which can revolutionize both monitoring and toxicological assessment. The aim of this session is to provide novel insights on the mechanisms of action of immunotoxic compounds focusing on microRNA and microvesicles. Recently, differential expressions of miRNAs and association with several immunologic and inflammatory disorders have been reported, which have important implications in immunotoxicology assessment. miRNAs can influence regulatory mechanisms of inflammation in both inducing and contrasting acute and chronic inflammation. In addition, research on microvesicles also is an emerging and developing field. Studies available to date identified several exposures or lifestyle factors able to modify the trafficking of microvesicles, including air pollutants, cigarette smoke, and oxidative stress. The first speaker will guide the audience in the world of microRNAs from discovery to their role in physiological and pathological conditions, with emphasis on tumors and immunosurveillance, to their use as biomarkers. The second speaker will present data showing influences of environmental exposures on EV-encapsulated RNAs and potential links with several adverse health outcomes, including immunotoxicity. The last two speakers will focus on the role of microRNAs in allergic phenomena both in humans and in experimental models. Challenges, limitations, and opportunities in this emerging field in environmental health sciences will be discussed.

1027 Non-Coding RNAs—From Bench to Bedside

G. A. Calin. *University of Texas, Houston, TX.* Sponsor: E. Corsini

The newly discovered differential expression in numerous tissues, key cellular processes, and multiple diseases for several families of long and short non-coding RNAs (ncRNAs, RNAs that do not codify for proteins but for RNAs with regulatory functions), including the already famous class of microRNAs (miRNAs), strongly suggest that the scientific and medical communities have significantly underestimated the spectrum of ncRNAs whose altered expression has significant consequences in diseases. MicroRNA and other short or long non-coding RNAs alterations are involved in the initiation, progression, and metastases of human cancer. The main molecular alterations are represented by variations in gene expression, usually mild and with consequences for a vast number of target protein coding genes. The causes of the widespread differential expression of non-coding RNAs in malignant compared with normal cells can be explained by the location of these genes in cancer-associated genomic regions, by epigenetic mechanisms, and by alterations in the processing machinery. MicroRNA and other short or long non-coding RNAs expression profiling of human tumors has identified signatures associated with diagnosis, staging, progression, prognosis, and response to treatment. In addition, profiling has been exploited to identify non-coding RNAs that may represent downstream targets of activated oncogenic pathways, or that are targeting protein-coding genes involved in cancer. Recent studies proved that miRNAs and non-coding ultraconserved genes are main candidates for the elusive class of cancer-predisposing genes and that other types of non-coding RNAs participate in the genetic puzzle, giving rise to the malignant phenotype. Last but not least, the shown expression correlations of these new ncRNAs with cancer metastatic potential and overall survival rates suggest that at least some member of these novel classes of molecules could potentially find use as biomarkers or novel therapeutics in cancers and other diseases.

1028 Effects of Environmental Exposures on Microvesicles Release and Their Contents

A. Baccarelli. *Columbia University, New York, NY.* Sponsor: E. Corsini

Interest in intercellular communication has risen in recent years, with an increasing awareness of the complexity of its contributions to diverse physiological processes. In particular, the identification of extracellular vesicles (EVs) as novel mediators of intercellular communication has re-focused research efforts in the field. The number of human studies of EVs-using a number of body fluids including blood, urine, saliva, amniotic fluid, and breastmilk, have grown exponentially in the past few years. Several investigations have focused on EV-packaged non-coding RNAs, which are released into EVs by the cell of origin and may reprogram gene expression in recipient cells. EVs have been likened to environmentally-sensitive systems such as the inflammatory and endocrine systems, which are a primary target of environmental pollutants in humans. However, human data linking environmental exposures to alterations in EVs and EV-encapsulated miRNAs are still sparse. In this presentation, we will propose possible conceptual models linking environmental exposures to EVs. We will present preliminary data showing influences of environmental exposures on EV-encapsulated RNAs and suggesting potential links with adverse health outcomes, including immunotoxicity. We will discuss challenges and limitations and discuss opportunities in this emerging field in environmental health sciences.

1029 Circulating microRNAs and Prediction of Airway Hyperresponsiveness

K. G. Tantisira. *Harvard Medical School, Boston, MA.* Sponsor: E. Corsini

Airway hyperresponsiveness is a cardinal feature of asthma. While clinically measured via non-specific agents such as methacholine and histamine, other agents, including pollen, smoke, and chemical inhalation, can cause significant airway hyperresponsiveness. Identification of miRNAs associated with airway responsiveness may have biologic, prognostic, and therapeutic relevance. Murine models have identified several miRNAs associated with airway hyperresponsiveness, including miR-126 and let-7a; silencing of these miRNAs has demonstrated improvement in airway hyperresponsiveness and other asthma phenotypes. Circulating miRNA have the potential to serve as clinical biomarkers of human airway hyperresponsiveness and asthma. There is an evolving literature surrounding circulating miRNAs in asthma; for airway hyperresponsiveness, the association of a number of the miRNAs with methacholine-induced PC20 changes in a cohort of childhood asthmatics has been reported. Two of these miRNAs, miR-16-5p and miR-30d-5p, form central hubs in miRNA-predicted gene networks and are associated with changes in airway smooth muscle growth and size. MiRNAs have also been used to provide a prognostic signature for the natural history of asthma with good predictive power for resolution of airway responsiveness over time. Thus, miRNAs in general, and circulating miRNAs specifically, appear to have an evolving role in the understanding of airway hyperresponsiveness and may shed future light on inhalational and toxicologic lung disorders.

1030 microRNA in Experimental Models of Chemical Sensitization

S. E. Anderson. *NIOSH, Morgantown, WV.*

Allergic disease is an important occupational health concern, with work-related asthma and allergic contact dermatitis being the most frequently diagnosed occupational illnesses. Understanding the mechanisms behind allergic disease is critical for treatment and prevention. The regulatory potential of microRNAs (miRNAs) has been recognized in a variety of disease states, including allergic disease; however, the roles of miRNAs in chemical sensitization are largely unknown. Increased expression of multiple miRNAs during toluene 2,4-diisocyanate (TDI) sensitization was observed, and several putative mRNA targets identified for these miRNAs were directly related to regulatory T-cell (Treg) differentiation and function, including Foxp3 and Runx3. Specifically, miR-210 expression increased in the mouse draining lymph node (dLN) and Treg subsets following dermal TDI sensitization. Alterations in dLN mRNA and protein expression of Treg-related genes/putative miR-210 targets (foxp3, runx3, ctla4, and cd25) were observed at multiple time points following TDI exposure and in *ex vivo* systems. A Treg suppression assay, including a miR-210 mimic, was utilized to investigate the suppressive ability of Tregs. Cells derived from TDI-sensitized mice treated with miR-210 mimic had less expression of miR-210 compared to the acetone control, suggesting other factors, such as additional miRNAs, might be involved in the regulation of the functional capabilities of these cells. These novel findings indicate that miR-210 may have an inhibitory role in Treg function during TDI sensitization. Because the functional roles of miRNAs have not been previously elucidated in a model of chemical sensitization, these data contribute to the understanding of the potential immunologic mechanisms of chemical-induced allergic disease.

1031 Toxicological Implication of Copper in Neurodegenerative Diseases

M. Kitazawa. *University of California Irvine, Irvine, CA.*

Copper (Cu) is an essential transition metal and required for many normal physiological functions, including energy production, free radical scavenging, connective tissue production, iron mobilization, and neurotransmission. However, excessive intake due to occupational or environmental exposure to divalent Cu(II) has been implicated as a risk for various human diseases. When administered, almost all Cu ions are bound to ceruloplasmin (Cp), and the remainder, non-Cp-bound Cu (labile Cu), is bound to albumin, transcuprein, various peptides, and amino acids in plasma. For its chemical reactivity, the plasma level of free Cu is tightly controlled by the above-mentioned Cu-binding proteins. Recent studies have clearly indicated that environmental exposure to Cu in adults accelerates cognitive decline and may increase the risk of developing Alzheimer's disease (AD)-like neuropathology by elevating non-ceruloplasmin-bound Cu in plasma. This session will bring together the experts who are actively engaging in investigating chemistry of Cu in biological systems, Cu neurotoxicity, and its underlying

The Toxicologist

Supplement to
Toxicological Sciences

57th Annual Meeting and ToxExpo™

San Antonio, Texas
March 11–15, 2018

OXFORD
UNIVERSITY PRESS

ISSN 1096-6080
Volume 162, Issue 1
March 2018

www.academic.oup/toxsci

The Official Journal of
the Society of Toxicology

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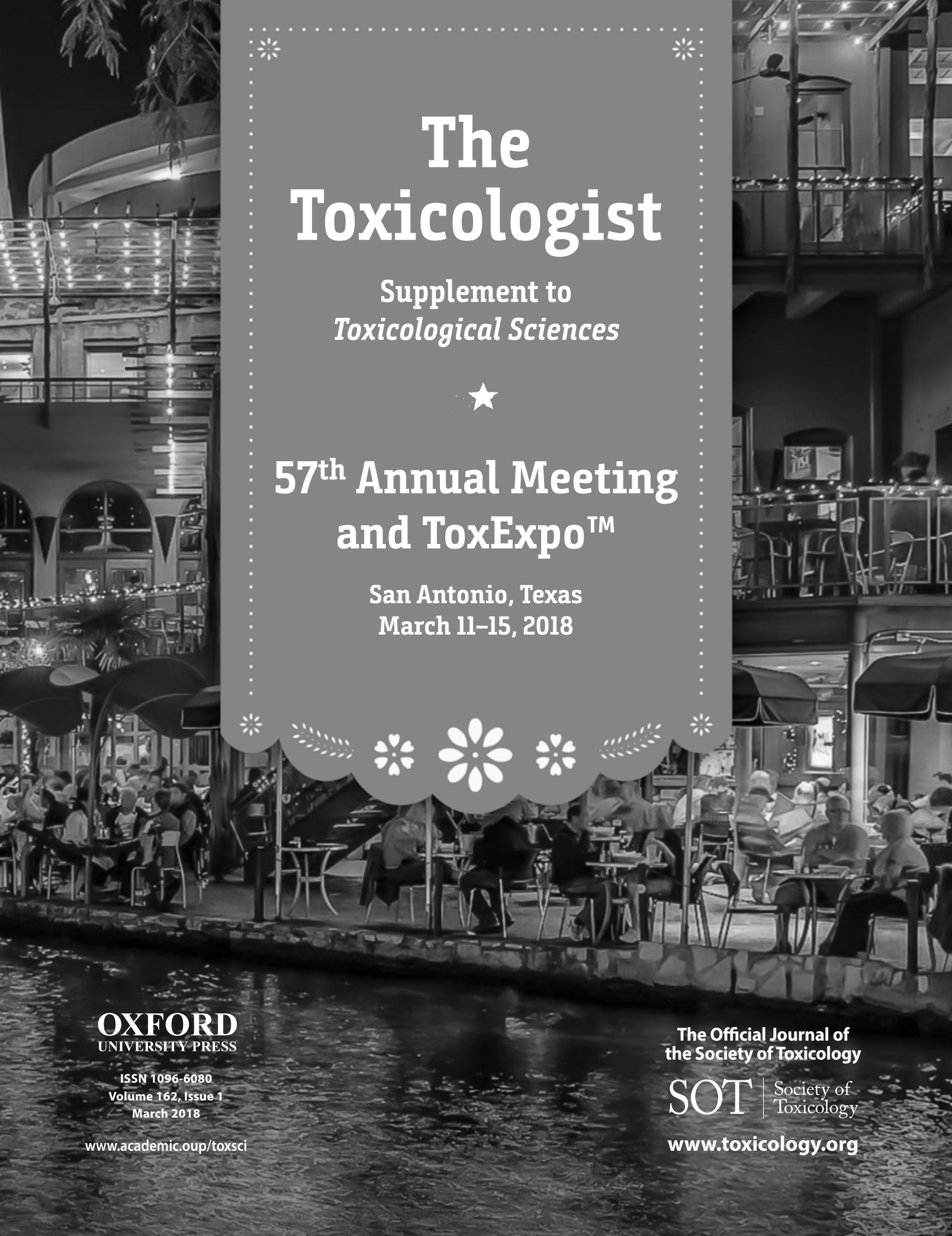

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