iaTreg. In particular synovium CPLs/iaTreg reveal 7 common dysregulated pathways; MHC II antigen presentation, T cell costimulation, IFN γ pathway, apoptosis, viral response, bacteria response and chemotaxis.

Conclusion: Overall the data indicate immune-phenotypic convergence between CPLs/iaTregs, that is strengthen across disease/spatial states. These findings underscore a potential mechanistic role of the inflammatory microenvironment in shaping two functionally dichotomic populations, relevant to disease pathogenesis and progression.

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SAT0025

THE EFFECT OF DIMETHYL FUMARATE ON PLASMABLAST DIFFERENTIATION TRANSCRIPTIONAL PROGRAMMES IN SYSTEMIC LUPUS ERYTHEMATOSUS

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Background: Dimethyl fumarate (DMF), is an immunomodulatory drug approved for the treatment of Multiple Sclerosis (MS) and Psoriasis. The exact mechanism of action of DMF is not entirely known. Anti-inflammatory and immunomodulatory effects have been observed, including the upregulation of NRF-2, the inhibition of TIGAR and the block of the E2 ubiquitin-conjugating enzyme UBE13. Further evidence from MS patients suggests a modulation on B cell activation. Although beneficial effects of DMF have been observed in animal models of lupus nephritis and limited cases human cutaneous lupus, the effect of DMF on B cell maturation transcriptional programmes in systemic Lupus Erythematosus (SLE) has not been fully investigated.

Objectives: To examine the effect of DMF on SLE plasmablast differentiation and identify the transcriptomic changes in cultured SLE B cells after DMF administration.

Methods: B cells were isolated from the peripheral blood of SLE patients (n=15) by negative magnetic sorting. B cell differentiation toward plasmablasts was induced in-vitro by stimulation with TLR-7 agonist Resiquimod, CD40L, IL-2, IL-10 and IL-15 for 5 days in the presence of DMF 25 μ M or vehicle, added 24h after plating. IgG and IgM production were quantified in the supernatant by ELISA. In-vitro differentiated B cells were immunophenotyped by 10-colour flow cytometry in order to identify Naïve (CD27⁺IgD⁺), Memory (CD27⁺IgD⁺), IgD⁺ Memory (CD27⁺IgD⁺), Double Negative (DN) (CD27⁺IgD⁺) B cells, pre-plasmablasts (pre-PBs) (CD27⁺, CD20^{low}, CD38⁺) and plasmablasts (PBs) (CD27⁺, CD20^{low}, CD38⁺). Naïve B cells and PBs from 3 patients were isolated by fluorescence-activated cell sorting and underwent to RNA-sequencing followed by pathway analysis.

Results: DMF administered from day 2 led to a relative increase in the percentage of Naïve B cells (p=0.002) and a substantial reduction in Memory B cells (p=0.005), while the proportion of DN cells and IgD⁺ Memory B cells were not altered. DMF reduced the percentage of PBs (p=0.003), in contrast, the percentage of pre-PBs was significantly increased (p=0.006). Consistently, IgG and IgM secretion were significantly reduced (p<0.001). DMF treatment induced significant transcriptional changes in both PBs and Naïve B cells, with 269 and 652 genes modulated in PBs and Naïve B cells, respectively (Paj <0.05). Pathway analysis highlighted the downregulation of a number of pathways: detoxification of reactive oxygen species, transcriptional regulation of cell cycle inhibitor

p21, mitophagy and Pink/Parkin Mediated mitophagy, interleukin-12 signalling, TP53 and p53 regulation, PERK mediated endoplasmic unfolded protein response, and NF- κ B mediated cell survival. Conversely, pathways related to epigenetic regulation, RUNX1 signalling, Rho and GTPase signalling were upregulated.

Conclusion: Our results show that Dimethyl Fumarate exerts a significant inhibition on SLE plasmablast differentiation and antibody production. The transcriptomic analysis allowed to dissect B cell transcriptional programmes activated in the context of autoimmune B cell differentiation in SLE. The transcriptional perturbations induced by DMF highlighted some of the gene expression pathways necessary for plasmablast differentiation and survival. In addition, these data provide new insight into DMF pharmacodynamics and may support the repositioning of DMF in the treatment of SLE.

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SAT0026

IMPACT OF TOCILIZUMAB ON IMMUNE PHENOTYPES IN PATIENTS WITH LARGE VESSEL VASCULITIS

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Background: The pathogenesis of large vessel vasculitis (LVV) such as Takayasu arteritis (TAK) and giant cell arteritis (GCA) consists of the immune abnormalities including the interaction between vascular dendritic cells, macrophages and T cells. It is reported that genetic polymorphisms in the immune-modulating cytokine genes such as *IL6* and *IL12B* are associated with LVV. However, little is known about pathological immune cell subsets targeted by immunosuppressants and/or molecular-target therapy such as IL-6 blockade.

Objectives: The aim of this study was to assess the relationship between the phenotype of peripheral immune cells with clinical manifestations and responsiveness to the treatment in patients with LVV.

Methods: Peripheral blood mononuclear cells were obtained from 22 patients with active LVV (TAK 7, GCA 15) and 19 healthy donors (HD). All patients were treated with high dose glucocorticoid (GC). The study included the patients treated with immunosuppressive agents such as azathioprine and methotrexate (n=8) or with anti-IL-6 receptor antibody tocilizumab (n=7). The blood samples were taken at baseline and week 24 after treatment. The peripheral immune cell subset was defined based on comprehensive 8-color flow cytometric analysis for human immune system termed "the Human Immunology Project" by NIH and FOCIS⁽¹⁾, and the correlation with clinical characteristics and responsiveness to the therapies were evaluated.

Results: The proportion of CD3⁺CD4⁺CXCR3⁺CCR6⁺CD38⁺HLA-DR⁺ activated Th17 cells and CD3⁺CD4⁺CXCR5⁺ICOS⁺CD38⁺ activated Tfh cells in patients with TAK and that of activated Th17 cells and CD19⁺CD20⁺CD27⁺IgD⁺ double negative effector B cells in patients with GCA were significantly higher compared with HD. At baseline, the frequency of activated Tfh cells showed positive correlation and that of CD4⁺CCR4⁺CD25⁺CD127^{low} T regulatory (Treg) cells showed negative correlation with disease activity scores such as Indian Takayasu Activity Index (ITAS)2010⁽²⁾ and ITAS.A (CRP) in both TAK and GCA. The immunosuppressive therapy improved the disease activity in all patients. The frequency of activated Tfh cells was reduced by 24-week treatment with high dose GC and immunosuppressants in TAK and GCA. However, the frequency of Th17 cells was not changed by those treatments. Of note, tocilizumab decreased the proportion of activated Th17 cells and increased the proportion of Treg cells in both TAK and GCA.

Conclusion: The results indicated that the abnormal T cell differentiation correlated with disease activity of LVV. Although Tfh cell activation was improved, Th17 cell activation was not changed by the conventional immunosuppressive agents. By contrast, tocilizumab reduced Th17 cells and increased Treg cells, indicating that IL-6 blockade may correct the impaired balance of Th17 and Treg cells in patients with LVV.