1218 CELL CYCLE DYSREGULATION BY ARSENITE: IMPLICATIONS FOR ITS CHEMOTHERAPEUTIC ACTIONS.

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Arsenic has been implicated in certain human cancers. It also is being used currently as an anti-leukemia agent. Arsenite is effective in treating acute promyelocytic leukemias expressing the PML-RARα oncoprotein. However, arsenite induces apoptosis in a variety of cancer cells regardless of PML-RARα expression. We have been studying arsenite effects on U937 cells, a human promonocytic leukemia that lacks PML-RARα. Low micromolar levels of arsenite induce U937 cells to differentiate as assessed by increased CD11b expression and increased directional motility in a chemotaxis assay. Thus, the anti-leukemic effects of clinically achievable levels of arsenite may be due to the induction of cell differentiation rather than cell death. Both arsenite-induced apoptosis and differentiation are preceded by cell cycle changes. Using bromodeoxyuridine (BrdU) and flow cytometry, we have found that arsenite impairs cell cycle transit. Cell synchronization and BrdU pulse-chase experiments have established that arsenite delays progression through all cell cycle phases with the most pronounced effect being delayed transit through G2/M followed by mitotic arrest-associated, caspase-3 dependent apoptosis in a fraction of the cells. Over the long term (i.e., ~96), arsenite induces the accumulation of cells in G1. Given the importance of the cyclin-dependent kinase inhibitor p21 in regulating G1 to S phase transition and U937 cell differentiation, we have hypothesized that arsenite-induced differentiation is preceded by increased p21 activity and arrest in G1. As regulation of p21 is largely transcriptional, the effects of arsenite on p21 mRNA levels as well as other cell cycle regulators is being measured by ribonuclease protection assay. Arsenite-induced changes in p21 mRNA and protein abundance are being correlated with the onset of cell cycle arrest and differentiation, and a causal role for p21 in these processes also is being examined. These studies are providing an explanation of how disruption of distinct cell cycle stages is linked to the anti-leukemogenic effects of arsenite. (Supported by ES01247).

1219 MOLECULAR EVENTS DURING TRANSPLACENTAL INORGANIC ARSENIC CARCINOGENESIS IN MICE: ABERRANT ACTIVATION OF GENES LINKED TO CELL CYCLE DYSREGULATION.

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Defining carcinogenic mechanisms is critical to assessing the human health hazard of arsenic exposure. As gestation is a time of high sensitivity to chemical carcinogenesis, we have performed several *in utero* exposure studies with inorganic arsenic. Pregnant mice received drinking water containing sodium arsenite at various levels, and the offspring were observed for up to 2 years. As adults, male offspring consistently developed hepatocellular carcinoma (HCC) and adrenal tumors, while female offspring showed ovarian and lung tumors, as well as uterine and oviduct preneoplasia. The livers of adult male mice bearing arsenic-induced HCC after *in utero* exposure showed marked over-expression of estrogen receptor-alpha (ER) at both the protein and RNA levels. ER is an estrogen activated transcription factor mediating cell proliferation. ER was intensely localized within the liver cell nucleus, indicating the active form. Activation of hepatic cyclin D1, which can be turned on by ER, was also seen in arsenic exposed mice. Cyclin D1 is critical in cell cycle regulation and, if over-expressed, is considered a hepatic oncogene. *In utero* arsenite induced hypomethylation of the ER promoter region DNA, probably accounting for its over-expression. The cyclin D1 promoter was constitutively unmethylated, and unaltered by arsenic exposure, indicating over-expression was a secondary event. As further evidence that ER over-expression had functional impact, a female pattern of metabolic enzymes occurred in adult male liver after *in utero* arsenic exposure, including over-expression of female-dominant CYP2A4 and CYP2B9, and reduced expression of male-dominant CYP7B1. In summary, altered gene expression occurred in the livers of adult mice bearing HCC induced by *in utero* arsenite exposure that likely resulted in cell cycle dysregulation and enhanced proliferation. Thus, aberrant estrogen signaling, possibly from methylation errors, may play a role in liver cancers induced by *in utero* arsenic exposure.

1220 OCCUPATIONAL SKIN EXPOSURE: CURRENT TRENDS AND FUTURE DIRECTIONS FROM THE FIELD TO GENOMICS.

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The purpose of this symposium is to address important and emerging areas of occupational skin toxicology with respect to current trends and future directions from the field to genomics. For many years, skin has been considered primarily as a route of exposures for toxic chemicals and not as a target organ. As a result, research in skin toxicology per se is extremely underemphasized and under-represented in the discipline of toxicology. Advances in cellular and molecular skin biology have provided insightful opportunities to explore dermal toxicology at different levels. There is no doubt occupational and environmental exposures play a substantial role in skin maladies. A comprehensive discussion of recent developments and trends in occupational skin toxicology will provide novel approaches to elucidate exposure outcomes. This group of selected topics will bring together leading experts representing diverse perspectives in this important field. Ample time will be allotted for full discussion of major skin programs and current findings in Europe and the US. This symposium will address innovative issues in the area of skin toxicology ranging from disease incidences and causes to dermal toxicogenomics.

1221 A RASH OVERVIEW OF OCCUPATIONAL SKIN DISEASES.

B. D. Lushniak. *DSHEFS, NIOSH, Cincinnati, OH.* Sponsor: A. Shvedova.

The importance of skin exposures in occupational settings has become more apparent. Skin can serve as both a target organ of occupational exposures as well as a route of absorption. This presentation will review the field activities of the National Institute for Occupational Safety and Health (NIOSH) involving direct effects on the skin and dermal exposure responses. It will review the wide spectrum of occupational skin diseases (OSDs), describe the epidemiology and public health importance of OSDs, emphasize the causes of contact dermatitis, and review results from NIOSH surveillance and health hazard evaluation investigations.

1222 MOLECULAR MECHANISMS OF ANTIOXIDANT DEFENSE IN THE SKIN.

A. A. Shvedova. *HELD/PPRB, NIOSH, Morgantown, WV.*

Antioxidant deficiency is a component of nutrition shortage. A growing body of evidence suggests that exposure to a number of occupational and environmental toxicants caused oxidative stress leading to short or long-term antioxidant deficiency and cellular dysfunction. Antioxidants, including vitamin E, vitamin C, glutathione and beta-carotene are among the body's natural defense mechanisms against oxidative stress. The skin is recognized as a barrier to absorption, a primary target and route of entry to the systemic circulation. The skin cells may create an oxidative or reductive environment, depending on predominance of redox processes catalyzed by both enzymic and non-enzymic systems. The talk will focus on recent advances in genetic and molecular mechanisms of chemical induced oxidative skin injury, oxidation of skin cellular constituents by reactive oxygen species leading to necrotic/apoptotic death pathways, phospholipid oxidation and signaling, bio-markers of oxidative stress determined in human cells and skin tissues obtained from alimentary vitamin E deficient and knockout tocopherol (alpha) transporter protein Ttpa mice. Value of antioxidants in occupational exposures causing skin damage will be addressed.

1223 BASIC AND CLINICAL ASPECTS OF SKIN DISEASES.

K. D. Cooper. *Case Western University, Cleveland, OH.* Sponsor: A. Shvedova.

Skin toxicants share an ability to cause activation of cell signaling, often resulting in inflammatory and immunologic mechanisms. Skin has a limited number of reaction patterns, usually represented by various specific diseases. Allergic, irritant and atopic contact dermatitis, psoriasiform dermatitis/psoriasis, sunburn/photoxicity, and physical trauma to the epidermis represent some of the reactions that can occur in response to occupational toxicant exposures. Discussed here will be the pathogenesis of allergic contact dermatitis, atopic dermatitis, psoriasis and photoinjury. Keratinocyte inflammatory mediators, cytokines and chemokines can often initiate or propagate cellular immunologic mechanisms. These include Langerhans cell migration, T cell recruitment and activation, macrophage activation, and associated epidermal changes, ranging from spongiosus to hyperplasia or dermal-epidermal junction targeted toxicity to basal keratinocytes. Psoriasis as a model of Type I T cell mediated immune reactions (IFNg, IL-12, TNF) will be compared to the Type II immune responses (IgE, IL-4, 5, 13) associated with Atopic Dermatitis. The immunomodulatory effects of skin perturbation will be exemplified by the intersecting innate and adaptive immune response mechanisms initiated by solar radiation photons in the UVA and UVB region.

Society of Toxicology
43rd Annual Meeting
Baltimore, Maryland

THE TOXICOLOGIST

a supplement to
TOXICOLOGICAL SCIENCES

An Official Journal of the Society of Toxicology

Volume 78, Number S-1, March 2004

Preface

This issue of *The Toxicologist* is devoted to the abstracts of the presentations for the symposium, workshop, roundtable, platform and poster sessions of the 43rd Annual Meeting of the Society of Toxicology, held at the Baltimore Convention Center, Baltimore, Maryland, March 21-25, 2004.

An alphabetical Author Index, cross referencing the corresponding abstract number(s), begins on page 443.

The document also contains a Keyword Index (by subject or chemical) of all the presentations, beginning on page 473.

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