073/pnas.1603435113
44. Seybert A, Posthuma CC, van Dinten LC, Snijder EJ, Gorbalenya AE, et al. A complex zinc finger controls the enzymatic activities of nidovirus helicases (2005) J Virol 79: 696-704. https://doi.org/10.1128/jvi.79.2.696-704.2005
45. White JM, Deolos SE, Brecher M and Schornberg K. Structure and mechanisms of viral membrane fusion proteins: multiple variations on a common theme (2008) Crit Rev Biochem Mol Biol 44: 189-219. https://doi.org/10.1080/10409230802058320