

21 January 2010

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Chem-Bio News – S&T Edition

1. IMMOBILIZATION OF ACETYLCHOLINEESTERASE-CHOLINE OXIDASE ON A GOLD-PLATINUM BIMETALLIC NANOPARTICLES MODIFIED GLASSY CARBON ELECTRODE FOR THE SENSITIVE DETECTION OF ORGANOPHOSPHATE PESTICIDES, CARBAMATES AND NERVE AGENTS:

"Paraoxon ethyl, satin [sic – sarin], and aldicarb could be detected up to 150-200 nM, 40-50 nM, and 40-60 mc M respectively at 30-40% inhibition level of AChE enzyme and followed linearity in wide range concentration."

2. A MONOCLONAL IMMUNOGLOBULIN G ANTIBODY DIRECTED AGAINST AN IMMUNODOMINANT LINEAR EPITOPE ON THE RICIN A CHAIN CONFERS SYSTEMIC AND MUCOSAL IMMUNITY TO RICIN:

"These data are important in terms of vaccine development, since they firmly establish that preexisting serum antibodies directed against residues 161 to 175 on RTA are sufficient to confer both systemic and mucosal immunity to ricin."

3. ENERGETICS AND DYNAMICS OF THE REACTIONS OF O(P-3) WITH DIMETHYL METHYLPHOSPHONATE AND SARIN:

"The reaction barriers, reaction enthalpies, transition state Structures, and excitation functions are generally similar for DMMP and sarin, with some moderate differences for methyl elimination energetics, which indicates DMMP will likely be a good substitute for sarin in many O(P-3) chemical investigations."

4. CENTRAL ORIGIN OF THE ANTINOCICEPTIVE ACTION OF BOTULINUM TOXIN TYPE A:

"The results demonstrate the necessity of retrograde axonal transport and involvement of the central nervous system for the antinociceptive activity of BTX-A."

5. DEVELOPMENT OF IMMUNOGLOBULIN M MEMORY TO BOTH A T-CELL-INDEPENDENT AND A T-CELL-DEPENDENT ANTIGEN FOLLOWING INFECTION WITH VIBRIO CHOLERAE O1 IN BANGLADESH:

"The IgM memory response to CTB was negatively correlated with the IgG plasma antibody response to CTB, and there was a trend toward negative correlation between the IgM memory and IgA plasma antibody responses to LPS."

6. ST-246 INHIBITS IN VIVO POXVIRUS DISSEMINATION, VIRUS SHEDDING, AND

SYSTEMIC DISEASE MANIFESTATION: *"Taken together, these data suggest that ST-246 would play a dual protective role if used during a smallpox bioterrorist attack. First, ST-246 would provide therapeutic benefit by reducing the disease burden and lethality in infected individuals."*

7. THE VIBRIO CHOLERAE QUORUM-SENSING AUTOINDUCER CAI-1: ANALYSIS OF THE BIOSYNTHETIC ENZYME CQSA:

"Thus, both CAI-1 and amino-CAI-1 have potential as lead molecules in the development of an anticholera treatment."

8. DOMAIN 4 OF THE ANTHRAX PROTECTIVE ANTIGEN MAINTAINS STRUCTURE AND BINDING TO THE HOST RECEPTOR CMG2 AT LOW PH:

"Our results suggest that receptor release is not driven solely by a pH-induced unfolding of domain 4."

9. MOLECULAR EVIDENCE FAVOURING STEP-WISE EVOLUTION OF MOZAMBIQUE VIBRIO CHOLERAE O1 EL TOR HYBRID STRAIN:

"Since Indian hybrid El Tor strains carry either free RS1 or pre-CTX prophage in their large chromosomes, it is possible that the Mozambique hybrid El Tor strain has evolved from these progenitor strains by step-wise deletion of CTX genetic elements from their large chromosomes."

10. DESIGN OF AEROSOL SAMPLER TO REMOVE RADON AND THORON PROGENY

INTERFERENCE FROM AEROSOL SAMPLES FOR NUCLEAR EXPLOSION MONITORING: *"The*

MOUDI [Micro-Orifice Uniform-Deposit Impactor] was also used to verify the naturally occurring radioactivity distribution using Pb-212 gamma spectra."

11. BACILLUS ANTHRACIS CAPSULE ACTIVATES CASPASE-1 AND INDUCES INTERLEUKIN-1BETA RELEASE FROM DIFFERENTIATED THP-1 AND HUMAN MONOCYTE-DERIVED

DENDRITIC CELLS: "These results demonstrate that *B. anthracis* PGA elicits IL-1beta production through activation of ICE in PMA-differentiated THP-1 cells and hMoDCs, suggesting the potential for PGA as a therapeutic target for anthrax."

12. MARBURG VIRUS EVADES INTERFERON RESPONSES BY A MECHANISM DISTINCT FROM EBOLA VIRUS:

"This study shows that MARV inhibits IFN signaling by a mechanism different from that employed by the related EBOV. It identifies a novel function for the MARV VP40 protein and suggests that MARV may globally inhibit Jak1-dependent cytokine signaling."

CB Daily Report

Chem-Bio News

IMMOBILIZATION OF ACETYLCHOLINEESTERASE-CHOLINE OXIDASE ON A GOLD-PLATINUM BIMETALLIC NANOPARTICLES MODIFIED GLASSY CARBON ELECTRODE FOR THE SENSITIVE DETECTION OF ORGANOPHOSPHATE PESTICIDES, CARBAMATES AND NERVE AGENTS

Journal of Technology & Science
January 17, 2010

"A novel, highly sensitive amperometric biosensor, based on electrode position of gold-platinum bimetallic nanoparticles onto 3-aminopropyltriethoxy silane modified glassy carbon electrode for the detection of paraoxon ethyl, aldicarb, and sarin has been developed. The biosensor consists of acetylcholinesterase (AChE)/choline oxidase (ChOx) immobilized by cross-linking with glutaraldehyde on a modified electrode."

"The properties of nanoparticles modified electrodes are characterized by scanning electron microscopy (SEM), energy dispersive X-ray (EDX), cyclic voltammograms (CVs) and electrochemical impedance spectroscopy (EIS). The synergistic action of Au and Pt nanoparticles showed excellent electrocatalytic activity with low applied potential for the detection of hydrogen peroxide (H₂O₂). The IC₅₀ and inhibition rate constant (K_i) values were determined for the inhibitors using immobilized enzymes on modified electrode and the data were compared by spectrophotometric determination of these kinetic parameters using free enzymes in solution."

"Paraoxon ethyl, sarin [sic - sarin], and aldicarb could be detected up to 150-200 nM, 40-50 nM, and 40-60 mc M respectively at 30-40% inhibition level of AChE enzyme and followed linearity in wide range concentration."

The full article can be found at: (S. Upadhyay, et. al., "Immobilization of acetylcholinesterase-choline oxidase on a gold-platinum bimetallic nanoparticles modified glassy carbon electrode for the sensitive detection of organophosphate pesticides, carbamates and nerve agents" *Biosensors & Bioelectronics*, 2009;25(4):832-838). Link not available.

[Return to Top](#)

A MONOCLONAL IMMUNOGLOBULIN G ANTIBODY DIRECTED AGAINST AN IMMUNODOMINANT LINEAR EPITOPE ON THE RICIN A CHAIN CONFERS SYSTEMIC AND MUCOSAL IMMUNITY TO RICIN

Drug Week
January 15, 2010

"A monoclonal immunoglobulin G antibody directed against an immunodominant linear epitope on the ricin A chain confers systemic and mucosal immunity to ricin,' are detailed in a study published in *Infection and Immunity*. According to recent research from the United States, "Due to the potential use of ricin and other fast-acting toxins as agents of bioterrorism, there is an urgent need for the development of safe and effective antitoxin vaccines. A candidate ricin subunit vaccine (RiVax) consisting of a recombinant attenuated enzymatic A chain (RTA) has been shown to elicit protective antitoxin antibodies in mice and rabbits and is currently being tested in phase I human clinical trials."

"However, evaluation of the efficacy of this vaccine for humans is difficult for a number of reasons, including the fact that the key neutralizing B-cell epitopes on RTA have not been fully defined. Castelletti and colleagues (*Clin. Exp. Immunol.* 136:365-372, 2004) recently identified a linear epitope on RTA, spanning residues L161 to I175, as a primary target of serum antibodies derived from humans who had been treated with ricin immunotoxin. While affinity-purified polyclonal IgG antibodies against this region of RTA were capable of neutralizing ricin *in vitro*, their capacity to confer protection against ricin challenge *in vivo* was not determined. In this report, we describe the production and characterization of GD12, a murine monoclonal IgG1 antibody specifically directed against residues 163 to 174 (TLARSFIIICIQM) of RTA. GD12 bound ricin holotoxin with high affinity ($K(D)$ [dissociation constant], 2.9×10^{-9} M) and neutralized it with a 50% inhibitory concentration of approximately 0.25 microg/ml, as determined by a Vero cell-based cytotoxicity assay. Passive administration of GD12 was sufficient to protect BALB/c mice against intraperitoneal and intragastric ricin challenges. These data are important in terms of vaccine development, since they firmly establish that preexisting serum antibodies directed against residues 161 to 175 on RTA are sufficient to confer both systemic and mucosal immunity to ricin."

"The potential of GD12 to serve as a therapeutic following ricin challenge was not explored in this study."

The full article can be found at: (L.M. Neal, et. al., "A monoclonal immunoglobulin G antibody directed against an immunodominant linear epitope on the ricin A chain confers systemic and mucosal immunity to ricin". *Infection and Immunity*, 2010;78(1):552-61). Link not available.

[Return to Top](#)

ENERGETICS AND DYNAMICS OF THE REACTIONS OF O(P-3) WITH DIMETHYL METHYLPHOSPHONATE AND SARIN

News of Science

January 17, 2010

"Electronic Structure and molecular dynamics calculations were performed on the reaction systems O(P-3) + sarin and O(P-3) + dimethyl methylphosphonate (DMMP), a sarin Simulant. Transition state geometries, energies, and heats of reaction for the major reaction pathways were determined at several levels of theory, including AM1, B3LYP/6-311+G(d,p), and CBS-QB3."

"The major reaction pathways for both systems are similar and include H-atom abstraction, H-atom elimination, and methyl elimination, in rough order from low to high energy. The H-atom abstraction channels have fairly low barriers (similar to 10 kcal mol⁻¹) and are close to thermoneutral, while the other channels have relatively high energy barriers (>40 kcal mol⁻¹) and a wide range of reaction enthalpies. We have also found a two-step pathway leading to methyl elimination through O-atom attack on the phosphorus atom for DMMP and sarin. For sarin, the two-step methyl elimination pathway is significantly lower in energy than the single-step pathway. We also present results of O(P-3) + sarin and O(P-3) + DMMP reaction cross sections over a broad range of collision energies (2-10 kms⁻¹ collision velocities) obtained using the direct dynamics method with an AM1 semiempirical potential. These excitation functions are intended as an approximate guide to future hyperthermal measurements, which to our knowledge have not yet examined either of these systems>"

"The reaction barriers, reaction enthalpies, transition state Structures, and excitation functions are generally similar for DMMP and sarin, with some moderate differences for methyl elimination energetics, which indicates DMMP will likely be a good substitute for sarin in many O(P-3) chemical investigations."

The full article can be found at: (P.F. Conforti, et. al., "Energetics and Dynamics of the Reactions of O(P-3) with Dimethyl Methylphosphonate and Sarin. Journal of Physical Chemistry a, 2009;113(49):13752-13761). Link not available.

[Return to Top](#)

CENTRAL ORIGIN OF THE ANTINOCICEPTIVE ACTION OF BOTULINUM TOXIN TYPE A

Drug Week

January 22, 2010

"Here we provide behavioural evidence for an axonal transport and the central origin of the antinociceptive effect of botulinum toxin type A (M-A). In rats we investigated the effectiveness of BTX-A on "mirror pain" induced by unilateral repeated intramuscular acidic saline injections (pH 4.0)."

"Since experimental evidence suggest that bilateral pain induced by acidic saline is of central origin, peripheral application of BTX-A should have no effect on this type of pain. However, here we demonstrated that the unilateral subcutaneous BTX-A (5 U/kg) application diminished pain on the ipsilateral, and on the contralateral side too. When injected into the proximal part of a distally cut sciatic nerve, BTX-A still reduced pain on the contralateral side. Colchicine, an axonal transport blocker, when injected into the ipsilateral sciatic nerve, prevented the effect of the peripheral BTX-A injection on both sides. Additionally, when BTX-A (1 U/kg) was applied intrathecally in the lumbar cerebrospinal fluid, the bilateral hyperalgesia was also reduced."

"The results demonstrate the necessity of retrograde axonal transport and involvement of the central nervous system for the antinociceptive activity of BTX-A."

The full article can be found at: (L. Bachrojecky, et. al., "Central origin of the antinociceptive action of botulinum toxin type A". Pharmacology Biochemistry and Behavior, 2009;94(2):234-238). Link not available.

[Return to Top](#)

DEVELOPMENT OF IMMUNOGLOBULIN M MEMORY TO BOTH A T-CELL-INDEPENDENT AND A T-CELL-DEPENDENT ANTIGEN FOLLOWING INFECTION WITH VIBRIO CHOLERAE O1 IN BANGLADESH

Health & Medicine Week

January 11, 2010

"Development of memory B cells of the immunoglobulin G (IgG) and IgA isotypes to V. cholerae O1 antigens, including serotype-specific lipopolysaccharide (LPS) and the B subunit of cholera toxin (CTB), after cholera infection has been demonstrated. Memory B cells of the IgM isotype may play a role in long-term protection, particularly against T-cell-independent antigens, but IgM memory has not been studied in V. cholerae O1 infection. Therefore, we assayed acute-and convalescent-phase blood samples from cholera patients for the presence of memory B cells that produce cholera antigen-specific IgM antibody upon polyclonal stimulation in in vitro culture. We also examined the development of serological and antibody-secreting cell responses following infection. Subjects developed significant IgM memory responses by day 30 after infection, both to the T-cell-independent antigen LPS and to the T-cell-dependent antigen CTB. No significant corresponding elevations in plasma IgM antibodies or circulating IgM antibody-secreting cells to CTB were detected. In 17 subjects followed to day 90 after infection, significant persistence of elevated IgM memory responses was not observed. The IgM memory response to CTB was negatively correlated with the IgG plasma antibody response to CTB, and there was a trend toward negative correlation between the IgM memory and IgA plasma antibody responses to LPS."

"We did not observe an association between the IgM memory response to LPS and the vibriocidal titer."

The full article can be found at: (E.A. Kendall, et. al., "Development of immunoglobulin M memory to both a T-cell-independent and a T-cell-dependent antigen following Infection with *Vibrio cholerae* O1 in Bangladesh". *Infection and Immunity*, 2010;78(1):253-9). Link not available.

[Return to Top](#)

ST-246 INHIBITS IN VIVO POXVIRUS DISSEMINATION, VIRUS SHEDDING, AND SYSTEMIC DISEASE MANIFESTATION

Virus Weekly

January 19, 2010

"Here, we show that ST-246 treatment not only results in the significant inhibition of vaccinia virus dissemination from the site of inoculation to distal organs, such as the spleen and liver, but also reduces the viral load in organs targeted by the dissemination. In mice intranasally infected with vaccinia virus, virus shedding from the nasal and lung mucosa was significantly lower (similar to 22- and 528-fold, respectively) upon ST-246 treatment. Consequently, virus dissemination from the nasal site of replication to the lung also was dramatically reduced, as evidenced by a 179-fold difference in virus levels in nasal versus bronchoalveolar lavage. Furthermore, in ACAM2000-immunized mice, vaccination site swabs showed that ST-246 treatment results in a major (similar to 3,900-fold by day 21) reduction in virus detected at the outside surfaces of lesions. Taken together, these data suggest that ST-246 would play a dual protective role if used during a smallpox bioterrorist attack. First, ST-246 would provide therapeutic benefit by reducing the disease burden and lethality in infected individuals."

"Second, by reducing virus shedding from those prophylactically immunized with a smallpox vaccine or harboring variola virus infection, ST-246 could reduce the risk of virus transmission to susceptible contacts."

The full article can be found at: (A. Berhanu, et. al., "ST-246 Inhibits In Vivo Poxvirus Dissemination, Virus Shedding, and Systemic Disease Manifestation". *Antimicrobial Agents and Chemotherapy*, 2009;53(12):4999-5009). Link not available.

[Return to Top](#)

THE VIBRIO CHOLERAEE QUORUM-SENSING AUTOINDUCER CAI-1: ANALYSIS OF THE BIOSYNTHETIC ENZYME CQS A

Malaria Weekly

January 18, 2010

"*Vibrio cholerae*, the bacterium that causes the disease cholera, controls virulence factor production and biofilm development in response to two extracellular quorum-sensing molecules, called autoinducers. The strongest autoinducer, called CAI-1 (for cholera autoinducer-1), was previously identified as (S)-3-hydroxytridecan-4-one."

"Biosynthesis of CAI-1 requires the enzyme CqsA. Here, we determine the CqsA reaction mechanism, identify the CqsA substrates as (S)-2-aminobutyrate and decanoyl coenzyme A, and demonstrate that the product of the reaction is 3-aminotridecan-4-one, dubbed amino-CAI-1. CqsA produces amino-CAI-1 by a pyridoxal phosphate-dependent acyl-CoA transferase reaction. Amino-CAI-1 is converted to CAI-1 in a subsequent step via a CqsA-independent mechanism. Consistent with this, we find cells release ≥ 100 times more CAI-1 than amino-CAI-1. Nonetheless, *V. cholerae* responds to amino-CAI-1 as well as CAI-1, whereas other CAI-1 variants do not elicit a quorum-sensing response."

"Thus, both CAI-1 and amino-CAI-1 have potential as lead molecules in the development of an anticholera treatment."

The full article can be found at: (R.C. Kelly, et. al., "The *Vibrio cholerae* quorum-sensing autoinducer CAI-1: analysis of the biosynthetic enzyme CqsA". *Nature Chemical Biology*, 2009;5(12):891-895). Link not available.

[Return to Top](#)

DOMAIN 4 OF THE ANTHRAX PROTECTIVE ANTIGEN MAINTAINS STRUCTURE AND BINDING TO THE HOST RECEPTOR CMG2 AT LOW PH

Medical Letter on the CDC & FDA

January 10, 2010

"Domain 4 of the anthrax protective antigen (PA) plays a key role in cellular receptor recognition as well as in pH-dependent pore formation. We present here the 1.95 angstrom crystal structure of domain 4, which adopts a fold that is identical to that observed in the full-length protein."

"We have also investigated the structural properties of the isolated domain 4 as a function of pH, as well as the pH-dependence on binding to the von Willebrand factor A domain of capillary morphogenesis protein 2 (CMG2). Our results provide evidence that the isolated domain 4 maintains structure and interactions with CMG2 at pH 5, a pH that is known to cause release of the receptor on conversion of the heptameric prepore (PA(63))(7) to a membrane-spanning pore."

"Our results suggest that receptor release is not driven solely by a pH-induced unfolding of domain 4."

The full article can be found at: (A.S. Williams, et. al., "Domain 4 of the anthrax protective antigen maintains structure and binding to the host receptor CMG2 at low pH". Protein Science, 2009;18(11):2277-2286). Link not available.

[Return to Top](#)

MOLECULAR EVIDENCE FAVOURING STEP-WISE EVOLUTION OF MOZAMBIQUE VIBRIO CHOLERAЕ O1 EL TOR HYBRID STRAIN

Health Risk Factor Week

January 12, 2010

'Molecular evidence favouring step-wise evolution of Mozambique Vibrio cholerae O1 El Tor hybrid strain,' are discussed in a new report. "The ctxAB operon, encoding cholera toxin (CT) in Vibrio cholerae, is carried by the genome of a filamentous phage, CTXPhi. Usually, specific CTXPhi infect each of the two important biotypes, classical and El Tor, of epidemic V. cholerae strains belonging to serogroup O1, and are called CTX(class)Phi and CTX(ET)Phi, respectively."

"However, an unusual hybrid El Tor strain carrying CTX(class)Phi caused the cholera epidemic in Mozambique in 2004. To understand the evolution of that strain, we have further analysed some representative hybrid El Tor strains isolated in Kolkata, India, in 1992, and the results indicate that both the Mozambique and the Indian strains are infected with a unique CTX(class)Phi having only four copies of the tandem heptamer repeat sequence 5'-TTTTGAT-3' present in the ctxAB promoter (P(ctxAB)) region, like in CTX(ET)Phi. Usually, the P(ctxAB) of the classical biotype contains seven to eight copies of such sequences. However, sequence analyses of the P(ctxAB) regions of several classical strains indicated that the copy number of heptamer repeat sequences might vary from four to eight copies, which was previously unknown. Since the hybrid strains analysed in this study carry four copies of the heptamer sequences, it may thus serve as a marker to trace the strain in future. Interestingly, while the Mozambique strain is devoid of an El Tor-specific free RS1 element or pre-CTX prophage, the Indian hybrid strains carry such elements. The free RS1 has been mapped, cloned and sequenced. As in pre-CTX and CTX prophages, multiple copies of free RS1 elements were found to be integrated in tandem in the large chromosomal dif site."

"Since Indian hybrid El Tor strains carry either free RS1 or pre-CTX prophage in their large chromosomes, it is possible that the Mozambique hybrid El Tor strain has evolved from these progenitor strains by step-wise deletion of CTX genetic elements from their large chromosomes."

The full article can be found at: (K. Halder, et. al., "Molecular evidence favouring step-wise evolution of

Mozambique *Vibrio cholerae* O1 El Tor hybrid strain". *Microbiology*, 2010;156(Pt 1):99-107). Link not available.

[Return to Top](#)

DESIGN OF AEROSOL SAMPLER TO REMOVE RADON AND THORON PROGENY INTERFERENCE FROM AEROSOL SAMPLES FOR NUCLEAR EXPLOSION MONITORING

Science Letter

January 12, 2010

"A Nuclear Explosion Monitoring Inertial Impactor (NEMII) system was developed to physically separate naturally occurring radionuclides from those produced in nuclear weapons explosions. Studies show that aerosols containing natural activity have an aerodynamic diameter in the range of 0.1-1.0 μm . It has been established that atmospheric nuclear explosions produce radioactive aerosols with aerodynamic diameters $< 0.1 \mu\text{m}$ and surface explosion produce a bimodal distribution of radioactive particles with aerodynamic diameters both $> 1.0 \mu\text{m}$ and $< 0.1 \mu\text{m}$. A high volume (66 $\text{m}^3 \text{h}^{-1}$) impactor was designed to separate the particles into three size distributions: aerosols with aerodynamic diameters $> 1.0 \mu\text{m}$, between 0.1 and 1.0 μm , and smaller than 0.1 μm . Calculations based on previous work for high-volume impactors were completed to obtain the impactor geometry that yields the desired cutoff values."

"The components of the aerosol impactor were manufactured or obtained and then assembled. In addition, a submicrometer aerosol generation system was assembled to benchmark the NEMII system against a commercial Micro-Orifice Uniform-Deposit Impactor (MOUDI)."

"The MOUDI was also used to verify the naturally occurring radioactivity distribution using Pb-212 gamma spectra."

The full article can be found at: (J. Weaver, et. al., "Design of aerosol sampler to remove radon and thoron progeny interference from aerosol samples for nuclear explosion monitoring". *Journal of Radioanalytical and Nuclear Chemistry*, 2009;282(3):687-692). Link not available.

[Return to Top](#)

BACILLUS ANTHRACIS CAPSULE ACTIVATES CASPASE-1 AND INDUCES INTERLEUKIN-1BETA RELEASE FROM DIFFERENTIATED THP-1 AND HUMAN MONOCYTE-DERIVED DENDRITIC CELLS

Drug Week

January 15, 2010

"Bacillus anthracis capsule activates caspase-1 and induces interleukin-1beta release from differentiated THP-1 and human monocyte-derived dendritic cells,' is the subject of a report. "The poly-gamma-d-glutamic acid (PGA) capsule is one of the major virulence factors of *Bacillus anthracis*, which causes a highly lethal infection. The antiphagocytic PGA capsule disguises the bacilli from immune surveillance and allows unimpeded growth of bacilli in the host."

"Recently, efforts have been made to include PGA as a component of anthrax vaccine; however, the innate immune response of PGA itself has been poorly investigated. In this study, we characterized the innate immune response elicited by PGA in the human monocytic cell line THP-1, which was differentiated into macrophages with phorbol 12-myristate 13-acetate (PMA) and human monocyte-derived dendritic cells (hMoDCs). PGA capsules were isolated from the culture supernatant of either the pXO1-cured strain of *B. anthracis* H9401 or *B. licheniformis* ATCC 9945a. PGA treatment of differentiated THP-1 cells and hMoDCs led to the specific extracellular release of interleukin-1beta (IL-1beta) in a dose-dependent manner. Evaluation of IL-1beta processing by Western blotting revealed that cleaved IL-1beta increased in THP-1 cells and hMoDCs after PGA treatment. Enhanced processing of IL-1beta directly correlated with increased activation of its upstream regulator, caspase-1, also known as IL-1beta-converting enzyme (ICE). The extracellular release of IL-1beta in response to PGA was ICE dependent, since the administration of an ICE inhibitor prior to PGA treatment blocked

induction of IL-1beta."

"These results demonstrate that B. anthracis PGA elicits IL-1beta production through activation of ICE in PMA-differentiated THP-1 cells and hMoDCs, suggesting the potential for PGA as a therapeutic target for anthrax."

The full article can be found at: (M.H. Cho, et. al., "Bacillus anthracis capsule activates caspase-1 and induces interleukin-1beta release from differentiated THP-1 and human monocyte-derived dendritic cells". Infection and Immunity, 2010;78(1):387-92). Link not available.

[Return to Top](#)

MARBURG VIRUS EVADES INTERFERON RESPONSES BY A MECHANISM DISTINCT FROM EBOLA VIRUS

By Charalampos Valmas, Melanie N. Grosch, Michael Schümann, Judith Olejnik, Osvaldo Martinez, Sonja M. Best, Verena Krähling, Christopher F. Basler, Elke Mühlberger

PloS Pathogens

January 15, 2010

"Previous studies have demonstrated that Marburg viruses (MARV) and Ebola viruses (EBOV) inhibit interferon (IFN)- α/β signaling but utilize different mechanisms. EBOV inhibits IFN signaling via its VP24 protein which blocks the nuclear accumulation of tyrosine phosphorylated STAT1. In contrast, MARV infection inhibits IFN α/β induced tyrosine phosphorylation of STAT1 and STAT2. MARV infection is now demonstrated to inhibit not only IFN α/β but also IFN γ -induced STAT phosphorylation and to inhibit the IFN α/β and IFN γ -induced tyrosine phosphorylation of upstream Janus (Jak) family kinases. Surprisingly, the MARV matrix protein VP40, not the MARV VP24 protein, has been identified to antagonize Jak and STAT tyrosine phosphorylation, to inhibit IFN α/β or IFN γ -induced gene expression and to inhibit the induction of an antiviral state by IFN α/β . Global loss of STAT and Jak tyrosine phosphorylation in response to both IFN α/β and IFN γ is reminiscent of the phenotype seen in Jak1-null cells. Consistent with this model, MARV infection and MARV VP40 expression also inhibit the Jak1-dependent, IL-6-induced tyrosine phosphorylation of STAT1 and STAT3. Finally, expression of MARV VP40 is able to prevent the tyrosine phosphorylation of Jak1, STAT1, STAT2 or STAT3 which occurs following over-expression of the Jak1 kinase. In contrast, MARV VP40 does not detectably inhibit the tyrosine phosphorylation of STAT2 or Tyk2 when Tyk2 is over-expressed. Mutation of the VP40 late domain, essential for efficient VP40 budding, has no detectable impact on inhibition of IFN signaling. This study shows that MARV inhibits IFN signaling by a mechanism different from that employed by the related EBOV. It identifies a novel function for the MARV VP40 protein and suggests that MARV may globally inhibit Jak1-dependent cytokine signaling."

The full article can be found at: <http://www.plospathogens.org/article/info%3Adoi%2F10.1371%2Fjournal.ppat.1000721;jsessionid=2E04B770C322AA1C15EEE6886A5C439F>

[Return to Top](#)

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