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Altered Regulation of CD46 Expression and Processing in MS

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CD4+ proINS 76-90 (SLQPLALEGSLQKRG) specific T cells using soluble fluorescent MHC class II tetramers. Subjects with type 1 diabetes (T1D; n=10) and healthy controls (n=8) with high levels of peripheral proINS -specific T cells were characterized by the presence of a "disease-susceptible" polymorphism in the INS-VNTR gene. Conversely, subjects with a "protective" polymorphism in the INS-VNTR gene had nearly undetectable levels of proINS tetramer-positive T cells. Using tetramers to isolate proINS -specific T cells from subjects with both INS-VNTR genotypes, transcript arrays (Affimetrix) followed by quantitative Q-PCR profiling have identified several induced pro-apoptotic genes (FASLG, TNF, TNFSF11), and cytokine (IL-2, IFN γ , IL-22, IL1B, IL-10, IL-7) and chemokine (CCL22) pathways in controls, but not diabetic subjects, likely representing a second peripheral mechanism for maintenance of tolerance to self antigens. These results strongly imply a direct relationship between genetic control of autoantigen expression and peripheral autoreactivity, in which proINS genotype restricts the quantity and quality of the potential T cell response.

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OR.10. Altered Regulation of CD46 Expression and Processing in MS

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The regulator of complement activity CD46 acts as a costimulatory molecule for T cells and promotes their differentiation into Tr1 cells, secreting notably the anti-inflammatory cytokine IL-10. We previously demonstrated that CD46 pathway is dysregulated in T cells from patients with multiple sclerosis (MS), as IL-10 secretion is impaired. Herein, we have followed CD46 expression upon T cell activation in cells from a cohort of healthy donors and patients in the RRMS stage. Upon CD46 activation, we first observed the cleavage of its ectodomains by MMPs, which is regulated by the TCR. By homology to Notch, this generates a C-terminal fragment (CTF) that can be further cleaved by the gamma-secretase enzymatic complex. Indeed, loss of expression of both cytoplasmic isoforms occurred after activation, which could be partly restored by addition of a gamma-secretase inhibitor. We did not observe a defect in cleavage of CD46 ectodomain in T cells from patients with MS. However, the loss of CD46 cytoplasmic tails was not observed in T cells from patients. CD46 processing was required for its functions, as demonstrated by the following results: i) addition of gamma-secretase inhibitors to T cell culture inhibited IL-10 production by CD46-activated T cells; ii) expression of a pre-cleaved CTF-cyt1 fragment of CD46 resulted into increased IL-10 production; iii) our preliminary data suggest that both tails are found in the nucleus of activated T cells. Altogether, this suggests that an altered CD46 processing might be at least partly responsible for its defective role in MS.

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OR.11. Citrullinated Fibrinogen Stimulates TNF Release via TLR4 and Citrullinated Fibrinogen Immune Complexes Co-stimulate through TLR4 and the Fc Gamma Receptor

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Extravasation of fibrin(ogen) is a characteristic pathologic finding within the RA synovium. Citrullinated proteins have been demonstrated at many sites of inflammation and citrullinated fibrin(ogen) has been consistently identified within the RA synovium. The presence of anti-citrulline protein antibodies characterizes RA and has been associated with increased RA severity. The innate immune receptor TLR4 is critical in murine models of RA and has been implicated in human RA. Several studies have demonstrated TLR4 dependent signaling by non-microbial damage associated molecules including fibrin(ogen). In this study we demonstrate a dose dependent ability of native and cFb to stimulate macrophage TNF secretion and confirm that this process is TLR4 (and MyD88) dependent. Notably, cFb displayed approximately ten-fold increased potency over native fibrinogen. In-vitro generated cFb containing IC stimulated TNF release at levels significantly above that seen with cFb alone via a process dependent on the combination of TLR4 and the Fc gamma receptor. This study demonstrates that citrullination of fibrinogen dramatically increases its potency on TLR4 mediated TNF release and that cFb IC can co-stimulate through TLR4 and the Fc gamma receptor. Given that citrullination is ubiquitous to sites of inflammation, the ability to increase the potency of an innate damage associated molecule via citrullination is highly novel with potentially broad generalization to the field of innate immunity. Additionally, the ability of cFb containing IC to co-stimulate TNF release provides a potential pathogenic mechanism for RA associated auto-antibodies in the initiation and propagation of synovial inflammation.

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OR.12. Blockade of CD94/NKG2A Prevents EAE

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NK cells are important members of the innate immune system that have been implicated in anti-microbial and anti-tumor defense as well as in maintenance of tolerance and control of autoimmune diseases. The activity of NK cells is regulated by a delicate balance of both activating and inhibitory receptors. CD94/NKG2A is an inhibitory receptor expressed in mice mainly on NK and a subset of CD8+ T cells recognizing the non-classical class I molecule Qa-1. Targeting CD94/NKG2A receptor by blocking its interaction with Qa-1 by a monoclonal antibody is a new therapeutic approach to increase NK cell activity in the treatment of