CD47 prevents the elimination of diseased fibroblasts in scleroderma.

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Public Summary:
Scleroderma is a devastating fibrotic autoimmune disease. Current treatments are partly effective in preventing disease progression but do not remove fibrotic tissue. Here, we evaluated whether scleroderma fibroblasts take advantage of the “don’t-eat-me-signal” CD47 and whether blocking CD47 enables the body’s immune system to get rid of diseased fibroblasts. To test this approach, we used a Jun-inducible scleroderma model. We first demonstrated in patient samples that scleroderma upregulated transcription factor JUN and increased promoter accessibilities of both JUN and CD47. Next, we established our scleroderma model, demonstrating that Jun mediated skin fibrosis through the hedgehog-dependent expansion of CD26+Sca1– fibroblasts in mice. In a niche-independent adaptive transfer model, JUN steered graft survival and conferred increased self-renewal to fibroblasts. In vivo, JUN enhanced the expression of CD47, and inhibiting CD47 eliminated an ectopic fibroblast graft and increased in vitro phagocytosis. In the syngeneic mouse, depleting macrophages ameliorated skin fibrosis. Therapeutically, combined CD47 and IL-6 blockade reversed skin fibrosis in mice and led to the rapid elimination of ectopically transplanted scleroderma cells. Altogether, our study demonstrates the efficiency of combining different immunotherapies in treating scleroderma and provides a rationale for combining CD47 and IL-6 inhibition in clinical trials.

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