vation, including EGFR transactivation by Src and metalloprotease activation. Finally, other studies on airway epithelium have examined signaling pathways by which Cr(VI), at non-cytotoxic concentrations, selectively induces and silences genes. Cr stimulates Src family kinases (SFK) Lck and Fyn, but not Src or Yes, and stimulation of SFKs leads to selective activation of JNK. However, although Cr induces ROS generation, SFK-dependent JNK activation occurs independent of metal-induced oxidative stress.

1510 MAP KINASE SIGNALING CASCADES

M. H. Cobb. *Pharmacology, The University of Texas Southwestern Medical Center at Dallas, Dallas, TX.* Sponsor: A. Villalobos.

The introductory talk will serve as a review of MAP kinase signaling cascades. It will define the four most prominent groups of MAPKs, ERK1/2, ERK5, c-jun N-terminal kinases (JNKs), and p38 proteins, and describe the fundamental organization of the three-tiered MAP kinase activation module composed of a MAPK kinase kinase, a MAPK kinase, and a MAPK that is common to each MAPK signaling cascade. The biochemical basis for activation of each MAPK by selective stimuli and their respective down stream targets (both cytosolic and nuclear) will be discussed in the context of their physiological function. The potential for these kinase cascades overlap and cross-talk with other signaling elements will be introduced, as a basis for specific examples described in greater detail in subsequent talks.

1511 MAP KINASE ACTIVATION AND METALS: ALTERED REDOX STATE OR ENZYME MODIFICATION?

H. J. Forman. *UC Merced, Merced, CA.* Sponsor: A. Villalobos.

As oxidative stress is a common response to various metals, a review will be presented of the role of MAPKs in the cell's response to oxidative stress. First, the relationships of physiological cell signaling to redox homeostasis and of cellular dysfunction to oxidative stress will be presented. This will be followed by a consideration of the chemistry of redox signaling. The role of oxidants generated through metal-catalyzed reactions will be discussed in terms of potential mechanisms. Highlighted in this discussion will be the mechanisms through which the MAPK cascades are activated by oxidants and electrophiles specific examples of which are activation of the JNK pathway by hydrogen peroxide and the activation of Nrf2 by 4-hydroxy-2-nonenal (HNE). The role of the MAPK pathways as mediators of cytoprotective mechanisms will be illustrated by HNE-induction of gamma-glutamyl transpeptidase through ERK and p38MAPK and glutamate-cysteine ligase through JNK both of which are key to adaptive increase in glutathione caused by HNE.

1512 METAL-INDUCED OXIDATIVE STRESS AND CELLULAR RESPONSES

X. Shi. *NIOSH, Morgantown, WV.* Sponsor: A. Villalobos.

Reactive oxygen species (ROS) generated by metals play an important role in the etiology of various diseases and cancers. Metals generate ROS by two general pathways. One is direct interaction of metals with cellular molecules without involvement of signaling transduction. For example, flavenzymes reduce Cr(VI) to Cr(V) in the presence of NAD(P)H; oxygen is reduced to superoxide radical that generates hydrogen peroxide by dismutation; Cr(VI) also reacts with hydrogen to generate hydroxyl radicals by a Fenton-like reaction. Alternatively, metals may generate ROS by stimulation of cells; this involves expression of NADPH oxidase by various signal molecules. Metals may induce various cellular responses by ROS mediated reactions. For example, Cr(VI) may activate MAPKs and their down stream targets, such as NF-KB and AP-1. NF-KB inhibits of Cr(VI)-induced cell death. Inhibition of NF-KB by IKKβ-KM or IKKβ deficiency results in spontaneous cleavage of Bcl-xL antiapoptotic protein due to elevated caspase-3 activity. Exogenous antiapoptotic proteins (cIAP1), a caspase inhibitor, partially inhibits Cr(VI)-induced cell death; thus caspases are involved in Cr(VI)-induced cell death. In response to Cr(VI), p53 protein is phosphorylated at Ser15 and acetylated at Lys382. ERK phosphorylates p53 at Ser15 site. Via ERK and p38, Cr(VI) also upregulates p21 and cdc2 and causes degradation of cdc25C, leading to growth arrest at G2/M. Specific ROS affect specific MAPKs and cell growth regulatory proteins with different potencies. Cr(VI) induces hypoxia-inducible factor-1 (HIF-1) activity by specific expression of HIF-1α but not HIF-1β subunit and increases vascular endothelial growth factor (VEGF) expression. p38 signaling is required for Cr(VI)-induced HIF-α expression, but PI3-K and ERK are not required for Cr(VI)-induced HIF-1 expression. Hydrogen peroxide is responsible for HIF-1 induction and VEGF expression. By ROS-mediated mechanisms, As, Ni and V also activate MAPKs and other oxidative responsive proteins to induce cellular responses, such as activation of PI3-K/Akt pathway, NF-KB, AP-1, p53, nuclear factor of activated T cells (NFAT), HIF-1, cell cycle arrest, and apoptosis.

1513 ZN2+-INDUCED MAPK AND EGFR ACTIVATION IN HUMAN AIRWAY EPITHELIAL CELLS (HAEC) ARE MEDIATED BY PHOSPHATASE INHIBITION

J. M. Samet[1, 3], Y. Kim[2], T. Tal[3], P. Bromberg[2], W. Wu[2] and L. M. Graves[2, 3]. [1]*Human Studies Division, USEPA, Chapel Hill, NC,* [2]*Center for Environmental Medicine and Lung Biology, University of North Carolina, Chapel Hill, NC and* [3]*Curriculum in Toxicology, University of North Carolina, Chapel Hill, NC.* Sponsor: A. Villalobos.

We have previously shown that exposure of cultured human airway epithelial cells to Zn2+ induces activation of the MAPKs ERK, JNK and P38, as well as the tyrosine kinase receptor EGFR. Studies aimed at identifying the mechanism of signal initiation in Zn2+-induced MAPK and EGFR phosphorylation have revealed multiple levels of activation, including EGFR transactivation by Src and activation of metalloproteases. Since Zn2+ acts a potent tyrosine phosphatase activity inhibitor, we examined the possibility that Zn2+ induces signaling by impairing EGFR- and MAPK-directed dephosphorylation activities in HAEC. Acute challenge of cultured HAEC with 500 uM Zn2+ resulted in a significant decrease in the rate of dephosphorylation of exogenous P-EGFR relative to controls exposed to media alone. This effect was observed in lysates prepared from cells exposed to Zn2+ as well as in intact cells treated with Zn2+. Moreover, diminished dephosphorylation activity was detected towards auto- as well as trans-phosphorylation sites in the EGFR. Similarly, ERK2-directed dephosphorylation activity by HAEC lysates was markedly reduced following treatment of HAEC with Zn2+. These findings suggest that signal transduction events induced by exposure to Zn2+ are initiated not by the direct induction of kinase activation, but through the inhibition of critical phosphatases whose activities oppose baseline kinase activity and normally function to maintain signaling quiescence in resting cells. THIS ABSTRACT OF A PROPOSED PRESENTATION DOES NOT NECESSARILY REFLECT EPA POLICY.

1514 JNK ACTIVATION BY CHROMIUM IN THE LUNG

A. Barchowsky. *Department of Environmental and Occupational Health, University of Pittsburgh Graduate School of Public Health, Pittsburgh, PA.*

Inhaled hexavalent chromium (Cr(VI)) promotes pulmonary diseases through poorly defined mechanisms that may involve both direct metal interactions with proteins and indirect signaling through generation of reactive oxygen species (ROS). Human lung epithelial cells were exposed to non-cytotoxic concentrations of Cr(VI) to investigate the hypothesis that Cr(VI) selectively activates cell signaling to both induce and silence genes. These studies demonstrated that non-toxic doses of Cr(VI) stimulated the Src family kinases (SFK) Lck and Fyn, but not Src or Yes. Stimulation of SFKs led to selective activation of JNK, relative to ERK or p38 MAP kinase. While Cr(VI) slightly elevated ROS levels, much higher non-selective and toxic levels of exogenous ROS were needed to stimulate SFKs and JNK. Thiol oxidation and the adaptor protein p130cas (Cas) were common requirements for Cr(VI) and H2O2 to activate JNK. However, Cr(VI) and H2O2 had differential effects on the SFKs that may account for divergence of the metal and ROS signaling pathways. Finally, Cr(VI), but not H2O2, directly activated purified Fyn in vitro, which confirmed the selective action of the metal. These data indicate that Cr(VI), at levels which are relevant to human exposures, selectively stimulates cell signaling to regulate gene induction and silencing. This selective action of Cr(VI) does not always require ROS signaling in airway epithelial cells, which suggests a possible mechanism that distinguishes Cr(VI)-induced diseases from general inflammatory diseases.

1515 ADVANCED TECHNOLOGIES AND APPROACHES FOR QUANTITATIVE BIOMONITORING FOR CHEMICAL EXPOSURES

C. Timchalk and T. Karla. *Pacific Northwest National Laboratory, Richland, WA.*

There is a need to develop sensitive and novel approaches that can be used for biological monitoring of both occupational and environmental exposures to a broad-range of chemical agents, and to rapidly determine the potential implications of these exposures to human health. This symposium will highlight technology that focuses on the application of bio-analytical chemistry for assessing low level chemical exposure, coupled to the development of sensitive, selective, rapid, and cost-effective sensors for toxicity screening, biomonitoring, and development of field deployable platforms. These approaches can be applied to identify novel biomarkers

SOT | Society of Toxicology

The Toxicologist

Supplement to *Toxicological Sciences*

An Offical Journal of the Society of Toxicology

45th Annual Meeting and ToxExpo™

San Diego, California

OXFORD
UNIVERSITY PRESS

ISSN 1096-6080
Volume 90, Number 1, March 2006

www.toxsci.oupjournals.org

Preface

This issue of *The Toxicologist* is devoted to the abstracts of the presentations for the symposium, platform, poster discussion, workshop, and poster sessions of the 45th Annual Meeting of the Society of Toxicology, held at the San Diego Convention Center, San Diego, March 5–9, 2006.

An alphabetical Author Index, cross referencing the corresponding abstract number(s), begins on page 500.

The issue also contains a Keyword Index (by subject or chemical) of all the presentations, beginning on page 534.

The abstracts are reproduced as accepted by the Program Committee of the Society of Toxicology and appear in numerical sequence.

Copies of *The Toxicologist* are available at $45 each plus $5 postage and handling (U.S. funds) from:

Society of Toxicology
1821 Michael Faraday Drive, Suite 300
Reston, VA 20190

www.toxicology.org