Lupus and T-Cells

Bruce Richardson, Ph.D. M.D., Professor of Internal Medicine, University of Michigan Medical School

By: Sheridan Reed, Office of Research Editorial Assistant

Dr. Richardson, a professor of Internal Medicine, Rheumatology, focuses on understanding Lupus in T-Cells. After earning his M.D. and Ph.D. in Immunology from the University of Chicago, he went on to complete his fellowship at University of Southern California San Francisco where he studied antigen-specific T cell clones. Dr. Richardson gained inspiration for his epigenetic research from Peter Jones at the University of Southern California, who was treating embryonic fibroblasts with the drug 5-azacytidine, a DNA methylation inhibitor. After using the same drug to treat cloned antigen specific T-Cells, Dr. Richardson realized that the cells had become autoreactive and were responding to self antigen presenting cells without added antigen, resembling autoreactive cells that cause lupus in animal models.

Lupus is a disease that affects an estimated 5 million people worldwide. It is a product of both the appropriate genetic background and environmental stimuli that promote both the onset of the diseases and flare-ups. Lupus is also known to affect women 6-10 times more often than it affects men. Dr. Richardson has dedicated the majority of his research time to exploring these two risk factors, environmental stimulus and gender.

Dr. Richardson has made dramatic breakthroughs on the lupus forefront. His DNA methylation findings coupled with his identification of affected genes can help clinicians by avoiding drugs and environmental exposures that can promote the development of lupus or lupus flares. He credited the Biomedical Research Core Facilities here at the University of Michigan as an important resource for his success. Utilizing the services of DNA Sequencing Core, the Transgenic Animal Model Core, the Flow Cytometry Core, and the Microscopy and Image Analysis Laboratory, Dr. Richardson was able to investigate his hypotheses effectively and efficiently. “The cores were the reason I came and the reason I stayed,” he said.

Based on his findings with 5-azacytidine, Dr. Richardson proposed the possibility that drugs that cause lupus might also inhibit DNA methylation. Through experiments done with Hydralazine (used to treat hypertension) and Procainamide (used to treat cardiac arrhythmias), he found his hypothesis to be true; when T-Cells are exposed to DNA methylation inhibitors, lupus flares. He also determined that the more demethylated the appropriate genes in the T-cells were, the more severe the lupus flare. Lastly, he found that the amount of DNA methyltransferase in T-Cells I was decreased in lupus patients. Dr. Richardson drew the conclusion that DNA methylation inhibition was an important, environmentally sensitive risk factor for lupus and lupus flares.
Next he explored the observation that lupus disproportionately affects more women than men. There are currently 50 known lupus genes that mostly assort independently. He also found that in order for a man to have the same severity of a lupus flare as a woman he must either have more lupus genes, or have a greater degree of T-Cell demethylation. Upon further research, Dr. Richardson determined that the second X-chromosome has turned on in women who are suffering from a lupus flare and the severity of the lupus flare is proportional to how reactivated the X-chromosome and other genes qre. Men who suffer from Klinefelter syndrome are also at a higher risk than normal men, for developing lupus.