LAG3+ Regulatory T Cells Restrain Interleukin-23-Producing CX3CR1+ Gut-Resident Macrophages during Group 3 Innate Lymphoid Cell-Driven Colitis


Defects in mucosal immune tolerance can lead to inflammatory bowel disease (IBD) such as Crohn’s disease and ulcerative colitis. It is known that Interleukin-22 (IL-22)-producing group 3 innate lymphoid cells (ILC3) maintain gut homeostasis but can also promote IBD. The authors sought to determine key mechanisms and regulation of ILC3-dependent colitis. They used a Custom CodeSet containing key autoimmune genes to profile direct lysate from FFPE tissue sections. The group demonstrated that LAG-3+ Treg cells suppress the production of proinflammatory cytokines by CX3CR1+ macrophages and thereby inhibit ILC3-driven colitis.

Comparison of RT-qPCR and NanoString in the Measurement of Blood Interferon Response for the Diagnosis of Type I Interferonopathies

Pescarmona et al., Cytokine. 2019 Jan;113:446-452

The publication focuses on an inflammatory response that is all too common with type I interferonopathies such as that seen in various autoimmune disorders. Type I interferonopathies refer to rare Mendelian genetic disorders such as Aicardi-Goutières Syndrome (AGS) as well as more frequent and polygenic autoimmune diseases like systemic lupus erythematosus (SLE). Yet, detection of type I interferon (IFN) remains challenging as it is usually present in low amounts in sera.

The aims of this study were (1) to set up a routine clinical test to measure the interferon response and (2) to compare the results obtained with two techniques: RT-qPCR and NanoString. For that, the group quantified the expression of six IFN stimulated genes (ISGs) previously found to reflect the overall exposure to IFNs in patients with AGS, lupus and other interferonopathies. 200 ng of RNA was utilized with a Custom CodeSet. Compared to RT-qPCR, NanoString technology does not require reverse transcription or amplification of genetic material that are the two main causes of bias with RT-qPCR. Also, because NanoString can be used to multiplex different genes, other interesting target genes like IL-1β, IL-6 or TNF-α can be easily added to the assay with minimal effort. The correlation between these two methods was strong for each of the ISGs and thus for the IFN score. Moreover, ROC curves established with each technique in a pediatric cohort demonstrated high sensitivity and negative predictive value for the diagnosis of interferonopathies. In terms of analytical performance, both methods achieved similar results, but NanoString was quicker, easier to multiplex, and nearly fully automated.

Fas Ligand Promotes an Inducible TLR-dependent Model of Cutaneous Lupus-like Inflammation

Mande et al., J Clin Invest. 2018 Jul 2;128(7):2966-2978

While it is well established that Toll-like receptors TLR7 and TLR9 are both implicated in the activation of autoreactive B cells and other cell types associated with SLE pathogenesis, paradoxically Tlr9 KO mice develop more of a severe disease, indicating a negative feedback mechanism. To investigate this further, the authors developed an inducible rapid-onset murine model of systemic autoimmunity that depends on T cell detection of a membrane-bound OVA fusion protein expressed by MHC class II cells, expression of TLR7, expression of the type I IFN receptor, and loss of expression of TLR9.

100 ng of RNA from mouse skin biopsies was profiled using the mouse and human PanCancer Immune Profiling panels. The group followed up with validation work in human samples by comparing gene expression profiles of lesioned skin obtained from subjects with lupus or psoriasis to that of healthy controls. Results demonstrated the strength of NanoString as a discovery tool and a lot of overlapping genes were deregulated in both the human and mouse model. Many of the ISGs and chemokines highly upregulated in the mouse model were also upregulated in human lupus lesions and, to a lesser extent, in psoriasis lesions, further supporting the relevance of the mouse model to human lupus like symptoms. Importantly, of all the genes investigated, FasL was found to be the key effector mechanism in the skin in mouse models, as the transfer of FasL-deficient DO11gld T cells completely failed to elicit overt skin lesions. FasL was also upregulated in human cutaneous lupus erythematosus (CLE) biopsies. Overall, the authors’ model provides a relevant system for exploring the pathophysiology of lupus as well as the negative regulatory role of TLR9.
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*The Plasma Biomarker Soluble SIGLEC-1 is Associated with the Type I Interferon Transcriptional Signature, Ethnic Background and Renal Disease in Systemic Lupus Erythematosus*


The authors developed a novel research immunoassay to detect the circulating soluble form of the monocyte-specific surface receptor sialic acid binding Ig-like lectin 1 (SIGLEC-1). SIGLEC-1 is a cell-adhesion molecule involved in the initial contacts with sialylated pathogens and mediates phagocytosis and endocytosis of pathogens, thereby promoting efficient immune responses to limit infection. SIGLEC-1 is expressed exclusively in cells of the myeloid lineage, namely tissue-resident macrophages and monocyte-derived dendritic cells. In blood, expression of surface SIGLEC-1 is restricted to CD14+ monocytes and has been previously reported to be increased in several autoimmune diseases, including lupus, rheumatoid arthritis, systemic sclerosis (SSc) and primary biliary cirrhosis.

RNA from SLE samples and age and sex-matched healthy donors was extracted from freshly isolated PBMCs. 50 ng of total RNA was hybridized with a Custom CodeSet containing 56 interferon response genes previously identified as discriminative of the IFN signature.

The data highlights the comparison of SIGLEC-1 with other markers of disease activity, specifically the correlation between the SIGLEC-1 concentration and the canonical IFN transcriptional signature obtained through NanoString analysis. In conclusion, in combination with additional available IFN-regulated biomarkers, the SIGLEC-1 bioassay could help improve the capacity to dissect the molecular heterogeneity of complex conditions associated with an overt IFN response and identify subsets of common and rare autoimmune and inflammatory diseases, collectively classified as interferonopathies.

*T Helper 1 Cellular Immunity Toward Recoverin Is Enhanced in Patients With Active Autoimmune Retinopathy*

Lundy et al., *Front Med* (Lausanne). 2018 Sep 13;5:249

The paper describes the phenomenon of autoimmune retinopathy (AIR) which causes rapidly progressive vision loss that is treatable but is often confused with other forms of retinal degeneration including retinitis pigmentosa (RP). Currently, to determine if autoimmunity against retinal antigens is present in these patients, Western blot and histological assays have been developed as laboratory diagnostic tests to detect anti-retinal antibodies (ARA).

RNA from 14 samples in each group was purified from whole blood collected in PAXgene tubes, and 100 ng of the purified RNA was used with the Human Immunology Panel. To understand whether there were systemic differences in immune associated gene expression, mRNA levels in whole blood of a set of immunologically important genes were quantified from samples in each group. Gene expression of the major lymphocyte markers CD8, CD56, and CD19 was similar between the three groups but expression of the CD4 gene was higher in the AIR groups than in the RP group or controls. Many of the upregulated genes were transcription factors associated with lymphocyte activation, particularly those implicated downstream of cytokine receptors.

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