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Diversity of genes and pathways associated to autoimmunity in lupus mice

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Understanding the pathogenesis of autoimmune diseases remains one of the major challenges of modern immunology. High-throughput analysis, including the study of the association of genetic variants to disease and the global analysis of gene-expression profiles provide the basis for in depth analysis of the molecular pathogenesis of diseases. We examined global gene expression profiles by immunocompetent cells in healthy (C57BL/6-J and Balb/c-J) and lupus (MRLlpr/lpr) mice by means of Affymetrix GeneChip™ Mouse Genome 430 2.0 microarrays to identify differentially- expressed genes (DEG) and pathways in autoimmunity. Regardless of differences between BOT strains of healthy mice, pathways over-represented in lpr-mice were: positive regulation of immune response, response to interferon-β, cell killing, immune response-regulating signaling pathway, response to interferon-γ (GO-biological process); plus: abnormal response to infection, abnormal immune system physiology, abnormal innate immunity, abnormal cytokine secretion, abnormal adaptive immunity (GO-phenotype), among several others. Further analysis by means of CIBERSORTTM revealed that lpr-mice over-represented genes correspond to T follicular helper (Tfh) and plasma cells. By flow cytometry, relative numbers of both CD4+ and CD8+ T cells in the spleen were decreased, whereas B220+ CD5+ cells were greatly increased. Comparing to data from NZB/NZW F1 lupus mice available in public databases, there was a similar increase in plasma cell genes, but BW mice had an increased representation of memory CD4+ cell genes instead of Tfh. Among the most relevant DEGs found in lpr-mice (all of them overexpressed) were cytokines (Il21, Il10, Il4, Ifn-γ etc.), chemokines (Ccl8, Ccl2, Ccl3, Ccl4, Cxcl10, Cxcl11, etc.) and their receptors (Ccr1, Ccr2, Cxcr3), costimulatory surface molecules (Cd28, Ctla-4, Pd-1, Icos, Slamf6, Lag3, Btn1a1), signal transduction (Tnk1, Pik3ap1, Grp84, Lat), transcription (Gfi1, E2f) proteins, and many others (Brca1, Brca2). In conclusion, our results suggest, as expected, that murine lupus is a highly complex syndrome in which varying patterns of gene expression, due to different genetic backgrounds yield closely resembling clinical phenotypes of what we know as systemic lupus erythematosus.

Biography

José Moreno is an MD from the National University of Mexico, with clinical training in Rheumatology and PhD in Immunology with major focus on immunobiology of antigen processing and autoimmunity. He did two postdoctoral trainings in Dallas (Southwestern Medical College) and Heidelberg (Deutsches Krebsforschungszentrum). He has published over 50 papers in international peer-reviewed journals and his currently the Director of Research of Hospital Juárez de México. He is a Member of the National Academy of Medicine (Mexico).

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