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FMDV Multi-VP1e Can Induces Potection against Lethal FMDV Challenge

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In this study, we evaluated a recombinant protein-based vaccine candidate for foot-and-mouth disease viruses (FMDV). To construct multi-epitope-based protein for FMDV vaccine, we selected epitope sites containing G-H loop and C-terminus known as major immunogenic sites in VP1 region from three serotypes FMDVs, O1/Manisa/Turkey/69, A/Pocheon/001/KOR/2010 and Asia1/Shamir/89, which had ever occurred or threatened in Korea and we conjugated each epitope sites. Multi-VP1e protein was expressed in soluble form and purified by FPLC and IMAC system. Mice were inoculated with multi-VP1e protein emulsified with ISA 201 every two weeks by I.M injection and we demonstrated that multi-VP1e protein vaccine can induce humoral and cellular immunity and completely protect from lethal infection of FMDV Asia1/Shamir/89. Additionally, multi-VP1e protein vaccine induced the production of sufficient neutralizing antibodies against each three serotypes of FMDV in pig and effectively protected pigs from FMDV Asia1/Shamir/89 challenge. Thus, multi-VP1e protein vaccine which derived from E. coli expression system may be a safe and effective vaccine candidate against diverse FMDV. [The Ministry for Food, Agriculture, Forestry and Fisheries, Republic of Korea (Grant no. 315044031)]

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HDAC6 Regulates RIG-I Mediated Viral RNA Sensing

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RIG-I is a key cytosolic sensor that detects RNA viruses through its C-terminal region and activates the production of antiviral interferons (IFNs) and proinflammatory cytokines. While post-translational modification has been demonstrated to regulate RIG-I signaling activity, its significance for the sensing of viral RNAs remains unclear. Here, we first show that the RIG-I C-terminal region undergoes deacetylation to regulate its viral RNA sensing activity and that the HDAC6-mediated deacetylation of RIG-I is critical for viral RNA detection. HDAC6 transiently bound to RIG-I and removed the lysine 909 acetylation in the presence of viral RNAs, promoting RIG-I sensing of viral RNAs. Depletion of HDAC6 expression led to impaired antiviral responses against RNA viruses, but not against DNA viruses. Consequently, HDAC6 knockout mice were highly susceptible to RNA virus infections compared to wild-type mice. These findings underscore the critical role of HDAC6 in the modulation of the RIG-I-mediated antiviral sensing pathway. [The Ministry for Food, Agriculture, Forestry and Fisheries (Grant No. 315044031), Republic of Korea]

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Inhibition of Highly Pathogenic Avian Influenza (HPAI) Virus by a Peptide Derived from vFLIP through Its Direct Destabilization of Viruses

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The antiviral activities of synthesized Ka2-helix peptide, which was derived from the viral FLICE-like inhibitor protein (vFLIP) of Kaposi's sarcoma-associated herpesvirus (KSHV), against influenza A virus (IAV) were investigated *in vitro* and *in vivo,* and mechanisms of action were suggested. In addition to the robust autophagy activity of the Ka2-helix peptide, the present study showed that treatment with the Ka2 peptide fused with the TAT peptide significantly inhibited IAV replication and transmission. Moreover, TAT-Ka2 peptide protected the mice, which were challenged with lethal doses of highly pathogenic influenza A H5N1 or H1N1 viruses. Mechanistically, we found that TAT-Ka2 peptide destabilized the viral membranes, depending on their lipid composition of the viral envelop. In addition to IAV, the Ka2 peptide inhibited infections with enveloped viruses, such as Vesicular Stomatitis Virus (VSV) and Respiratory Syncytial Virus (RSV), without cytotoxicity. These results suggest that TAT-Ka2 peptide is a potential antiviral agent for controling emerging or re-emerging enveloped viruses, particularly diverse subtypes of IAVs. [The Ministry for Food, Agriculture, Forestry and Fisheries (Grant No. 316043-3)]

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Mucosal Administration of Conserved sM2HA2 and Cholera Toxin Subunit A1 (CTA1) Fusion Protein with PC-NPs Induces Protection against Divergent Influenza Subtypes

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To develop a safe and effective mucosal vaccine that broad cross protection against seasonal or emerging influenza A viruses, we generated a mucosal influenza vaccine system combining the highly conserved matrix protein-2 (sM2), fusion peptide of hemagglutinin (HA_2), the well-known mucosal adjuvant cholera toxin subunit A1 (CTA1) and poly-ɣ-glutamic acid (ɣ-PGA)-chitosan nanoparticles (PC NPs), which are safe, natural materials that are able to target the mucosal membrane as a mucosal adjuvant. The mucosal administration of sM2HA2CTA1/PC NPs could induce a high degree of systemic immunity at the site of inoculation as well as at remote locations and also significantly increase the levels of sM2- or HA2-specific cell-mediated immune response. In challenge tests in BALB/c mice with 10 MLD_{50} of Influenza H5N1, H1N1, H5N2, H7N3 or H9N2 viruses, the recombinant sM2HA2CTA1/PC NPs provided cross protection against divergent lethal influenza subtypes and also the protection was maintained up to six months after vaccination. Thus, sM2HA2CTA1/PC NPs could be a promising strategy for a universal influenza vaccine. [The Ministry for Food, Agriculture, Forestry and Fisheries (Grant No. 315044031, 316043-3)]

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Inhibition of Respiratory Syncytial Virus Replication in vitro and in vivo by Coptidis Rhizoma Extract

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Coptidis Rhizoma is derived from the dried rhizome of Ranunculaceous plants and is a commonly used traditional Chinese medicine. Although *Coptidis Rhizoma* is commonly used for its many therapeutic effects, antiviral activity against RSV has not been reported in detail. In this study, we evaluated the antiviral activities of *Coptidis Rhizoma* extract (CRE) against RSV in human respiratory tract cell line (HEp2) and BALB/c mice. An effective dose of CRE significantly reduces the replication of RSV in HEp2 cells and reduces the RSV-induced cell death. This antiviral activity against RSV was through the induction of type I interferon-related signaling and the antiviral state in HEp2 cells. More importantly, oral administration of CRE exhibited prophylactic effects in BALB/c mice against RSV. In HPLC analysis, we found the presence of several compounds in the aqueous fraction and among them; we confirmed that palmatine was related to the antiviral properties and immune-modulation effect. Taken together, CRE and its components play roles as immunomodulators and could be a potential source as promising natural antivirals that can confer protection to RSV. [No. K16281 awarded to the Korean Institute of Oriental Medicine by the Ministry of Education, Science and Technology]

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The Recombinant *Lactobacillus*-Displayed CTA1-Conjugated PEDSe Antigen Induces Protective Mucosal Immune Responses against Porcine Epidemic Diarrhea (PED) Virus

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PED virus (PEDV), the causative agent of PED belongs to the member of Coronaviridae, is enveloped RNA virus. PEDV infection has been one of the major concerns of the Korean swine industry and even though several commercial vaccines have been developed, PEDV has continually emerged, causing tremendous harm to the swine farms. For the development of an effective PEDV vaccine that provides broad cross protection against existing PEDV strain and emerging subtypes, we used PEDSe multi-epitope (Spike multi-epitope, Se=COE, SS2, SS6) gene with non-toxic mucosal immunogenic adjuvant, Cholera toxin subunit A1 (CTA1) for the construction and we display PEDSe multi-epitope with CTA1 on the surface of Lactobacillus casei (pgsA-CTA1-PEDSe/L. casei) using the pgsA surface display system. Oral or intranasal inoculations of pgsA-CTA1-PEDSe/L. casei into mice induced more potent mucosal, humoral and cell-mediated immune responses. Additionally, we checked the long lasting immune responses to produce neutralizing antibodies against PEDV infection. Thus, the recombinant L. casei (pgsA-CTA1-PEDSe/L. casei) could be a promising mucosal vaccine candidate against currently circulating PEDV. [The Ministry for Food, Agriculture, Forestry and Fisheries, Republic of Korea (Grant no. 316043-3)]

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Downregulation of RIG-I Mediated Type I IFN Signaling by Foot-and-Mouth Disease Virus 2B

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Foot and mouth disease virus (FMDV) genome encodes several viral proteins which can enforce multiple strategies to escape host defense mechanisms. Such functions basically target on impairing the host innate immune system including Type-I interferon (IFN) pathway. Here, we demonstrate a novel function of FMDV 2B which downregulate the Type-I interferon signaling by interfering the RIG-I mediated signal transduction. In the IFN-related luciferase reporter assay, FMDV 2B induced the down-regulation of IFN or ISRE promoter activity. In the virus replication study, FMDV 2B overexpressed Raw 264.7 cells showed a higher rate of diverse RNA virus replication in comparison to normal raw cell and exhibit a minimal secretion of type I interferon and also inhibit the induction response of IFN-related or interferon stimulatory genes. As a mechanism, we observed RIG-I undergo proteasomal degradation upon FMDV 2B expression by K-48-linked polyubiquitination. These results suggest that FMDV 2B negatively regulates the Type I interferon pathway and advances the pathogenesis and lead for severe FMD infections. [The Ministry for Food, Agriculture, Forestry and Fisheries, Republic of Korea (Grant no. 315044031)]

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Inhibitory Effects of Bee Venom and Its Components against Viruses in vitro and in vivo

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Bee venom (BV) from honey bee (Apis Melifera L.) contains at least 18 pharmacologically active components including melittin (MLT), phospholipase A_2 (PLA_2) and apamin etc. BV is safe for human treatments dose dependently and proven to possess different healing properties including antibacterial and antiparasitidal properties. Nevertheless, antiviral properties of BV have not well investigated. Hence, we identified the potential antiviral properties of BV and its component against a broad panel of viruses. Co-incubation of non-cytotoxic amounts of BV and MLT significantly inhibited the replication of enveloped viruses such as Influenza PR8, VSV, RSV *and* HSV. Additionally, BV and MLT also inhibited the replication of non-enveloped viruses such as *EV-71 and Coxsackie-H3. Such antiviral properties were mainly determined by* virucidal mechanism. In vivo study, MLT protected mice which were challenged with lethal doses of pathogenic influenza A H1N1 viruses. *Therefore,* these results provides the evidence that BV and MLT could be a potential source as a promising antiviral agent, especially to develop as a broad spectrum antiviral agent. [The Small and Medium Business Administration, Republic of Korea (Grant no. S2165234)].

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Roles of FAF1 in NADPH Oxidase Activation in Response to TLR2 Stimulation

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FAF1 is known as a component of the death-inducing signaling complex in Fas-mediated apoptosis and regulates NF-κB activity as well as ubiquitination and proteosomal degradation. However, biological roles of FAF1 are still poorly understand in antibacterial immunity. Here we checked whether FAF1 modulate antibacterial immunity. Overexpression of FAF1 in Raw264.7 enhances the production of inflammatory cytokines and ROS upon Listeria monocytogenes infection or TLR ligand treatment. Controversially, knockdown of FAF1 in raw 264.7, BMDM derived from $FAF1^{gt/gt}$ mice shows lower level of pro-inflammatory cytokines and ROS. Consistent with in vitro data, $FAF1^{gt/gt}$ mice exhibited susceptibility upon infection of Listeria monocytogenes. Bacterial titer of spleen from $FAF1^{gt/gt}$ mice is higher than that of spleen from WT mice. Reversely, cytokines level of serum from $FAF1^{gt/gt}$ mice is lower than those of serum from WT mice. As a molecular mechanism, FAF1 binds to p67phox, which is component of NADPH oxidase complex and enhanced p67phox stability. These findings suggest that FAF1 positively regulates NADPH oxidase activation and NF-κB signaling pathway by interaction with p67phox upon bacterial infection or TLR stimulation. [The National Research Foundation of Korea (Grant no. 2015020957)]

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Clostridium Butyricum S45-5 (CBS45-5) Has an Antiviral Activity in vitro and in vivo

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This study aimed to investigate the potential antiviral activity of Clostridium species using in vitro and in vivo model. For this purpose, we tested antiviral properties with 122 strains of Clostridium species isolated from infant fecal samples and selected the Clostridium butyricum S45-5 (CBS45-5). Pretreatment of an effective dose CBS45-5 significantly reduced the replication of diverse RNA or DNA viruses both in immune and epithelial cells by establishing the antiviral state, by production of Interferons or proinflammatory cytokines. Moreover, oral administration of CBS45-5 for 2 weeks exhibited prophylactic effects in BALB/c mice against lethal doses of highly pathogenic influenza A subtypes (H1N1, H5N2 or H7N3). CBS45-5 inoculated mice displayed reduced lung viral titers and faster weight recovery. Further, CBS45-5 inoculated mice showed increase levels of IgA, IL-6, IFN-λ and IFN-β secretion in the serum, SIF and BALF. These results suggested that CBS45-5 can induce the cellular antiviral state in vitro and in vivo. Consequently, CBS45-5 could be a potential source of promising probiotic or used to design other antiviral/anti-influenza agents. [The Technology Innovation Program, 10046418 (TGM0721311) of the Ministry of Trade, Industry & Energy].

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Dense Granule Protein 7 of *Toxoplasma gondii* Has the Antiviral Activity in vitro and in vivo by Inducing Antiviral State

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Dense Granule Protein-7 (GRA-7) which well-studied as a vaccine candidate, is an excretory protein of *T. gondii*. However, the roles of GRA-7 against virus infection are not completely investigated. Here, we identified the antiviral properties of GRA-7 *in vitro* and *in vivo* against diverse viruses. Non-toxic amounts of GRA-7 antigen significantly inhibited the replication of Influenza PR8, VSV, and HSV on RAW264.7 cells. GRA-7 also displayed antiviral activity in epithelial (HEK293T and HELA) cells against VSV, PR8, HSV, and Adenoviruses. For the detail explanation of these antiviral activities, we checked the induction of type I interferon and pro-inflammatory cytokines both in mRNA and cytokine levels upon treatment of GRA-7 *in vitro*. Moreover, intra-nasal inoculation of GRA-7 protected BALB/c mice from lethal infection with Influenza A virus (H1N1). Furthermore, intra-nasal administration of GRA-7 in BALB/c mice showed lower lung viral titer, when challenge with RSV. Therefore, these results clearly showed that GRA-7 has an antiviral activity both *in vitro* and *in vivo* suggesting the potential use of GRA-7 antigen as a candidate drug for prophylactic purposes. [The Ministry for Food, Agriculture, Forestry and Fisheries (Grant No. 315044031, 316043-3)]

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NQO1 Negatively Regulates the Type I Interferon Signaling against Virus Infection

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NQO1 (NAD(P)H:quinone oxidoreductase 1) is a well-known antioxidant protein which has enzymatic activity related to chemoprotection of ROS induced damages. Although NQO1 is involved in several part of immune response or cancer prevention, its role in viral infection has never been investigated. In this study, we showed the role of NQOI as a negative regulator of antiviral immune response. Knockdown of FAF1 in several cell lines or knockout in BMDM cells derived from NQOI-KO mice markedly enhances resistance to RNA virus infection and shows higher level of inflammatory cytokines and type I interferon production. Controversially, Overexpression of NQOI in various cell types reduced the production of inflammatory cytokines and Type I interferons upon virus infection. Consistent with in vitro results, upon infection of Vesicular Stomatitis virus (Indiana strain), NQOI-KO mice exhibited marked resistance to virus infection and increased level of IFN-β and IL-6 from serum. These findings suggest that NQOI is a negative regulator that modulates the NF-κB and Type I interferon signaling pathway against virus infection. [The National Research Foundation of Korea (Grant no. 2015020957)]

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Released Tryptophanyl-tRNA-Synthetase Functions as a Cytokine on Virus Infection

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Tryptophanyl-tRNA Synthetase (WRS) is one of the aminoacyl tRNA synthetase that possess non-canonical functions. Full-length WRS is released during bacteria infection as an important factor priming toll-like receptor 4 (TLR4) - myeloid differentiation factor 2 (MD2) complex to elicit innate immune response. However, role of full-length WRS in virus infection remains unknown. Here, we show that full-length WRS is secreted by immune cells in the early time of virus infection and functions as an antiviral cytokine. Treatment of recombinant WRS promotes production of inflammatory cytokines and type 1 interferons, and curtails virus replication in THP-1 and Raw264.7 cells. However, we could not observe the similar effects in epithelial cells, TLR4-/- BMDMs, and MD2-/- BMDMs. In vivo, intravenous and intranasal administration of recombinant WRS provoke innate immunity and block vesicular stomatitis virus replication. These findings suggest that secreted full-length WRS has a non-canonical function in activating and mediating innate immune responses to virus infection as well as to bacterial infection. [The Ministry for Food, Agriculture, Forestry and Fisheries (Grant No. 315044031, 316043-3)]