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SYSTEMIC SCLEROSIS

Promoting apoptosis is key to reversing fibrosis

The resolution of tissue fibrosis remains an unmet clinical need in patients with systemic sclerosis (SSc; also known as scleroderma), an autoimmune disease that produces damaging fibrotic tissue in multiple organs. Although the mechanisms by which fibrosis persists have been the focus of intense research, a unifying theory that links previous knowledge of fibroblast-to-myofibroblast transition, response to mechanical stimulation and apoptosis had not been proposed, until now.

In a study published in *Science Translational Medicine*, David Lagares and colleagues put forward a new theory of how myofibroblasts can sense the stiffness of the surrounding extracellular matrix and use these cues to regulate their readiness to undergo apoptosis in a process known as mitochondrial priming.

"Mitochondrial priming measures the proximity of a cell to the apoptotic threshold and is determined by the relative balance between pro-apoptotic and anti-apoptotic members of the BCL-2 family of proteins in a cell's mitochondria," states Lagares. "In this study we have demonstrated that the phenotypic transformation of quiescent fibroblasts into activated myofibroblasts driven by matrix stiffness increases the mitochondrial priming of these cells, effectively pushing them closer to the apoptotic threshold."

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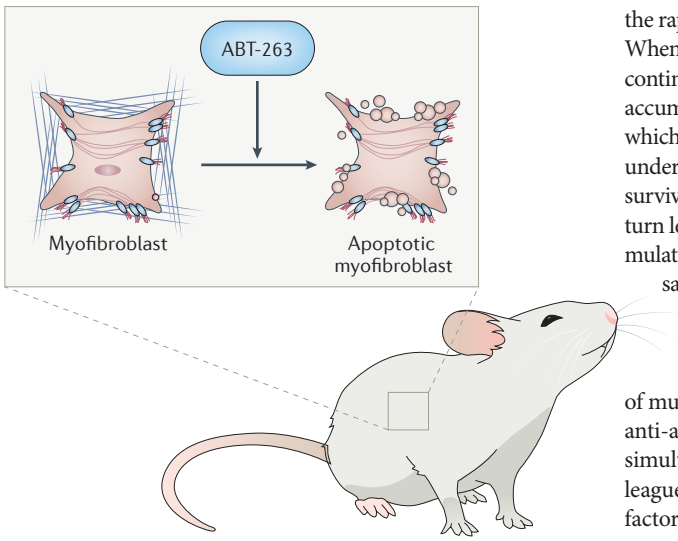
The ability of myofibroblasts to sense their environment and trigger apoptosis is a key part of the tissue regeneration process. "During normal tissue repair, changes in the biophysical properties of the extracellular matrix lead to increased mitochondrial priming in myofibroblasts, making them highly susceptible to apoptosis," explains John Varga, who was not involved in this study. "A reduction in matrix stiffness, which occurs as the repair is completed, leads to the rapid elimination of these cells. When injury leads to a fibrotic scar, continued mechanosignalling leads to accumulation of pro-survival proteins, which prevent the myofibroblast from undergoing apoptosis. The persistent survival of activated myofibroblasts in turn leads to persistent matrix accumulation and unresolving fibrosis," says Varga.



Using a technique known as a BH3 profiling assay, in which the relative expression of multiple pro-apoptotic and anti-apoptotic factors are measured simultaneously, Lagares and colleagues identified the pro-survival factors necessary for the persistence of myofibroblasts in fibrotic tissue. "Mitochondria in activated myofibroblasts, but not quiescent fibroblasts, are primed by death signals such as the pro-apoptotic protein BIM, which creates a requirement for tonic expression of the anti-apoptotic protein BCL-x_L to sequester BIM and ensure myofibroblast survival," says Lagares. "In this 'primed for death' state, myofibroblasts become particularly susceptible to apoptosis induced by 'BH3 mimetic' drugs that inhibit BCL-x_L, such as ABT-263."

To test this theory, the researchers examined the effects of ABT-263 in mice with bleomycin-induced dermal fibrosis. Once-daily oral administration of ABT-263 reduced established fibrosis after 28 days of treatment in this model compared with vehicle-treated animals. Histology of skin sections revealed a 74% reduction in the number of myofibroblasts in fibrotic skin at day 28 from mice treated with ABT-263 compared with vehicle-treated mice.

Interestingly, when the researchers performed BH3 profiling assays on fibroblasts from patients with SSc, they discovered interpatient variation with respect to the predominating anti-apoptotic BCL-2 family member proteins in these cells, suggesting that a personalized approach might be required to target apoptosis with BH3 mimetic drugs in patients with SSc. "Of note, these studies were performed with *ex vivo* serially passaged skin fibroblasts in culture," warns Varga. "So, although the clinical relevance of the findings is still uncertain, future work might further validate the predictive value of BH3 profiling as a precision medicine tool in scleroderma, and further explore the safety and specificity of targeting activated myofibroblasts via disrupting mitochondrial priming," he concludes.

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ORIGINAL ARTICLE Lagares, D. *et al.* Targeted apoptosis of myofibroblasts with the BH3 mimetic ABT-263 reverses established fibrosis. *Sci. Trans. Med.* **9**, eaal3765 (2017)