A mast cell receptor is associated with fibrosis and itch in systemic sclerosis

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Abstract

Systemic sclerosis (SSc) is an autoimmune connective tissue disease characterized by symmetric fibrosis of the skin and multiple internal organs. The mechanisms that trigger early fibrotic changes remain unclear. Mast cells are known to infiltrate human SSc lesional skin in early disease stages, yet the role of mast cells in initiating fibrosis and pruritus in SSc remains debated, in part due to unclear pathways of mast cell activation. Here, we show that mast cells, via the receptor Mrgprb2, contribute to fibrosis in the bleomycin (BLM)-induced skin fibrosis mouse model. Mast cells accumulate in the skin of BLM-treated wild-type (WT) but not Mrgprb2-knockout *(Mrgprb2*$^{-/-}$) mice. *Mrgprb2*$^{-/-}$ mice show attenuated disease severity, with reduced collagen deposition and lower expression of matrix metalloproteinases and inflammatory markers associated with fibrosis. BLM treatment also increases pruritus in WT mice in the early stages of the model; an effect reduced in *Mrgprb2*$^{-/-}$ mice. This is the first report of itch in this model of skin fibrosis, further linking it to clinical SSc, where pruritus is an early and prevalent symptom affecting nearly half of patients.In a parallel human cohort, lesional SSc skin harbors significantly more mast cells than paired non-lesional skin from the same patients, demonstrating that mast cell accumulation is specific to affected tissue. Lesional mast cell counts also track with skin disease severity, correlating with modified Rodnan skin score and patient-reported skin tightness. Together, these findings implicate Mrgprb2-mediated mast cell activity in both fibrosis and pruritus in SSc, highlighting mast cells as a candidate therapeutic target in this understudied disease process.