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**“Activity-Dependent Atherogenic Remodeling in Systemic Lupus Erythematosus
Revealed by Integrated Transcriptomics and Proteomics”**

Systemic lupus erythematosus (SLE) is associated with accelerated atherosclerosis and ~3-fold increased cardiovascular mortality. Current immunosuppressive therapies do not fully prevent cardiovascular events, suggesting persistent atherogenic pathways beyond standard immune targets. While individual atherogenic biomarkers have been reported in SLE, no study simultaneously integrated whole blood transcriptomics and dual-platform proteomics across full spectrum disease activity. Hence, our aim was to identify treatment-resistant and activity-associated atherogenic signatures in well characterized cohort of SLE patients. We analyzed publicly available whole-blood transcriptomic and proteomic data (GSE318067) from SLE patients (n=41; inactive–severe disease) and matched healthy donors (n=34) across Affymetrix microarray (19,658 loci; n=41), SomaLogic SOMAscan (1,320 proteins; n=34), and Myriad RBM DiscoveryMAP (281 proteins; n=34). Differential expression between SLE and healthy donors was previously performed using linear models with Benjamini-Hochberg (BH)-adjusted $P < 0.05$ and fold-change thresholds ≥ 1.5 (transcripts) and ≥ 1.3 (proteins). Disease activity-associated gradients were assessed using Kruskal-Wallis tests, with pairwise Mann-Whitney U tests and BH correction. Atherosclerosis-related mediators were broadly dysregulated across platforms, with concordance in CXCL10, CSF1, MMP3, MMP7, and CD5L. Lipid handling pathways showed macrophage lipid stress, including upregulation of ABCA1 (FC 1.65, adj.P=0.0004) and LIPA (FC 1.77, adj.P= 3×10^{-8}), alongside interferon-linked APOL6 (FC 1.92, adj.P=0.0001). PLA2G2A, a secreted phospholipase that remodels LDL phospholipids rendering particles more atherogenic, was proteomically elevated in active SLE (FC 1.41, adj.P=0.007) with a significant disease activity-dependent gradient (KW $p=0.008$). Endothelial activation was activity-associated, with increased VCAM1 (FC 1.59), ICAM1 (FC 1.44), SELE (FC 1.67), and VWF (FC 1.52). Macrophage foam-cell and inflammatory signaling increased with severity, including CSF1 (FC 1.53, dual-platform), SPP1 (FC 1.83), CD5L (FC 1.42–1.49, dual-platform), and CCL2 (FC 1.67). Plaque destabilization markers MMP3 (FC 2.05) and MMP7 were elevated across proteomic platforms, with MMP8 transcriptionally increased (FC 1.83). Pro-thrombotic remodeling included increased fibrinogen chains (FGA/FGB/FGG, FC 1.54–1.56) and decreased THBS1 (FC –1.55). Even in clinically inactive SLE, a coordinated atherogenic signature persists despite immunosuppression, encompassing lipid stress (ABCA1 $\uparrow$, LIPA $\uparrow$, APOL6 $\uparrow$), endothelial activation (VCAM1, ICAM1, SELE, VWF), macrophage foam-cell priming (CSF1, SPP1, CD5L, CCL2), plaque destabilization (MMP3, MMP7, MMP8), and pro-thrombotic remodeling (fibrinogen $\uparrow$, THBS1 $\downarrow$), amplifying further with disease severity. This treatment-resistant, activity-driven cardiovascular program identifies a critical unmet need for lipid-targeted and vascular co-management in SLE.