

influence the activity/availability of IKZF3 and promote autoimmunity.

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SINGLE CELL GENOMICS OF SELF-REACTIVE B CELLS REVEALS THE EVOLUTION FROM BENIGN TO PATHOGENIC AUTOANTIBODY AND STRATEGIES FOR EARLY DIAGNOSIS AND PERSONALISED TREATMENT

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Background Autoantibodies appear in the serum years before the development of clinical disease in patients ultimately diagnosed with systemic lupus erythematosus (SLE) or Sjögrens syndrome. The transition from benign to pathogenic autoimmunity is not understood. Anti-IgG rheumatoid factors provide an illuminating example of an autoantibody that persists, on average, more than four years prior to the development of systemic vasculitis and type II cryoglobulinemia. The aim of this study was to identify the pathogenic changes occurring in B cells making rheumatoid factor autoantibody during this transition.

Methods Massively parallel sequencing of peripheral blood B cell receptors (BCR) was combined with mass spectrometry peptide sequencing of serum rheumatoid factor autoantibodies to identify circulating B cells expressing IgM rheumatoid factors in 4 patients with SLE or Sjögrens syndrome. In a patient presenting with primary Sjögrens syndrome evolving to cutaneous vasculitis, blood samples before and after transition were subjected to single cell analysis of mRNA, genome methylation, and lymphocyte regulatory genes recurrently mutated in lymphoma and leukemia.

Results Circulating rheumatoid factor B cell clones and their matched serum autoantibodies were identified in 4 patients, 3 of whom, produced the stereotypic Wa-type rheumatoid factor with IGHV1-69 and IGKV3-20 variable domains. Longitudinal analysis of a patient before and after vasculitis revealed a single Wa-type rogue clone was responsible for the rheumatoid factor over a period of 6 years. Compared to the patients normal memory B cells, the rogue cells had aberrant gene expression corresponding to CD11c+CD21 low B cells observed in autoimmunity, and hypomethylation of gene regions aberrantly hypomethylated in chronic lymphocytic leukemia (CLL). A loss-of-function somatic mutation in a Kelch-like protein gene, KLHL6 identical to recurring CLL and lymphoma mutations was acquired by half of the rheumatoid factor B cells. KLHL6 mutant cells slowly accumulated antibody variable domain replacement mutations that did not alter binding affinity but caused IgM-IgG immune complexes to precipitate at temperatures below 25C.

Conclusions Transition from a benign to pathogenic rheumatoid factor was preceded by a lymphoproliferative disease mutation in the responsible B cells and resulted in

accumulation of antibody somatic mutations that diminish immune complex solubility. The ability to detect clones of the rheumatoid factor that are accumulating replacement mutations years prior to the patient developing cryoglobulinemia represents an opportunity to interfere with the conversion from asymptomatic seropositivity to clinical disease.

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ROLE OF STIGMA AND SOCIAL ISOLATION ON DEPRESSION IN PATIENTS WITH CHRONIC CUTANEOUS LUPUS ERYTHEMATOSUS

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Background Skin disorders can cause mental health problems associated with stigmatization and social isolation. We found that 26% of individuals with chronic cutaneous lupus erythematosus (CCLE) reported moderate to severe depressive symptoms. While patients perceptions of disrespectful office staff increased the risk of depression, emotional support was associated with a reduction. In this study, we examined the relationships between stigma, social isolation, and depression. We further examined if social isolation mediates the relationship between stigma and depression and whether sociodemographic characteristics may moderate those relationships.

Methods We conducted a cross-sectional study in a predominantly African American cohort of patients with primary CCLE from metropolitan Atlanta, Georgia, U.S. Depression, stigma and social isolation were assessed using the NIH PROMIS short forms. Linear and multiple regression were used to examine the relationship between depression, stigma and social isolation. Education attainment, poverty and race were explored as potential moderators.

Results Among 118 patients with a documented diagnosis of primary CCLE, 104 (88%) were female, 96 (81%) were African American, 54 (46.2%) completed high school or less, 40 (40.8%) lived in poverty and 34 (28.8%) self-reported moderate to severe depressive

Abstract 242 Table 1 Multiple linear regression models for predicting depression in CCLE

Predictor Variable	Model 1* (Mediator effect of Social Isolation)		Model 2** (Moderator effect of Education)	
	β	p-value	β	p-value
Stigma	-0.018	0.88	0.270	0.011
Social isolation	0.527	<0.0001		
Education (\leq high school)	-	-	-22.30	0.009
Stigma*Education (\leq high school)	-	-	0.454	0.004

*Controlled for age, race, gender and education; **Controlled for age, race and gender.