

CANNABINOID RECEPTORS IN SSc

Activating the cannabinoid receptor CNR2 (also known as CB2) could form the basis of a novel therapeutic approach for systemic sclerosis (SSc), according to a study in *Arthritis & Rheumatism*.

Using the mouse model of bleomycin-induced dermal fibrosis, the authors investigated the role of CNR2 in the pathogenesis of dermal fibrosis. They found that mice deficient for CNR2 (*Cnr2*^{-/-} mice) were more susceptible to bleomycin-induced dermal fibrosis than their wildtype littermates: lesions in the knockout mice were thicker and contained more leukocytes. To confirm the results of these genetic studies, the authors then turned to pharmacology. Wildtype mice treated with a specific CNR2 antagonist during bleomycin challenge developed thicker lesions than mice receiving saline. In addition, treatment of wildtype mice with a selective CNR2 agonist during bleomycin challenge blocked the profibrotic effects of bleomycin, resulting in thinner lesions in these mice.

Which cells are responsible for the fibrotic phenotype of *Cnr2*^{-/-} mice? “The phenotype of *Cnr2*^{-/-} mice was mimicked by transplantation of *Cnr2*^{-/-} mice bone marrow into *Cnr2*^{+/+} mice,” explains Jörg Distler, the lead investigator on this study, “indicating that leukocyte expression of CNR2 critically influences the development of experimental fibrosis in this model”.

Selective CNR2 agonists are currently being investigated in clinical trials for multiple sclerosis and, thus far, seem to be well tolerated. “First results from these trials indicate that a potent inhibition of the cannabinoid receptors can be achieved in humans and that the rate of severe adverse events of this class of drugs is low,” concludes Distler. “Thus, the results of our study might have direct clinical implications and stimulate the first clinical trials of these agents in patients with SSc and other fibrotic diseases.”

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Original article Akhmetshina, A. *et al.* The cannabinoid receptor CB2 exerts antifibrotic effects in experimental dermal fibrosis. *Arthritis Rheum.* 60, 1129–1136 (2009).