

and will never develop overt disease. Understanding differences in immune cell physiology between ANA+healthy individuals and individuals with clinical SLE remains a critical goal in the understanding of SLE pathogenesis across ethnicities.

Methods Blood specimens and information on disease activity were collected from European (EA) and African American (AA) individuals classified and matched in groups as ANA-healthy controls (n=24), ANA +healthy (n=24) or SLE patients (n=24). Single-cell analysis of cell surface markers was completed by mass cytometry on PBMCs and cellular heterogeneity was visualized using tSNE (figure 1A–B) and manual gating. Further, phospho-specific flow cytometry was used to measure basal levels of pERK, pPLCg2 and p38 and expression following CD3/CD28 (TCR) and anti-IgG and IgM (BCR) stimulation. Whole genome RNA-sequencing was performed on flow cytometry sorted T cells, B cells and monocytes from 35 matched ANA-, ANA +and SLE patients followed by weighted correlation network analysis (WGCNA) and pathway enrichment analyses.

Results Both European and African American SLE patients were distinguished from healthy individuals by T cell proliferation (p=0.002) (figure 1C), plasmacytoid dendritic cell activation (p=0.021) and elevated stem cell factor (p=0.0003). EA ANA+healthy individuals exhibited greater immune regulation with reduced T cell numbers (p=0.002) (figure 1C), decreased activation of dendritic cells (p=0.039) and transitional B cells (0.033), and elevated expression of the inhibitory receptor CD85j (p=0.042) on specific immune cell subsets compared to ANA- healthy subjects. Further, a module associated with hematopoiesis, T cell activation and intrinsic apoptosis signaling pathways is expressed at a higher level in T cells of EA ANA+individuals. In contrast, AA ANA+healthy individuals had elevated plasma levels of IL-6 (p=0.018) and reduced inhibitory receptor expression (p=0.0089) compared to ANA-healthy controls. Gene expression modules associated with viral responses and type I IFN pathway activation were identified in AA SLE patient B cells, while similar expression modules were only found in the monocytes of European American SLE patients.

Conclusions These results highlight the importance of stem cell factor and T cell expansion in SLE pathogenesis, and suggest that mechanisms of SLE pathogenesis differ by ethnicity. ANA +European Americans may have more effective regulatory mechanisms in place to prevent transition to classified autoimmune disease.

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CLINICIANS WITH LUPUS LOSING SKILLS AND DIVERSITY FROM HEALTH SERVICES RESULTS FROM AN ON-LINE SURVEY

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Background It is well-documented that people with systemic lupus erythematosus (SLE) have high levels of workplace disability and unemployment. We present the data from a sub-group of participants in an on-line survey designed to

understand the barriers and facilitators to employment in people with lupus as a first step towards solutions. Three hundred and ninety-three detailed questionnaires were returned, demonstrating that the overarching barriers to continuing employment were fluctuation, invisibility and fatigue, facilitators were flexibility in working pattern, part-time working understanding management and colleagues. Participants suffered from high levels of anxiety and distress about their loss of income and likely future inability to work. Those claiming benefits felt guilt, shame and humiliation.

Methods The on-line survey was conducted in UK adults with SLE, through the LUPUS UK website, and was designed to find out about the difficulties and successes that people with SLE have in maintaining employment. The data from participants working in a clinical profession or employed by the National Health Service (NHS) in a clinical-related activity were identified from the cohort. Their data is currently being analysed to see if those working in NHS organisations have consistently good experiences of workplace support and better chances of retention.

Results Fifty-five of the sample of 393 (14%) worked or had worked in the NHS in a clinical or clinically-related role. Roles include doctors, managers clinical coders, midwives, podiatrists, pharmacists, operating department assistants. The largest group were nurses including two in senior roles and untrained nursing assistants. Most of the sample had reduced hours or stopped working completely directly as a result of lupus, support was variable with some attributing workplace flexibility to NHS employment but others experiencing harassment. A recently introduced method of calculating sick leave militates against people with fluctuating conditions.

Conclusions SLE presents specific difficulties for maintaining employment fatigue, fluctuation and invisibility not addressed by current anti-discrimination legislation or currently-available reasonable adjustments. As Europe's largest employer with a core mission of treating illness the NHS could set an example of how to overcome barriers to employment in people with fluctuating conditions, like lupus. There is clear evidence of loss of skills from the organisation and emerging evidence from this study suggest variable support and levels of knowledge from managers and colleagues. Personal pain from loss of role and income were high in participants. Further data will be available.

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IKZF1 AND IKZF3 INHIBITION IMPAIRS B CELL DIFFERENTIATION AND MODULATES GENE EXPRESSION IN SYSTEMIC LUPUS ERYTHEMATOSUS

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Background Polymorphisms in IKZF1 (Ikaros) and IKZF3 (Aiolos), which are transcription factors essential for B cell activation, maturation and differentiation, have been associated with Systemic Lupus Erythematosus (SLE). However the functional role of IKZF1 and IKZF3 in the context of failed B

cell checkpoints and aberrant plasmablast development in SLE has not been previously characterised. Iberdomide (a cereblon modulator) known to induce the degradation of transcription factors IKZF1 and IKZF3 is being explored as a therapeutic target for SLE. The aim of this study was to utilise iberdomide to evaluate the effect of inhibition of IKZF1 and IKZF3 on transcriptional programmes underlying B cell differentiation, gene expression and immunoglobulin production in SLE B cells.

Methods CD19 +B cells were isolated from peripheral blood of 25 SLE patients and stimulated with IL-2, IL-10, IL-15, CD40L and TLR7 ligand Resiquimod for 5 days to induce plasmablast differentiation. In separate studies, B cells were treated from the outset with iberdomide (10 nM) or vehicle and subsequently differentiated, or differentiated plasmablasts (day 4) were treated with iberdomide or vehicle for 18 hour. Treated plasmablasts underwent fluorescence-activated cell sorting (FACS), and IgG/IgM secretion analysed with ELISA. FACS-sorted CD27-IgD+naïve B cells and CD20lowCD27+CD38+plasmablasts were subjected to bulk ultra-low input RNA-seq along with matched baseline B cells. Unsupervised clustering, differential gene expression and pathway analysis were performed on transcriptome data.

Results Day 0 iberdomide (n=9), but not day 4 iberdomide (n=16), significantly reduced the CD20lowCD27+CD38+plasmablast numbers following cell culture (p=0.03). Similarly, Day 0 iberdomide significantly decreased supernatant IgG/IgM concentrations (p=0.050 and 0.017, respectively), but not day 4 iberdomide. RNA-seq of sorted naïve B cells and plasmablasts cultured with day 4 iberdomide demonstrated significant differential gene expression in both populations (400 and 461 differentially modulated genes in naïve B cells and plasmablasts, FDR-adjusted p<0.05). Pathway analysis showed that IKZF1/IKZF3 inhibition resulted in downregulation of JAK-STAT signalling downstream of IL12 (FDR=7.92E-04), IL12 signalling (FDR=0.0014), and p53 signalling regulation of cell death (FDR=0.0043) and showed a trend to upregulation of RUNX1 signalling and Rho GTPase cycle.

Conclusions Iberdomide exposure significantly blocked SLE B cell differentiation into plasmablasts, but did not alter fully differentiated plasmablast viability, confirming the role of IKZF1 and IKZF3 in the process of B cell differentiation into aberrant plasmablasts in SLE. Our study demonstrates that IKZF1 and IKZF3 inhibition results in differential expression of key B cell development transcriptional gene modules in both SLE naïve B cells and plasmablasts.

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UNDERSTANDING SYSTEMIC LUPUS ERYTHEMATOSUS. A QUALITATIVE STUDY OF WOMEN WITH INACTIVE DISEASE

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Background Systemic lupus erythematosus (SLE) is a chronic and cyclic disease with an autoimmune characteristic caused by a combination of environmental, hereditary, stress or congenital predispositions. The acute period of the disease is experienced by the patients as debilitating and of adaptive

psychological changes. In the period of remission of the clinical symptoms of the disease, other adaptive psychological components are used as a way of dealing with the limitations imposed by the disease. Objective: To verify how people with systemic lupus erythematosus use adaptive psychological resources to deal with the disease in this asymptomatic period.

Methods This qualitative study was used to study 9 selected women after the application of SLEDAI (Systemic Lupus Erythematosus Systemic Activity Index) in the post-consultation period with scores equal to or less than 3. Subsequently, the first author's psychologist The qualitative research studies proposed the understanding of the phenomena observed in the scientific environment. The data collected through the recording of participants' speeches were analyzed through content analysis, using the theoretical framework of health psychology. The intention is always to understand the manifestation of something in a group, without the causal intention, only then to give visibility to new strategies both for therapeutic interventions and for new generalizable scientific studies. University Hospital of Southeastern Brazil. In this qualitative study, the strategy of saturation was used to calculate sample size and the number of individuals was held when we verified similarity in responses.

Results 9 female participants were selected. In the speeches of participants, the following topics were identified: Do not think about the existence of the disease; The return to daily activities; Living with other people; The perception of the current body.

Conclusions The perception of the possibility of reactivation of the disease, allows these participants a constant vigil of occasional symptoms that arise. It is such a way to have emotional control over the occasional symptoms that arise. Reviving in anticipation all the trajectory of a possible aggravation of the disease. It is the fear and rationalization of the possibility of reactivation of Systemic Lupus Erythematosus, which allows these participants to have adherence to the continuous treatment in this period.

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CELL BOUND COMPLEMENT ACTIVATION PRODUCTS IN COMBINATION WITH LOW COMPLEMENT C3 OR C4 HAVE HIGH DIAGNOSTIC YIELD IN SYSTEMIC LUPUS ERYTHEMATOSUS

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Background Cell Bound Complement Activation Products (CB-CAPs), are stable form of classical complement activation, *ex vivo*, and sensitive and specific marker of SLE. In the present study, we sought to compare the performances of CB-CAPs to gold standard low complement C3 or C4.