Gene Expression, Biomarkers, and Glial Cells in Nervous System Diseases

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ABSTRACT

Session 3 of the “Toxicologic Neuropathology” Symposium sponsored jointly by the Society of Toxicologic Pathology (STP) and the International Federation of Societies of Toxicologic Pathologists (IFSTP) focused on advances in the understanding of cellular and molecular mechanisms of the nervous system and neurodegenerative diseases, and on new information on the function and roles of microglia cells and astrocytes. This overview highlights the major themes of the presentations in General Session 3; these themes are covered in greater detail in four papers in this issue of Toxicologic Pathology.

Keywords: astrocytes; microglia; CSF biomarkers; molecular neuropathology.

The first presentation, by Dr. George H. Searfoss of Eli Lilly and Company (Indianapolis, IN), explored molecular mechanisms associated with the origins of delayed seizures in a rat kainic acid treatment model of mesial temporal lobe epilepsy. Using global gene expression analysis, Dr. Searfoss’s research team characterized genomic responses with seizures and hippocampal histological changes in rats, thereby linking critical genes with early and late histologic responses, including neuronal/synaptic plasticity, neurodegeneration, and inflammation (Sharma et al. 2009). The gene expression studies demonstrated the complexity of disease processes in which a number of modes of action contribute to the development of seizures. The presentation also underscored that pathologists, who are familiar with the specific cell types in the nervous system and their responses to injury and repair, are in a unique position to lead research projects or partner with teams of toxicologists, molecular biologists, and other scientists to investigate the pathogenesis of complex nervous system diseases.

The second presentation, by Dr. Thomas J. Montine of the University of Washington, UW Medicine (Seattle, WA), focused on biomarkers for such major human neurodegenerative diseases as Alzheimer’s disease (AD), microvascular brain injury (VBI), and Lewy body disease (LBD). Although microscopic evaluation remains the gold standard for a definitive diagnosis of neurodegeneration, significant progress is being made in developing biomarkers that are promising predictors of the clinical outcomes associated with dementia, a common finding in AD, VBI, and LBD (Sonnen et al. 2010). For example, in the early stages of AD, VBI, and LBD, cerebrospinal fluid (CSF) biomarkers such as amyloid fragment Aβ1-42 (Aβ42) and τ may be present in the CSF of patients and therefore may serve as markers of latent neurodegenerative disease although patients are cognitively normal. Given the complexity of neurodegenerative disease, a multifaceted approach that takes into consideration genetic risk factors, biomarkers, and neuroimaging will be critical in reaching an initial diagnosis, assessing therapeutic responsiveness, and evaluating clinical management of patients with specific neurodegenerative diseases.

The third presentation was by Dr. Clayton A. Wiley of the University of Pittsburgh School of Medicine (Pittsburgh, PA), who provided current concepts on the role of microglia in central nervous system (CNS) disease. Microglia play a vital role in immune surveillance in the nervous system (Martinez, Helming, and Gordon 2009; Nimmerjahn, Kirchhoff, and Helmchen 2009). Once thought of as “resting” macrophages in the nervous system, microglia are now considered to be tissue sentinels; they respond early and rapidly to various toxicologic or infectious insults and thereby play an important role in classical innate immunity. Microglia may also function by alternative pathways when stimulated by various agonists and play important roles in anti-inflammatory responses, tumor promotion, and matrix remodeling and repair. Furthermore, microglia may have both...
destructive effects (by releasing pro-inflammatory mediators) and beneficial effects (through active phagocytic mechanisms), the balance of which depends on the nature of the inciting agent. Modern medicine is taking advantage of these dual roles of microglia to develop therapies for diseases as diverse as Alzheimer’s disease and genetic storage diseases such as x-linked adrenoleukodystrophy.

The fourth presentation, by Dr. Michael Aschner of Vanderbilt University Medical Center (Nashville, TN), described our expanding knowledge of the role of astrocytes in nervous system biology and disease. It has become increasingly clear that astrocytes are an important component of the blood-brain barrier and also respond to neuronal injury (Aschner, Sonnewald, and Tan 2002; Kimelberg 2010). Astrocytes also play major roles in the metabolic support of neurons (such as metabolizing glucose to lactate to provide neurons with an energy source). Astrocytes also protect neurons from certain toxins such as ammonia and remove excessive glutamate from the extracellular space. In short, astrocytes are critical to normal brain function, and the role of astrocytes in nervous system disease is complex. In some cases, astrocytes provide a neuroprotective effect by secreting neurotropic factors and antioxidants, whereas in other cases they may potentiate neuronal injury (such as when dysfunction of astrocyte mitochondria may result in oxidative stress). Examples of the roles of astrocytes in disease were discussed for Parkinson’s disease, Alzheimer’s disease, hyperammonemia, hepatencephalopathy, and ischemia.

REFERENCES