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The role of inflammation in health and disease: translating discovery into novel therapeutic approaches

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The 2012 Combined Annual Meeting of the Central Society for Clinical Research (CSCR) and the Midwestern Section American Federation for Medical Research (MWAFMR) was held April 26–27 in Chicago. The CSCR (now formally known as the Central Society for Clinical and Translational Research, or CSCTR), founded in 1928, is one of the oldest and largest academic medical societies in the Midwest. The primary objectives are to advance medical science, cultivate clinical research by the methods of the natural and behavioral sciences, correlate science with the art of medical practice, encourage scientific investigation, and disseminate this science among the members. The membership is a veritable Who's Who of the academic leadership of American medical schools. Past presidents include Robert Good, the father of modern immunology, Charles Rammelkamp, who identified streptococcus as the etiologic agent for rheumatic fever, John Hickam (after whom the Hickam Lecture is named), who created the prototype for modern Departments of Medicine as Chairman of Medicine at Indiana, and Donald Seldin, a giant of 20th century medicine who transformed the Department of Medicine at the University of Texas Southwestern into one of the top Departments in the nation.

The meeting has a rich annual tradition of providing a forum for young investigators, fellows and assistant/associate professors to present their research to leaders in their fields. Numerous travel awards and early career awards are given out to celebrate the accomplishments of young investigators and to encourage them on the pathway to independence. The meeting has a broad focus where the attendees learn about research in multiple disciplines while concentrating on common fundamental mechanisms of disease. For example, a thematic symposium at the meeting addressed the following question: what do atherosclerosis, multiple sclerosis and malignant melanoma have in common? Answer: inflammation plays a key role in the pathogenesis each of these diseases.

The symposium included presentations by accomplished researchers in each of these disciplines, beginning with Dr. Peter Libby, Mallinckrodt Professor of Medicine, Harvard University, and Chief of Cardiovascular Medicine, Brigham and Women's Hospital. Dr. Libby, a world renowned expert in atherosclerosis, summarized the extensive body of data linking inflammation to all phases of atherosclerosis, from its inception as a fatty streak to disruption of the advanced atherosclerotic plaque leading to acute coronary syndrome¹. He pointed out how inflammation is a cornerstone of the pathophysiology of atherosclerosis and many other chronic diseases, modulated by complex interactions between immune cells and the body's tissues and organs (Figure). In the case of atherosclerosis, conventional risk factors, such as hypertension, hyperlipidemia, diabetes and smoking inflame the endothelial

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lining to set the stage for lesion development. However, atherosclerosis frequently occurs in patients lacking conventional risk factors, and research presented later in the symposium by Dr. G. R. Scott Budinger, Associate Professor, Pulmonary and Cell and Molecular Biology, Northwestern University Feinberg School of Medicine, suggests that particulate air pollution may be an underappreciated but important contributing factor. Dr. Budinger cited epidemiologic data demonstrating an association between ambient particulate matter (PM) air pollution levels and daily death rates, with the majority of deaths presumably of cardiovascular origin. To elucidate the mechanisms, he established an animal model, which demonstrated a critical role for pulmonary macrophages inducing a prothrombotic state via expression of the cytokine IL-6 in response to PM². IL-6 plays a key role in the pathogenesis of atherosclerosis in experimental animal models, and its levels are strongly correlated with disease in humans, thus emphasizing the pathophysiological relevance of Dr. Budinger's work. The clinical importance of inflammation in atherosclerosis is supported by studies demonstrating that the inflammatory biomarker C-reactive protein (CRP) is a strong, independent risk factor for cardiovascular disease. Treatment with statins, which modulate both cholesterol levels and inflammation, in normolipidemic patients with elevated CRP levels reduced cardiovascular events, suggesting that inflammation could potentially be targeted as a goal for therapy in atherosclerosis³. This hypothesis will be tested in two randomized clinical trials of secondary cardiovascular prevention using low dose methotrexate and a monoclonal antibody to IL-1 β , which do not exert effects on plasma lipid levels or platelet function and are thus more specific for treating inflammation¹.

The role of inflammation in multiple sclerosis (MS) was discussed by Dr. Melissa Brown, Professor, Department of Microbiology/Immunology, Northwestern University Feinberg School of Medicine. Dr. Brown's group discovered that mast cells, which are best known for their participation in allergic responses, play a key role in a mouse model of MS⁴. Their work demonstrated that mast cells are critical for influx of T cells into the central nervous system (CNS), which in turn drives the autoimmune process in their experimental model. Subsequent studies unexpectedly revealed that mast cells populate the meninges, where they produce large amounts of tumor necrosis factor that attracts neutrophils to induce a breach in the blood-brain barrier⁵. This enables T cells to gain entry into the CNS to produce the myelin damage characteristic of MS. Their elegant studies have thus demonstrated a role for the meninges in autoimmune diseases of the CNS, provided novel insight into cellular mechanisms underlying MS, and identified a new therapeutic target for this debilitating disease.

Dr. Thomas Gajewski, Associate Professor, Ben May Department for Cancer Research at the University of Chicago, reminded us that inflammation is not all bad. In fact, the same T cells that mediate inflammation in atherosclerosis and MS play a key role in determining the responses to immunotherapy in patients with malignant melanoma. T cells reliably kill melanoma cells *in vitro*, and in 10–30% of patients, immunotherapy effectively reduces tumor burden. Unfortunately, in the majority of patients, melanoma cells evade T cells *in vivo*. Dr. Gajewski's group discovered that the endogenous level of expression of T cell chemokines by melanoma cell lines determines responses to immunotherapy, with cell lines expressing higher chemokine levels exhibiting enhanced susceptibility to immunotherapy⁶. This research may lead to a personalized approach to treating patients with melanoma by identifying those who are more or less likely to respond to immunotherapy and tailoring treatment accordingly. Moreover, in the future, it may be possible to modify melanoma tumors *in vivo* to facilitate T cell recruitment and activation in order to enhance tumor killing and improve the response to immunotherapy.

The symposium was highly interactive. Attendees had the opportunity to ask in-depth questions of experts working in the field in order to learn the nuances. The intimate

atmosphere created an optimal environment for understanding how ongoing research is likely to change the way medicine is practiced in the future.

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Figure 1.