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Project Summary
Scleroderma is a chronic autoimmune disease of unknown etiology characterized by fibrosis of the skin which can spread progressively to vital organs, with fatal consequences. There is currently no cure for scleroderma, and the mechanisms for disease initiation and pathogenesis remain undefined. Research efforts to study scleroderma have been limited by the lack of a mouse model mouse model that recapitulates both autoimmune and fibrosis aspects of this disease. We developed a novel conditional knockout mouse model in which the phosphoinositide dependent kinase- 1 (PDK1) is specifically ablated in a subset of $CD4^+$ effector/memory T cells and regulatory T cells (Tregs), which are also concomitantly labeled with a fluorescent reporter YFP molecule, enabling tracking of the mutant PDK1-deficient cell populations *in vivo*. This novel PDK1 ablation model (designated PDK1-CKO) spontaneously and progressively develops two key features of scleroderma:
skin fibrosis marked by increased collagen deposition, and a striking elevation in Th2-like and pro-inflammatory cytokines in serum. Moreover, the proportion of regulatory T cells is reduced compared to effector T cells, which are mostly activated Th2 cells in lymphoid organs. We propose that study of the mechanisms for disease progression and immune dysregulation in the PDK1-CKO model can provide new insights into immune-mediated skin fibrosis and pathologies observed in human SSC. In this exploratory/developmental research proposal, we will further characterize disease pathology, immune dysregulations, and autoimmune manifestations in PDK-CKO mice, and assess their resemblance to human SSC. We will also probe for SSC-associated gene signatures in the skin of PDK-CKO mice for a precise assessment of features of human disease in our model. We will also dissect immune mechanisms for T cell-mediated skin fibrosis, focusing on
the role of Tregs and pathogenic Th2 effector cells in localized and systemic immune pathology using bone marrow chimeras and cell transfer. In addition, we will assess the role of Th2 cytokines in promoting skin fibrosis and disease pathology. Results from the proposed studies can lead to new insights into how scleroderma and immune-mediated skin fibrosis is controlled *in vivo* and new targets for therapeutic modulation of this disease.
