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SUPERANTIGENIC ACTIVATION OF T LYMPHOCYTES AND ENDOTHELIAL CELLS: A MECHANISM FOR SUPERANTIGEN-INDUCED VASCULITIS

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Introduction: Superantigens (SAgs) are potent stimulators of T cells bearing specific Vβ T cell receptors (TCR), and although controversial, may have a pathogenetic role in Kawasaki disease (KD) and other childhood systemic vasculitides. We examined a novel mechanism of SAg-induced T cell/endothelial cell activation, and specifically investigated the hypothesis that the endothelial cell may operate as a "non-professional" SAg-presenting cell for T cells bearing specific Vβ TCRs.

Methods: To assess the ability of the endothelial cell to present SAg to T cells, human umbilical vein endothelial cells (HUVECs) with and without pretreatment with γ-interferon (to upregulate MHC Class II) were co-cultured for 4 hours in the presence or absence of purified allogeneic T cells with SEB, or TSST-1. After staining of the co-cultured cells with fluorescent conjugated monoclonal antibodies, flow cytometric analysis was performed on the HUVECs and T cells to examine surface expression of endothelial cell activation markers (cell adhesion molecules), Vβ-specific T cell activation (CD69), and Vβ-specific T cell adherence to the endothelial cell monolayer in vitro.

Results: Co-culture of purified T cells (CD3+, <0.8% expressing HLA-DR) with HLA-DR expressing HUVECs and TSST-1 or SEB resulted in Vβ-restricted CD4 and CD8 activation as determined by surface expression of the T cell activation marker CD69 (Vβ2 activation for TSST-1; Vβ3 and 12 activation for SEB). Additionally, there was CD4 T cell (but not CD8 T cell) Vβ-restricted adherence at 4 hours to the HUVEC monolayer. ICAM-1 and E-selectin expression was upregulated only on the HLA-DR expressing HUVECs following exposure to TSST-1 or SEB in the presence of CD3+ T cells.

Conclusion: In vitro, in the presence of the Th-1 cytokine γ-interferon, the endothelial cell becomes a competent SAg-presenting cell. This results in massive T cell activation and CD4 adherence to the endothelium, consequently resulting in endothelial cell activation. If this mechanism is operational in Kawasaki disease or other childhood vasculitides, it may be possible to block SAg-mediated vascular injury with SAg-peptide antagonists, providing a novel, specific, and potentially nontoxic therapy.

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ANALYSIS OF AUTOANTIBODY REPERTOIRES IN SMALL AND MEDIUM SIZED VESSEL VASCULITIS: EVIDENCE FOR DISEASE-SPECIFIC PERTURBATIONS IN CLASSIC POLYARTERITIS NODOSA (PAN), MICROPOLYANGIITIS (MPA), CHURG-STRAUSS SYNDROME (CSS) AND WEGENER'S GRANULOMATOSIS (WG)

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Objective: To analyze autoantibody repertoires in patients with small and medium sized vessel vasculitis.

Method: Using a quantitative immunoblotting technique on extracts of normal human kidney, liver, lung, muscle and medium sized artery tissues, we analyzed the reactivities of serum IgM, serum IgG and purified serum IgG from patients fulfilling the ARA and Chapel Hill criteria for the diagnosis of classic PAN, WG, MPA or CSS. Blood samples were obtained from 20 patients with PAN, 10 patients in each other group at the time of diagnosis and before treatment, and 60 age- and sex-matched healthy controls. Sera were tested at the same IgG (200 μg/ml) and IgM (20 μg/ml) concentrations.

Results: Repertoires of reactivities of purified serum IgG and of serum IgG of patients with WG, MPA and CSS significantly differed from those of controls and other patients, as assessed by multivariate statistics. IgM repertoires from PAN and MPA but not of WG and CSS patients significantly differed from those of controls and other patients. Antibody reactivities specific to PAN patients were directed toward muscle, liver and/or artery 30 and 40 Kda antigens; one antibody reactivity directed toward 85 Kda antigen in lung was specific to CSS patients.

Conclusion: Autoantibody repertoires from patients with PAN, WG, CSS and MPA are disease specific. Two IgG reactivities directed toward muscle, liver and artery antigens in the case of PAN and one IgG reactivity directed toward lung antigens in the case of CSS were identified.

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