2024 Pilot Grant

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Project Title: Exploring Target Cells Contributing Higher Interferon Status Through cGAS-STING Pathway in Sjögren's Disease

Sjögren's disease (SjD) is a common systemic autoimmune disease with heterogeneous clinical presentation involving multiple biological pathways. The primary clinical symptoms include characteristic dry eyes, dry mouth, and profound fatigue. Currently, there are no approved and efficacious medications that can reverse disease progression or improve the main clinical complaints of SjD. One pathway that is classically involved in SjD is the Type-I interferon (IFN) signaling. However, the upstream mechanisms driving the increase in expression, or lack of feedback inhibition, of Type-I IFN is not elucidated deeply. The cGAS-STING pathway is a recently discovered intracellular pathogen sensing pathway that primarily responds to cytosolic double-stranded DNA. The cGAS-STING pathway has become a hot topic in immune and inflammatory diseases due to its ability to potently mediate the inflammatory response. Although a recent study offered the first direct evidence that cGAS-STING pathway is activated in systemic lupus erythematosus patients and modulates Type-I IFNs, the role of this pathway in SjD pathogenesis is unknown. Our preliminary bulk RNAseq data demonstrate enrichment of DNA Sensing Pathway and increased Type-I IFN-stimulated gene score in the blood and gland correlate with specific disease features in SjD. We discovered the novel findings that cGAS-STING proteins are activated in SjD and that correlates with Type-I IFN bioassay in sera. Based on these findings, we hypothesize that cGAS-STING pathway is chronically activated in SjD and contributes both local (glandular) and systemic (peripheral blood) symptoms via upregulated and persistent expression of IFNs. This study proposal aims to identify the specific cell types contributing cGAS-STING pathway in SjD-affected patient samples. This work will produce a deeper understanding of what happened as immune cell subset in SjD and support the future development of cGAS-STING proteins as targets for therapy.