

15 January 2009

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Chem-Bio News– S&T Edition

1. CYTOTOXICITY OF ARSENIC-CONTAINING CHEMICAL WARFARE AGENT DEGRADATION PRODUCTS WITH METALLOMIC APPROACHES FOR METABOLITE ANALYSIS:

“Metabolic changes to the arsenic species were found, and interestingly, at the lowest uptake levels, cytotoxicities were generally higher for the chemical warfare agent degradation products than the inorganic arsenic species.”

2. STRESS-MEDIATED INCREASES IN SYSTEMIC AND LOCAL EPINEPHRINE IMPAIR SKIN WOUND HEALING: POTENTIAL NEW INDICATION FOR BETA BLOCKERS:

“Here we aimed to examine an alternate explanation that the stress-induced hormone epinephrine directly impairs keratinocyte motility and wound re-epithelialization.”

3. EFFECTS OF ANTHRAX LETHAL TOXIN ON HUMAN PRIMARY KERATINOCYTES:

“Our results might explain why the exposure of keratinocytes to LeTx results in the recruitment of neutrophils to cutaneous infection sites, while the expression of several inflammatory biomarkers is diminished.”

4. BIOREMEDIATION OF TRACE COBALT FROM SIMULATED SPENT DECONTAMINATION SOLUTIONS OF NUCLEAR POWER REACTORS USING E. COLI EXPRESSING NICOT GENES:

*“In the present study using engineered *Escherichia coli* expressing NiCoT genes from *Rhodospseudomonas palustris* CGA009 (RP) and *Novosphingobium aromaticivorans* F-199 (NA), we report a significant increase in the specific capacity for Co removal (12 μ g/g) in 1-h exposure to simulated effluent.”*

5. IMPACT OF THE EARTHWORM LUMBRICUS TERRESTRIS ON THE DEGRADATION OF FUSARIUM-INFECTED AND DEOXYNIVALENOL-CONTAMINATED WHEAT STRAW:

“Consequently, earthworm activity contributes to the elimination of potentially infectious plant material from the soil surface.”

6. FUNCTIONAL INTERACTIONS BETWEEN ANTHRAX TOXIN RECEPTORS AND THE WNT SIGNALLING PROTEIN LRP6:

“As the physiological role of ATRs is probably to interact with the extracellular matrix, our findings raise the interesting possibility that, through the ATR-LRP6 interaction, adhesion to the extracellular matrix could locally control Wnt signalling.”

CB Daily Report

Chem-Bio News

CYTOTOXICITY OF ARSENIC-CONTAINING CHEMICAL WARFARE AGENT DEGRADATION PRODUCTS WITH METALLOMIC APPROACHES FOR METABOLITE ANALYSIS

By Karolin K. Kroening, Morwena J. V. Solivio, Mónica García-López, Alvaro Puga and Joseph A. Caruso

Metallomics (British Royal Society of Chemistry)

January, 2009

"The arsenic metallome in African Green Monkey kidney cells is probed by measuring cytotoxicity, cellular arsenic uptake and speciation studies on arsenic-containing chemical warfare agent degradation products (CWDPs) during cell uptake. Inorganic arsenic compounds and methylated species also were studied during cell uptake as a means of providing cytotoxicity information relative to the CWDPs. The degradation products used were phenylarsine oxide (PAO), phenylarsonic acid (PAA), diphenylarsinic acid (DPAA), triphenylarsine (TPA) and triphenylarsine oxide (TPAO). These are the warfare agents primary degradation products. The parent warfare agents (red agents) are diphenylarsine chloride (DA or referred to as Clark I) and diphenylarsine cyanide (DC or Clark II), sternutator agents, sneezing gases able to cause bronchial irritation. Cytotoxicity levels and cellular uptake were compared to those of inorganic species: sodium arsenite, NaAsO_2 [As(III)], sodium arsenate Na_2HAsO_4 [As(V)] and methylated arsenicals such as dimethylarsinic acid (DMA) and methylarsonic acid (MMA). The arsenic uptake was demonstrated in an African Green Monkey kidney cell line, CV-1. Quantification of lactate dehydrogenase activity released from damaged/dying cells was then measured via an LDH assay. The purpose of this study is to initially investigate toxicity to cells when exposed to different arsenic containing compounds over different concentrations and time ranges from 3 h to 24 h. Furthermore, exposed cells were then analyzed for different arsenic species by high performance liquid chromatography (HPLC) with inductively coupled plasma mass spectrometry to isolate and speciate arsenic fractions followed by nanoLC electrospray ionization mass spectrometry to analyze the molecular level changes of the arsenic based degradation products in the kidney cells. Metabolic changes to the arsenic species were found, and interestingly, at the lowest uptake levels, cytotoxicities were generally higher for the chemical warfare agent degradation products than the inorganic arsenic species."

The full article can be found at: http://www.rsc.org/delivery/_ArticleLinking/DisplayHTMLArticleforfree.asp?JournalCode=MT&Year=2009&ManuscriptID=b816980b&Iss=1

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STRESS-MEDIATED INCREASES IN SYSTEMIC AND LOCAL EPINEPHRINE IMPAIR SKIN WOUND HEALING

By Raja K. Sivamani, Christine E. Pullar, Catherine G. Manabat-Hidalgo, David M. Rocke, Richard C. Carlsen, David G. Greenhalgh, R. Rivkah Isseroff
PLoS Medicine
January 12, 2009

"Stress, both acute and chronic, can impair cutaneous wound repair, which has previously been mechanistically ascribed to stress-induced elevations of cortisol. Here we aimed to examine an alternate explanation that the stress-induced hormone epinephrine directly impairs keratinocyte motility and wound re-epithelialization. Burn wounds are examined as a prototype of a high-stress, high-epinephrine, wound environment. Because keratinocytes express the β 2-adrenergic receptor (β 2AR), another study objective was to determine whether β 2AR antagonists could block epinephrine effects on healing and improve wound repair."

"Conclusions

This work demonstrates an alternate pathway by which stress can impair healing: by stress-induced elevation of epinephrine levels resulting in activation of the keratinocyte β 2AR and the impairment of cell motility and wound re-epithelialization. Furthermore, since the burn wound locally generates epinephrine in response to wounding, epinephrine levels are locally, as well as systemically, elevated, and wound healing is impacted by these dual mechanisms. Treatment with beta adrenergic antagonists significantly improves the rate of burn wound re-epithelialization. This work suggests that specific β 2AR antagonists may be apt, near-term translational therapeutic targets for enhancing burn wound healing, and may provide a novel, low-cost, safe approach to improving skin wound repair in the stressed individual."

The full article can be found at: <http://medicine.plosjournals.org/perlserv/?SESSID=3970db708876466e4603c36d06a3d204&request=get-document&doi=10.1371/journal.pmed.1000012>

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EFFECTS OF ANTHRAX LETHAL TOXIN ON HUMAN PRIMARY KERATINOCYTES

Medical Letter on the CDC & FDA

January 18, 2009

"To investigate the effects of anthrax lethal toxin (LeTx) on human primary keratinocytes. We show here that human primary keratinocytes are resistant to LeTx-triggered cytotoxicity."

"All but one of the MEKs (mitogen-activated protein kinase kinases) are cleaved within 3 h, and the cleavage of MEKs in keratinocytes leads to their subsequent proteasome-mediated degradation at different rates. Moreover, LeTx reduced the concentration of several cytokines except RANTES in culture. Our results indicate that primary keratinocytes are resistant to LeTx cytotoxicity, and MEK cleavage does not correlate with LeTx cytotoxicity. Although LeTx is considered as an anti-inflammatory agent, it upregulates RANTES. According to a current view, the action of LeTx results in downregulation of the inflammatory

response, as evidenced by diminished expression of several inflammatory biomarkers. Paradoxically, LeTx has been reported to attract neutrophils to cutaneous infection sites. This paper, which shows that RANTES, a chemoattractant for immune cells, is upregulated after exposure of keratinocytes to LeTx, although a number of other markers of the inflammatory response are downregulated."

"Our results might explain why the exposure of keratinocytes to LeTx results in the recruitment of neutrophils to cutaneous infection sites, while the expression of several inflammatory biomarkers is diminished."

The full article can be found at: (S.S. Kocer, et. al., "Effects of anthrax lethal toxin on human primary keratinocytes". Journal of Applied Microbiology, 2008;105(6):1756-1767). Link not available.

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BIOREMEDIATION OF TRACE COBALT FROM SIMULATED SPENT DECONTAMINATION SOLUTIONS OF NUCLEAR POWER REACTORS USING E. COLI EXPRESSING NiCoT GENES

Biotech Business Week

January 12, 2009

"Our earlier work using various fungi and bacteria, with the aim of nuclear waste volume reduction, realized up to 30% of Co removal with specific capacities calculated up to 1 mu g/g in 6-24 h. In the present study using engineered Escherichia coli expressing NiCoT genes from Rhodospseudomonas palustris CGA009 (RP) and Novosphingobium aromaticivorans F-199 (NA), we report a significant increase in the specific capacity for Co removal (12 mu g/g) in 1-h exposure to simulated effluent. About 85% of Co removal was achieved in a two-cycle treatment with the cloned bacteria. Expression of NiCoT genes in the E. coli knockout mutant of NiCoT efflux gene (rcnA) was more efficient as compared to expression in wild-type E. coli MC4100, JM109 and BL21 (DE3) hosts. The viability of the E. coli strains in the formulation as well as at different doses of gamma rays exposure and the effect of gamma dose on their cobalt removal capacity are determined."

The full article can be found at: (G. Raghu, et. al., "Bioremediation of trace cobalt from simulated spent decontamination solutions of nuclear power reactors using E. coli expressing NiCoT genes". Applied Microbiology and Biotechnology, 2008;81(3):571-578). Link not available.

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IMPACT OF THE EARTHWORM LUMBRICUS TERRESTRIS ON THE DEGRADATION OF FUSARIUM-INFECTED AND DEOXYNIVALENOL-CONTAMINATED WHEAT STRAW

Journal of Technology & Science

January 25, 2009

"Important soil-borne fungal pathogens that preferably infect small grain cereals belong to the genus *Fusarium*. These pathogens produce the mycotoxin deoxynivalenol (DON), a cytotoxic agent, in infected cereal organs. This toxin frequently occurs in cereal residues like straw. So far it is unclear if DON degradation is affected by members of the soil food web within decomposing processes in the soil system. For this purpose, a microcosm study was conducted under controlled laboratory conditions to investigate the degradation activity of the earthworm species *Lumbricus terrestris* when exposed to *Fusarium*-infected wheat straw being contaminated with DON. Highly *Fusarium*-infected and DON-contaminated straw seemed to be more attractive to *L. terrestris* because it was incorporated faster into the soil compared with straw infected and contaminated at low levels. This is supported by a greater body weight gain (exposure time 5 weeks) and smaller body weight loss (exposure time 11 weeks) of *L. terrestris*, respectively, when highly contaminated straw was offered for different time periods. Furthermore, *L. terrestris* takes part in the efficient degradation of both *Fusarium* biomass and DON occurring in straw in close interaction with soil microorganisms."

"Consequently, earthworm activity contributes to the elimination of potentially infectious plant material from the soil surface."

The full article can be found at: (E. Oldenburg, et. al., "Impact of the earthworm *Lumbricus terrestris* on the degradation of *Fusarium*-infected and deoxynivalenol-contaminated wheat straw". *Soil Biology & Biochemistry*, 2008; 40(12):3049-3053). Link not available.

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FUNCTIONAL INTERACTIONS BETWEEN ANTHRAX TOXIN RECEPTORS AND THE WNT SIGNALLING PROTEIN LRP6

Medical Letter on the CDC & FDA
January 18, 2009

"To exert its activity, anthrax toxin must be endocytosed and its enzymatic toxic subunits delivered to the cytoplasm. It has been proposed that, in addition to the anthrax toxin receptors (ATRs), lipoprotein-receptor-related protein 6 (LRP6), known for its role in Wnt signalling, is also required for toxin endocytosis," scientists in Lausanne, Switzerland report (see also Anthrax).

"These findings have however been challenged. We show that LRP6 can indeed form a complex with ATRs, and that this interaction plays a role both in Wnt signalling and in anthrax toxin endocytosis. We found that ATRs control the levels of LRP6 in cells, and thus the Wnt signalling capacity. RNAi against ATRs indeed led to a drastic decrease in LRP6 levels and a subsequent drop in Wnt signalling. Conversely, LRP6 plays a role in anthrax toxin endocytosis, but is not essential. We indeed found that toxin binding triggered tyrosine phosphorylation of LRP6, induced its redistribution into detergent-resistant domains, and its subsequent endocytosis. RNAis against LRP6 strongly delayed toxin endocytosis."

"As the physiological role of ATRs is probably to interact with the extracellular matrix, our

findings raise the interesting possibility that, through the ATR-LRP6 interaction, adhesion to the extracellular matrix could locally control Wnt signalling."

The full article can be found at: (L. Abrami, et. al., "Functional interactions between anthrax toxin receptors and the WNT signalling protein LRP6". Cellular Microbiology, 2008; 10 (12):2509-2519). Link not available.

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