Exosomes and Immune Modulation in Pediatric SLE

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Project Summary/Abstract

Systemic lupus erythematosus (SLE) is a multi-organ rheumatologic disease characterized by immune dysregulation and a heterogeneous disease course, with heightened disease severity in pediatric patients. The lack of knowledge regarding the immune cellular and molecular events leading to SLE disease poses a significant hurdle in the effort to develop accurate disease biomarkers and selective therapeutic agents. The objective of this proposal is to elucidate the mechanisms by which serum-isolated exosomes modulate cytokine derangements in pediatric SLE pathogenesis. To achieve this goal, this proposal will use imaging flow cytometry platform, which offers the integration of fluorescencebased antibody detection and visual interrogation (microscopy) for each exosome microparticle event. Therefore, this analysis will allow phenotypic definition of the parent cells and offspring exosomes along with real time microparticle generation kinetics (Aim #1). To understand the immunoregulatory role of these SLE phenotypically characterized exosomes, healthy donor peripheral blood will be stimulated with SLE and healthy control exosomes (Aim #2a) and exosome-derived microRNAs (Aim #2b), intracellular single-cell cytokine production will be evaluated via flow cytometry. Preliminary studies have demonstrated that healthy donor blood cells exposed to SLE sera and SLE sera exosomes resulted in the activation of monocytes and the production of monocyte chemoattractant protein-1 (MCP1), macrophage inflammatory protein-1β (Mip1β), and interleukin-1 receptor antagonist (IL1RA). Comparison of serum exosome-derived microRNAs from SLE patients and healthy controls will demonstrate the specific components that likely drive such inflammatory signature. The proposed approach is innovative because it departs from the status quo by elucidating specific serum exosomemediated mechanisms underlying inflammatory perturbations in SLE. The proposed research is significant because it will likely identify novel therapeutic targets derived from serum exosomes and their microRNA components. The knowledge gained will have broad translational importance through application of this approach to other pediatric systemic rheumatologic disorders studied in the CARRA network.

Lay Summary

Pediatric lupus is an autoimmune disorder with diverse clinical presentations, affecting multiple organ systems. The clinical heterogeneity is a reflection of the underlying dysregulated immune system, which is still poorly understood. The goal of this proposal is to elucidate the mechanisms that govern immune derangements in pediatric lupus, which would provide the foundation for selective therapeutic interventions. To achieve this goal, this study will dissect the role of circulating serum particles in initiating inflammation in lupus. Exosomes are cell-derived small particles present in multiple bodily fluids including serum. Exosomes contain proteins and nucleic material that can modulate the function other cells. This study will compare the cellular origin and composition of exosomes from lupus patients' serum versus healthy control serum; and how the exosomes affect surrounding immune cells. This comparison will identify key

differences between lupus and healthy control serum exosomes, which can be used to identify novel therapeutic targets.