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**A pivotal role for cytotoxic CD8+ T cells in development of cardiac fibrosis**

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**Background/Introduction:** Pressure overload-induced cardiac fibrosis increases myocardial stiffness leading to reductions in cardiac performances and cardiac failure. CD8+ T cells have been shown to accumulate during development of fibrosis but their role has not been defined.

**Purpose:** We examined the role and significance of CD8+ T cells in development of cardiac fibrosis.

**Methods:** Trans-aortic constriction (TAC) or 2-kidney-1-clip (2K1C) procedures were used to generate pressure overload-induced cardiac fibrosis in mice. Rat anti-mouse CD8β (lyt-3) monoclonal antibody (clone YTS 156.7) was used to deplete CD8+ T cells. A mixed bone marrow chimera strategy was used to specifically delete innate receptor Natural Killer Group 2D (NKG2D) or cytotoxin perforin from CD8+ T cells.

**Results:** Depleting CD8+ T cells in mice subjected to TAC or 2K1C-renal hypertension attenuated left ventricular fibrosis by 93% and 84% without affecting blood pressure. In TAC mice this was associated with a 68% reduction in apoptotic cardiomyocytes, a 74% reduction in macrophage accumulation, a 65% reduction in TGF-beta positive cells and a 95% reduction in TGF-beta positive macrophages, whilst CD4+ T cells were unaffected. Cardiomyocytes in regions of developing cardiac fibrosis contained cytoplasmic DNA and expressed the NKG2D ligand, Rae-1, indicative of activation of a DNA damage response; CD8+ T cells expressed the NKG2D receptor. Deletion of the NKG2D receptor from CD8+ T cells attenuated cardiac fibrosis by 82%; deletion of cytotoxin perforin has similar effects.

**Conclusion(s):** We conclude that CD8+ T cells contribute to development of cardiac fibrosis by targeting stressed/damaged cardiomyocytes via an NKG2D-Rae-1 cytotoxic mechanism inducing their apoptosis. Macrophages then accumulate in the heart in response to increased numbers of apoptotic cardiomyocytes, clearing the apoptotic cells through engulfment and increasing their expression of the pro-fibrotic factor TGF-beta1.