Abstract BD-02 Figure 1 Metabolic control of pro-inflammatory T-cell lineage specification in SLE. Schematic molecular order of pathways upstream and downstream of activation of the mechanistic target of rapamycin (mTOR) in SLE. mTOR is activated on the surface of lysosomes in a state of amino acid sufficiency (V/L/I/Q/Kyn). Oxidative stress, in particular cysteine oxidation, also activates mTORC1 through association with Rheb. Given the results of our randomized double-blind placebo-controlled clinical trial showing that therapeutically effective reversal of GSH depletion by NAC blocks mTORC1 in vivo, GSH depletion will be considered the primary metabolic checkpoint of pro-inflammatory T-cell lineage specification in SLE. The depletion of GSH will be mechanistically connected to the depletion of cysteine (Cys) and NADPH and to the accumulation of kynurenine (Kyn) which have been uncovered by comprehensive metabolome studies of PBL from SLE and healthy subjects matched for age, gender, and ethnicity and processed in parallel. Blockade of mTOR with rapamycin reverses the depletion of effector-memory CD8 T cells and Tregs and the expansion of pro-inflammatory CD4’CD8' double-negative T cells in patients with active SLE in vivo. Red and blue arrows reflect direction of changes in SLE.

Abstracts

BD-03 ADHERENCE TO ANTIMALARIALS AND RISK OF TYPE 2 DIABETES MELLITUS IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS: A POPULATION-BASED COHORT STUDY

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Background Aside from their effect on disease activity in systemic lupus erythematosus (SLE) antimalarials have been shown additional benefits such as reducing the risk of diabetes. However, a recent systematic review reported sub-optimal adherence to antimalarials with rates as low as 25%. As medication adherence mediates patient outcomes, our objective was to evaluate the association between adherence to antimalarials...
Background Systemic lupus erythematosus (SLE) disease activity is characterized by tissue deposition of immune complexes and consumption of complement, which contribute to tissue injury. In clinical practice, it is common to encounter patients where either C3 or C4 is low in isolation, though the clinical implications of variation in C3 relative to C4 are unclear. Here we performed relationship-based clustering of SLE patients based on serum C3 and C4 levels to investigate if this could define distinct clinical subgroups of SLE patients.

Methods C3, C4 and other clinical and laboratory parameters were obtained from our proprietary database. A total of 151 SLE patients having an average of 38 (range 7–117) measurements of C3 or C4 were studied. To classify SLE patients based on the character of the relationship of C3 vs C4, we performed relationship-based clustering approach by defining linear fit parameters (including alpha, beta, standard error, and p values) followed by hierarchical clustering. The clusters obtained were screened in terms of their dependency to clinical data using chi square test or Fisher’s exact test, as appropriate, with significance defined as p<0.05.

Results Clustering based on multiple characteristics of the relationship between C3 and C4 identified 6 clusters of patients. Clusters 1 and 6 were small and did not have clear phenotypes. Cluster 2 and cluster 5 were both defined by strong correlations between C3 and C4 (Cluster 2 = r = 0.81, p<0.00001, Cluster 5 = r = 0.81, p=0.0016), though cluster 5 had a lower median C3 level (Cluster 2 C3=79.5, Cluster 5 C3=74.5). Cluster 3 had higher median levels of C3 and C4 (C3=106.0, C4=20.6), and the correlation between C3 and C4 was far less robust (r=0.60, p=0.44730). Cluster 4 was notable for the lowest median C3 and C4 levels (C3=69.8, C4=12.3), and no significant correlation between C3 and C4 was present (r=0.54, p=0.121143).

Individuals in cluster 2 were more likely to have Jaccoud arthropathy (OR 6.11, CI 1.59 to 24.47), or a history of avascular necrosis (AVN) (OR 4.38, CI 1.55 to 12.34), but less likely to have thrombocytopenia (OR 0.15, CI 0 to 0.98). Cluster 5 patients were more likely to have thrombocytopenia (OR 2.78, CI 1.04 to 7.43) and less likely to have AVN (OR 0.27, CI 0.05 to 0.99).

Conclusions C3 and C4 levels vary widely in SLE patients but generally fall into a few general patterns, which are associated with different clinical manifestations, and may provide novel insight into underlying biological differences between SLE patients.

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