in response to collagen, without impacting other platelet signaling pathways. This study advances our hypothesis2 that AHR influences multiple aspects of normal hematopoietic differentiation.

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S 1462 The AhR Regulates the Production and Specification of Bipotential Hematopoietic Progenitor Cells

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Recent studies demonstrate that the AHR may regulate the hematopoietic and immune systems during development in a cell-specific manner. Our results indicate that AHR has a physiological and functional role in normal hematopoietic development, and that modulation of the receptor in bi-potential hematopoietic progenitors can direct cell fate. Using a novel, iPSC-based, chemically-defined, serum and feeder cell-free culture system, we demonstrate that a functional AHR is expressed in hematopoietic progenitor cells (HPs), and that remarkably, AHR activation of these HPs drives an unprecedented expansion of HPs, megakaryocyte (Mk)- and erythroid-lineage cells. Further AhR modulation directs cell fate, with chronic AhR agonism permissive to erythroid differentiation and acute antagonism favoring megakaryocyte specification. These results demonstrate a new platform for studying human red blood cell and Mk development that allows for exponentially greater production of RBCs and Mks in comparison to existing methodologies. This strategy relies on the first of its kind definition of the role of the AHR receptor in normal hematopoietic development using specialized ligands in hematopoietic progenitor cells. A useful outcome for this work will be the utilization of this in vitro platform for the clinically relevant production of blood products. An iPSC-based system, such as the one described here in which sufficient numbers of cells can be produced, should facilitate future clinical adaptation involving the transfusion of iPSC-derived red blood cells and platelets without problems related to immunogenicity, contamination, or supply. Supported by NLHBI U01 HL107443-01, an American Society of Hematology (ASH) Scholar Award, the National Blood Foundation (NBF), PO1 ES11624, P42 ES007381, and the Art beCAUSE Breast Cancer Foundation.

S 1463 The AhR Controls Breast Cancer Stem Cell Development and Function

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Tumor metastasis is the cause of death in nearly all breast cancer patients. Recent evidence suggests that metastasis is mediated, to a disproportionate extent, by chemo-resistant, long-lived breast cancer stem-like cells (BCSLC). BCSLC cells are defined by their expression of aldehyde dehydrogenase (ALDH), a set of genes associated with "stem-ness", the ability to self-renew, expression of properties consistent with epithelial-to-mesenchymal transition (e.g., metastatic potential), and resistance to chemotherapeutics. Studies from several laboratories, including three laboratories represented in this symposium, suggest that the AHR, a protein historically associated with tumorigenesis, is involved in the development and/or function of blood stem cells which share some properties with cancer stem cells. Therefore, we postulated that the AHR may play a role in either the development or function of BCSLC. Here, we present data demonstrating elevated levels of constitutively active AHR in BCSLC from aggressive human ER-, PR-, Her2- ("triple negative") and inflammatory breast cancers. The results indicate that AHR hyper-activation with exogenous ligands (FICZ, TCDD, DMBA) increases and AHR inhibition with pharmacological or molecular agents decreases expression of BCSLC characteristics including expression of ALDH1, several stem cell-associated genes including Notch1, Nanog, and Oct 4, chemo-resistance, and the ability to grow and produce progenitor cells in spheroid colonies. These results further implicate the role of environmental chemicals in breast cancer risk through induction of BCSLC characteristics and have significant implications for the potential to target the AhR for cancer therapy. Supported by PO1 ES11624, P42 ES007381, and the Art beCAUSE Breast Cancer Foundation.

S 1464 Three Dimensions of Nanomaterial Pulmonary Toxicity: Innate Immunity, TLRs, and Inflammasomes

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Nanotechnology is rapidly developing, resulting in the production of numerous engineered nanoparticles. These materials have many potential uses in engineering, electronics, and medicine owing to their unique size, strength, functionality and surface properties. However, these novel properties also contribute to their potential health risk. A major route of exposure for engineered nanomaterials occurs through inhalation, potentially leading to pulmonary toxicity. Immune activation and inflammation represents a common response observed across many pulmonary studies of nanoparticle inhalation in rodents. However, our mechanistic understanding by which the materials elicit immune activation is limited. Recent accumulating evidence supports the proposal that the initial pulmonary immune response to nanoparticle exposure is mediated via the innate immune system driving inflammation. Presentations in this session are aimed at elucidating the mechanisms of these innate immune responses to engineered nanomaterial exposure in the lung. This will include exploration of macrophage phenotypes, inflammasome activation, Toll-like receptors and, lastly, will explore the degradation of nanomaterials by immune cells and their defensive products. The outcome of this session is to gain state-of-the-art information on the mechanisms of the critical innate immune system response in the toxicology of nanoparticles and ultimately the development of safe nanotechnologies.

S 1465 Inflammasome Activation in Nanoparticle-Induced Lung Inflammation

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The precise mechanisms responsible for engineered nanomaterial (ENM)-induced activity remain to be elucidated. Increasing evidence supports the notion that alveolar macrophages (AM) contribute to ENM-induced lung inflammation and pathology through the NLRP3 Inflammasome in a similar manner as has been implicated for a number of "danger" crystals in a process sometimes referred to as sterile inflammation. In order to characterize mechanisms involved in ENM inflammation studies have been conducted in vitro using THP-1 and NLRP3 KO cells and primary AM from mice and humans as well as in vivo studies using murine models. Two key steps regulate this process: 1) ENM-induced phagolysosomal membrane permeability (LMP) leading to the release of cathepsin B into the cytoplasm, which has been linked to NLRP3 Inflammasome assembly and Caspase-1 activation necessary for IL-1β to be cleaved from its pro-form, and 2) elimination of the NLRP3 Inflammasome complex by autophagy. The precise steps leading to LMP have not been defined, although generation of reactive oxygen species and/or some other property of ENM have been implicated. Acidification of lysosomes is necessary for LMP since imipramine and chloroquine can block NLRP3 Inflammasome activation and downstream inflammation. ENM length and surface characteristics of ENM are important factors in LMP. Increasing the aspect ratio and/or rigidity of ENM increases bioactivity, while carboxylation of ENM surfaces decreases bioactivity. Furthermore, while ENM induce autophagy, increasing autophagic flux can block IL-1β release from macrophages. Finally, comparing the outcomes from in vitro and in vivo studies suggest that IL-1β production from THP-1 cells can be used to predict in vivo outcomes and serve to prioritize in vivo studies.

S 1466 Lung and Pleural Innate Immune Responses to Engineered Nanomaterials

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The nanotechnology revolution offers enormous societal and economic benefits for innovation in the fields of engineering, electronics, and medicine. However, growing evidence indicates that some biopersistent engineered nanomaterials (ENMs), including carbon nanotubes (CNTs) and metal nanoparticles, have the potential to stimulate immune, inflammatory, or fibroproliferative responses in the lung and pleura. This presentation will focus on specific mechanisms through which CNTs or nickel nanoparticles modulate cellular signaling and innate immune responses of macrophages, fibroblasts, and mesothelial cells relevant to lung and pleural disease. One of the goals is to discuss new evidence from transgenic mouse models showing that these ENMs have the potential to shift allergic lung inflammation from a

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Supplement to *Toxicological Sciences*

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March 23–27, 2014 • Phoenix, Arizona

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OXFORD UNIVERSITY PRESS

ISSN 1096-6080
Volume 138, Issue 1
March 2014

www.toxsci.oxfordjournals.org