2024 High Impact Grant

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Project Title: Mechanisms of Fatigue in Sjögren's

Sjögren's disease (SjD) is chronic autoimmune disease in which the deleterious immune response is directed primarily towards the exocrine glands, including the lacrimal and salivary glands. Severe fatigue is common in SjD. There is only a limited understanding of the pathophysiology of fatigue in SjD. Overall, there are large areas of unmet medical needs in SjD, including understanding the pathophysiological mechanisms of the clinical manifestations. Our preliminary data demonstrate mitochondrial dysfunction in SjD patients, a novel finding. Also, fatigue is highly correlated with mitochondrial dysfunction. We find increased free radical damage and abnormal expression of mitophagy-related genes. These findings provide a powerful premise for the proposed work. The PI hypothesizes that mitochondrial dysfunction is associated with fatigue and is caused by abnormal mitophagy, with increased free radical generation by defective mitochondria. We propose the following specific aims to address our hypothesis: In Aim 1, we will determine the clinical associations and correlates of mitochondrial dysfunction among a large group of SjD patients, testing the hypothesis that mitochondrial dysfunction is correlated with fatigue. We further hypothesize that kynurenine levels, lowered by chronic, low-level inflammation, will be associated with mitochondrial dysfunction and fatigue in SjD. For Aim 2, we hypothesize that worsened free radical damage will be strongly associated with worsened mitochondrial function. Here, we will determine the role of free radicals in SjD mitochondrial dysfunction. In Aim 3, we will determine the role of mitophagy in SjD mitochondrial dysfunction, testing the hypothesis that not only will one of the two central pathways for mitophagy be abnormal within lymphocytes in the peripheral blood, but that this abnormal expression will be found among those patients with mitochondrial dysfunction and fatigue.