S 43 To Bug or Not to Bug the Immune System: Benefits and Consequences of Altering the Microbiome

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The Human Microbiome Project, a NIH initiative to understand the complexity, constitution, and diversity of microbes living on and in the human body, was recently completed in 2012. The term "Super-Organism" was coined to describe humans as a result of characterization of the breadth and diversity of microbes that live on the external surface as well as in the blood, tissues, and cells of the human body. What role do commensal organisms play in health and disease? What role do pathogenic microbes play in health and disease? For decades, a major emphasis in the field of immunotoxicology has been to understand the impact of environmental/occupational/therapeutic exposures on host defense against invading and opportunistic pathogens. Mounting evidence suggests that equal effort should be provided to understanding the relationship between the human microbiome and how alterations thereof can have profound implications for the development of complex immune and inflammatory diseases. Individuality of the microbiome contributes to immune-diversity, "metagenetic" diversity, and interindividual differences in susceptibility to many complex diseases, including allergic disease, autoimmune diseases, cancer, and others. Evidence suggests that development of an individual's microbiome begins before birth, and the nature of this colonization can influence susceptibility to disease later in life. In addition, homeostasis of the microbiome is under continual attack due to exposures encountered in daily life. Recent research shows that exposure to toxic chemicals can shift the dominant characteristics of the microbiome, thereby providing a strong contribution to disease susceptibility. Therefore, it is important to consider this research in the context of human health risk assessment. The purpose of this symposium is to provide evidence of beneficial and detrimental contributions of the microbiome to the development of immune and inflammatory diseases and provide insight into how microbiome research integrates into human health risk assessment.

S 44 Living with a Microbiome: The Role of Exposures and Toxicity in Shaping "The Completed Self"

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"The Completed Self" model for formation of the human-microbial superorganism in early life posits that: 1) symbiotic self completion is a critical step in the developmental programming of later-life health vs. disease, 2) the immune definition of self includes our internal microbial ecosystem, and 3) commensal-driven host metabolism and immune maturation are critical factors in subsequent tissue homeostasis. A consideration of humans as beyond-mammalian could shift our prevailing view of toxicity, health hazards, and preventive measures as well as the tools we employ for effective safety assessment. Prenatal, postnatal and even transgenerational epigenetic factors have the capacity to either support or interfere with the establishment of the microbiome and/or immune-microbiome interactions. Lack of self completion appears to be an important route to metabolic disorders, immune dysfunction, misregulated inflammation, tissue pathologies and chronic disease. Environmental risk factors (e.g., environmental chemicals, drugs, diet, physical and lifestyle factors) during development are considered in light of the goals of self completion in the child and a fully-developed immune system to support the newly-formed human-microbial symbiont.

S 45 Toxic Exposures and the Microbiome: Their Input Counts, Too

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Humans are colonized, on external and internal surfaces of the body, with a wide range of microorganisms known collectively as a microbiome defined by niche. Several studies have demonstrated that differences in the diversity or composition of the microbiome can be associated with disease states, including environmentally relevant diseases such as obesity and autism. The microbiome is exquisitely sensitive to external factors, such as birth route, diet, and antibiotic use, and recent data has indicated that it may also be affected by exposure to environmental chemicals. In addition, the microbiome itself influences our responses to exposures from environmental or occupational chemicals, pharmaceuticals, and foods, among other things. In fact, the gut microbiome has been proposed as an additional "portal" for understanding ADME in toxicology and epidemiology. This talk will focus on the role of the gut microbiome as a "gate keeper" between external exposures and internal dose, and the implications of these events for a more holistic understanding of metabolism prior to absorption and distribution. This talk will review state of the art information on this topic along with a discussion of the implications for understanding the contribution of the gut microbiome to host response and susceptibility.

S 46 The Human Microbiome and Autoimmunity

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The current concept of autoimmunity, in which the body creates autoantibodies against "self" was developed at a time when the human body was believed to be largely sterile. However, the discovery of the human microbiome calls for a re-evaluation of this model. The microbiome, which persists in tissue and blood, influences almost every human metabolic process. Numerous studies demonstrate dysbiosis of the microbiome in patients with autoimmune and inflammatory conditions, suggesting that autoantibodies are actually generated in response to persistent infectious agents. Intracellular pathogens associated with autoimmune disease often slow activity of the innate immune response by disabling expression by the VDR nuclear receptor. This causes a cascade of dysregulation that progressively moves the body away from a state of homeostasis. Such pathogens are able to directly interfere with transcription, translation, and DNA repair processes. Molecular mimicry between pathogen and host multiplies the scale and dysfunction of the interactome. The combined effects of different microbes on the interactome likely contribute to any single autoimmune diagnosis, the specifics of which result from the unique microbiome of each individual. This is reflected in the high levels of comorbidity observed among patients with inflammatory disease. The state of the microbiome and subsequently the innate immune response play a significant role in determining how individuals responds to toxic threats. We have retargeted an approved pharmaceutical in an effort to reactivate the VDR nuclear receptor in patients in inflammatory disease. This appears to strengthen the immune response and gradually correct microbial dysbiosis. Although the treatment generates significant immunopathology, patients are demonstrating both improved objective and subjective markers and some even exhibit recovery. We have anecdotal reports that levels of heavy metals, including mercury have decreased in patients over the course of therapy. This suggests that strengthening the innate immune response may allow the body to better manage toxic insult as it brings inflammatory disease under control.

S 47 The Microbiome in Human Health Risk Assessment: Where Do We Go from Here?

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It is recognized that the complex collection of microbes in our gut, the microbiome, plays a critical role in our health and well-being. It influences our responses, e.g., immunological, and reacts to environmental exposures, such as from food, drugs, and environmental contaminants. Regulatory agencies are putting a great deal of effort into understanding the sequence of mechanistic events that lead to disease. However, they haven't generally incorporated the importance of the microbiome to a great extent and how it can provide insight into human health risk assessment. We will likely need to rethink some of the risk assessments to take into account the contribution of the microbiome. Research will greatly help assessments by addressing the lack of understanding of how xenobiotic exposures can affect the composition and function of the microbiome as well as how the microbiome can affect bioavailability of contaminants and susceptibility to pathogens. Also, the interplay between chemical exposures and pathogens with commensal gut flora and with each other need to be examined as potential risk factors. While the microbiome raises the complexity of the research in disease etiology, it will help human health risk assessors to rethink how chemicals and pathogens interact with exposed people.

W 48 Developmental Programming of Hepatic Metabolism: Assessing the Impact of Perinatal Exposure to Xenobiotics

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It is becoming increasingly evident that epigenetics is important in the ontogeny of hepatic metabolism and transport pathways. This workshop highlights the most recent knowledge of the developmental regulation of hepatic metabolism through transcriptional and epigenetic mechanisms in rodents and humans. Interestingly,

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