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Investigating Herpes Simplex Virus 1 as a Trigger of Sjögren's Disease and its Neurologic Manifestations in Genetically Susceptible Mouse Models and in Patients

Abstract: Sjögren's disease (SjD) is a systemic autoimmune disorder characterized by progressive exocrine gland inflammation, leading to dry eyes and dry mouth. Up to 50% of patients develop systemic manifestations including neurologic involvement, and 5–10% develop lymphoma. There are no FDA-approved disease-modifying therapies, in part due to gaps in our understanding of disease immunopathology. Systemic autoimmunity is thought to arise when environmental exposures, particularly infections, act on a genetically susceptible host, yet existing spontaneous mouse models capture genetic susceptibility without incorporating environmental triggers, yielding variable phenotypes and poor recapitulation of human disease. We hypothesize that HSV-1 infection will break tolerance and drive an accelerated SjD phenotype in spontaneous mouse models of SjD, and that HSV-1 neurotropism will drive peripheral nerve damage, modeling the neurologic manifestations of SjD. In Aim 1, pre-diseased NOD.B10 and MRL/MpJ SjD-prone mice will receive unilateral ocular HSV-1 inoculation, and we will assess glandular function, autoantibody production, tissue pathology, and perform deep immunophenotyping. Leveraging HSV-1's neurotropism, we will evaluate peripheral nerve integrity including intraepidermal nerve fiber density, corneal nerve density, glandular innervation, and neuropeptide profiles to illuminate the poorly understood neurologic manifestations of SjD. In Aim 2, we will assess HSV-1 seroprevalence in the PI's SjD patient cohort (>100 participants) versus healthy controls and correlate serostatus with neurologic phenotype, glandular function, disease activity, and autoantibody profile. These novel models pairing a neurotropic infectious trigger with genetic susceptibility will provide critical tools to define disease mechanisms, inform therapeutic development, and support future R-equivalent applications.

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