Background: Systemic Lupus Erythematosus (SLE) patients have a 3-fold risk of CV events compared to the general population, mainly due to accelerated atherosclerosis that is not completely explained by the presence of traditional CV risk factors. Individuals with increased intimal medial thickness (IMT) carry a higher risk to develop carotid atherosclerosis. Accordingly, IMT acts as a marker of systemic vascular involvement.

Methods: We recruited SLE patients fulfilling 2019 EULAR/ACR classification criteria. Patients with other rheumatic, ophthalmological diseases, diabetes or the course of their disease. Moreover, cutaneous lesions are the first sign of systemic disease in 20% of SLE patients [1]. Skin requires a regulated and undisrupted mRNAs profile for a correct development and function. Studies show that miRNAs play a pathogenic role in autoimmune skin diseases such as Psoriasis [2]. Understanding of the role of deregulated miRNAs in CLE may enhance our knowledge about CLE pathogenesis which is currently not understood.

Objectives: Identify differentially expressed miRNAs in skin lesions to determine new markers of CLE pathogenesis.

Methods: Paired skin biopsies from CLE lesional (n=20) and non-lesional skin (n=20) were obtained. MiRNA microarray screening was performed using TaqMan MicroRNA Array. Validation was performed in a new cohort of FFPE skin samples by qRT-PCR (n=20). In situ hybridization was performed to identify the skin cell type involved in selected miRNAs. Next, in vitro experiments using primary skin and immune cells were performed in order to discover their role in CLE pathogenesis. A microarray screening and luciferase assay were performed to find miR-885-5p altered gene expression, molecular pathways and target genes.

Results: miR-885-5p was found downregulated in CLE lesional skin (-4.45 fold, p<0.01, respectively). Results were confirmed in a validation cohort. In situ hybridization revealed miR-885-5p was located in the epidermal keratinocytes in CLE non-lesional skin. Healthy keratinocytes presented an increased miR-885-5p expression compared with other relevant cell types such as fibroblasts (p<0.001) or PBMCs (p<0.001). Moreover stimulation with IFNα and UVB promoted a marked long-lasting downregulation of miR-885-5p (IFNα, 24h -67 fold (p<0.001); UVB, 24h -70 fold (p<0.001)).

Gene microarray of anti-miR-885-5p keratinocytes showed that the unique gene that was upregulated in all anti-miR-885-5p conditions was Psmb5. In vitro experiments demonstrated that Psmb5 is a direct target of miR-885-5p (74% of reduction p<0.001) and it is involved in epidermal inflammation by enhancing NFκB and inflammatory cytokines IL-1β, TNFα and CXCL8. In addition, we observed immune recruitment in UVB stimulated anti-miR885-5p keratinocytes and we found that this immune migration is mediated via miR-885-5p.