FIBROBLAST ACTIVATION AS A TARGET FOR CARDIAC FIBROSIS THERAPY

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Cardiac fibrosis is a major independent risk factor for adverse patient outcomes, including arrhythmias, cardiac dysfunction and failure, and death. Excessive deposition of extracellular matrix occurs as a result of activation of resident cardiac fibroblasts to myofibroblasts, which greatly increase matrix synthesis, alter their core metabolism, and become contractile in nature. Because this activation process is critical for fibrosis to occur, it is an intriguing target for anti-fibrosis therapies, which are currently completely lacking. We identified scleraxis as a transcription factor that specifically regulates the expression of genes necessary for fibroblast activation. Our previous *in vitro* work showed that scleraxis activates fibroblast to myofibroblast conversion, in part by directly transactivating key pro-fibrotic genes. Conversely, scleraxis loss prevents activation of fibroblasts by pro-fibrotic TGF or cell stretch. We have also shown that scleraxis regulates expression of glutaminase-1, ostensibly providing fuel through glutaminolysis to support myofibroblast function. We now report that scleraxis is required for fibroblast activation during pressure overload *in vivo*: fibroblast-specific scleraxis deletion completely attenuated fibrosis and significantly improved cardiac systolic function. Deletion of scleraxis four weeks after pressure overload induction by thoracic aortic constriction prevented further loss of cardiac systolic function, virtually eliminated fibrosis via myofibroblast loss, and reduced mortality at twelve weeks post-surgery to zero. Our work thus shows that scleraxis regulates fibroblast activation and myofibroblast maintenance, and blockade of scleraxis function shows the potential to arrest or prevent cardiac fibrosis, resulting in improved function and survival, and implicating scleraxis as an important target for anti-fibrosis therapy development.

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