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FIBROBLAST-SPECIFIC DELETION OF INTERLEUKIN-1 RECEPTOR 1 (IL-1R1) IS CARDIOPROTECTIVE IN AN EXPERIMENTAL MODEL OF MYOCARDIAL INFARCTION

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Rationale: Interleukin-1 (IL-1) plays an important role in driving inflammation and cardiac remodelling after myocardial infarction (MI), but the specific role of cardiac fibroblasts in this process is not known. We developed a mouse model in which the IL-1 receptor (IL-1R1) was inducibly deleted in fibroblasts, and investigated the impact on cardiac function and remodelling post-MI.
Methodology: A tamoxifen-inducible fibroblast-specific IL-1R1 hemizygous knockout mouse line (Col1a2-CreER(T)-Il1r1 fl/-) was created and characterized. Cre-negative littermates served as controls. Cardiac fibroblasts from fibroblast-specific knockout mice exhibited a 75% reduction in Il1r1 mRNA expression, and a similar reduction in IL-1 responses. Mice were injected with corn oil (vehicle) or tamoxifen (100 mg/kg/day) i.p. for 5 consecutive days and underwent experimental MI (permanent left anterior descending coronary artery ligation) at 10-12 weeks of age. Cardiac function was determined 4 weeks later by conductance pressure-volume catheter analysis. Molecular markers of remodelling were evaluated by real-time RT-PCR and histological staining.
Results: Control mice had significantly reduced ejection fraction 4 weeks after MI compared with sham animals (48% versus 62%; P=0.02; n=11/12). Importantly, ejection fraction was only partially reduced to 56% after MI in fibroblast-specific IL-1R1 knockout mice and was not significantly different to sham controls (P=0.45; n=11/12). IL-1R1 knockout mice showed reduced mRNA levels of remodelling genes (Col1a1, Col3a1, Mmp3, Tnc) after MI; differences confirmed at the histological level.
Conclusions: Cardiac fibroblast IL-1R1 plays a key role in regulating post-MI remodelling. Inhibition of IL-1R1 signalling may therefore be beneficial post-MI.
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