MATERIALS AND METHODS

Mice and animal husbandry

Female NOD and C57BL/6J (B6) mice were purchased from Jackson Laboratories. HLA-DQ8^{+}mII$^{-/-}$NOD (DQ8^{+}NOD) mice, TOM^{+}TA^{+}DQ8^{+}NOD, (TOM^{+}TA^{-} or TOM^{-} TA^{+})DQ8^{+} NOD mice, and RAG-1$^{-/-}$NOD mice were obtained from in-house colonies (18). Mice were maintained under specific pathogen-free conditions. All mouse experiments were reviewed and approved by the Institutional Animal Care and Use Committees at Joslin Diabetes Center and Harvard Medical School.

Human subjects

All participants were 18 years of age or older. Prior MI was defined according to standard criteria that included a history of ischemic ST segment changes with biomarker release, pathologic Q waves, or imaging evidence of loss of viable myocardium with attendant thinning and/or contractile dysfunction in the absence of a non-ischemic cause (S1). Myocarditis was defined by clinical, pathological (Dallas criteria myocarditis on endomyocardial biopsy) and cardiac MRI criteria as we have described (26). The diagnosis of T1D and T2D was made according to established guidelines (S2), and high resolution DQB1 genotyping and low resolution DRB typing (Invitrogen) was performed on DNA from all diabetic subjects. Healthy controls consisted of 78 consecutively recruited subjects with no family history of heart disease. Human studies were approved by the Joslin Diabetes Center Committee on Human Studies (Protocols 04-34, and 04-12) and Partner's Human Research (Protocols 2004p-000084 and 2004p-000585/10). Written informed consent was received prior to inclusion in these studies.

Experimental myocardial infarction

Ligation of the left anterior descending (LAD) coronary artery was performed in 7-8 wk-old female B6 and NOD mice as described (S3). Sham-operated controls were subjected to the same surgical procedures as the experimental animals, with the exception that the LAD was not manipulated.

Histology and immunohistochemistry

Heart, skeletal muscle, pancreas, submandibular salivery and thyroid tissues were fixed overnight in 10% formalin, embedded in paraffin, sectioned and stained with standard procedures for H&E or Masson's trichrome. Histology was assessed by a pathologist blinded to the mouse groups. Immunohistochemistry was performed on cryosections as described (17). Primary antibodies included: anti-CD4 (clone H129.19), biotinylated anti-CD8 (clone 53-6.7), and anti-B220 (clone RA3-6B2) (all from BD-Pharmingen). Secondary antibodies included peroxidase-conjugated streptavidin (BD-Pharmingen) and peroxidase-conjugated goat-anti-rat IgG (Jackson ImmunoResearch Laboratories Inc.). Stains were developed with 3, 3'-diaminobenzidine (DAB) substrates (BD-Pharmingen). Indirect immunofluorescence was performed on cryosections of RAG-1$^{-/-}$NOD heart as described (17). Slides were mounted using Vectashield and stained with DAPI (Vector Laboratories). Images were taken on a Zeiss LSM-410 confocal microscope (Zeiss, Germany).

Western blotting

Tissues were homogenized in lysis buffer containing PBS/2% SDS supplemented with 0.2 M PMSF, 1 μg/ml aprotinin, 1 mM MgCl2 and 1 U/ml benzonase (EMD Bioscience, USA). After 5 min incubation at 30 ºC for DNA digestion, samples were boiled for 5 min, centrifuged at 14,000 x g for 15 min and the supernatant were used for analysis.

Proteins were separated by 10% SDS-PAGE and transferred to nitrocellulose membrane as previously described (18).

Immunoprecipitation and identification of p100

Immunoprecipitation of the p100 band was performed from total mouse heart lysate in PBS/NP40/SDS Buffer (0.1% SDS, 1% NP-40, 150 mM NaCl in Phosphate Buffer, 200 mM PMSF). The lysate was centrifuged for 20 min at 14,000 x g at 4ºC, and the supernatant was then pre-cleared with 50 µl of Protein G Sepharose (GE Healthcare). 500 µl of the pre-cleared lysate was incubated with 10 µl of post-infarcted NOD mice sera for 2 h at 4ºC. For the antigen-antibody capture, we added 50 µl Protein G Sepharose and incubated for 1 h. The beads were washed five times with the PBS/NP-40/SDS buffer and resuspended in 2X electrophoresis sample buffer containing 50 mM DTT. After boiling for 5 min, samples were analyzed by SDS-PAGE and Coomasie Blue staining (BioRad). The resulting stained band of ~100 kDa was excised and used for protein identification by tandem mass spectrometry (Harvard Medical School Mass Spectrometry Core Facility, Boston, MA) and data mining was done using SEQUEST database matching analysis against SWISS-PROT database (Fasta 12.2, 619242 entries) with peptide threshold cutoffs defined by a ΔCN value $\geq$ 0.1 and a Sequest Xcorr $\geq$ 3.1, which indicate identity or extensive homology (>95%).

Cloning and expression of recombinant mouse Actn2

Mouse Actn2 (alpha-actinin-2; Actn2; NCBI reference number NM_033268; aa 1-895) cDNA was cloned from mouse heart RNA by RT-PCR using the following primers: Forward: 5'-TTGCACCATATGAATCAGATAGAGCCCGGCGTGCAG-3' and Reverse: 5'-TACCACTGCGGCCGCGAGGTCGCTTTCCCCGTAGAGGGC-3'. The Actn2 cDNA

was subcloned into His-Tag -containing pET-20b expression vector (Novagen) and the A His-Tag fusion protein of mouse Actn2 was expressed in *E.Coli* and purified through Ni-NTA affinity resin (Qiagen) and gel filtration column Hiload 16/60 Superdex 200 (GE Healthcare) according to manufacturer's protocol.

ELISA

High-binding EIA/RIA plates (Corning) were coated with 5 μg/ml mouse cardiac myosin in 0.1M $NaHCO_3$ (pH 9) at 4ºC overnight. After washing with distilled water, plates were blocked with 3% BSA/PBST (blocking buffer) for 2 h at room temperature. Sera were diluted at 1:400 with blocking buffer and added to washed plates, followed by incubation at 4ºC overnight. Immunoglobulin isotypes were detected by incubation with horseradish peroxidase-labeled goat anti-mouse Ig isotype antibodies (SouthernBiotech) at 1:250 for 3 h. ABTS was used as the substrate and absorbance was read at 405 nm. For Actn2, the same procedure was performed, except for replacing antigen coating buffer with 0.1 M $CaCO_3$ (pH 9), blocking buffer with Pierce Protein-Free T20 (TBS) Blocking Buffer (Thermo Scientific), and washing buffer with TBS containing 0.05% Tween-20. A positive titer was defined as a titer $\geq$ 1:100 on two or more consecutive occasions.

ELISPOT and proliferation assays

For ELISPOT assay, $2.5x10^6$ per ml of splenocytes were stimulated without or with 25 μg/ml mouse cardiac myosin or mouse Actn2 in complete AIM-V medium (Invitrogen) (supplemented with 50 μM 2-mercaptoethanol and 2 mM L-Glutamine) containing 2 ng/ml recombinant mouse IL-7 (R&D Systems) overnight at 37ºC. 96-well MultiScreen-IP plates (Millipore) were coated with 4 μg/ml anti-mouse IFN-γ (BD Pharmingen) in PBS

overnight at 4ºC, washed with PBS, and blocked with 1%BSA/PBS for 1 h at room temperature. 200 µl of cell suspension (containing $0.5x10^6$) were transferred to each well of blocked and PBS-washed plates in triplicates for each condition. After 20 h incubation, plates were washed with PBS containing 0.05% Tween-20 (PBST) and 2 µg/ml biotinylated anti-mouse IFN-γ antibody (BD Pharmingen) in 1%BSA/PBST was added to each well followed by incubation for 2 h at 37ºC. After wash, ExtrAvidin-alkaline phosphatase (Sigma-Aldrich) diluted at 1:1000 with 1%BSA/PBST was added to each well followed by incubation for 2 h at 37ºC. The plates were washed with PBST, followed by PBS. SIGMA*FAST* BCIP/NBT (Sigma-Aldrich) solution was added to each well for 1 min at room temperature. The reactions were stopped by washing the plates under tap water. Spots were counted using an automated immunospot reader (Cellular Technology Ltd). For proliferation assay, cardiac draining lymph node cells ($3x10^5$/well) were cultured in 96-well plates in complete AIM-V medium as described (S4). Antigens were added at various concentrations, and after 72 h incubation at 37°C cultures were pulsed with 1 µCi of ^{3}[H]-thymidine, and plates were harvested 18 h later.

Skeletal muscle injuries

Injuries to the tibialis anterior (TA) and triceps surae (TS) muscles of the hind limbs of anesthetized ~8-wk-old female NOD and B6 mice were performed as follows. For cold and crush injuries, a ~3 mm incision was made to expose the muscle. For cold injury, damage was caused by direct application to the muscle of a small piece of dry ice for 5 s (S5). For crush injury, a pair of small artery forceps was inserted mid-muscle, and the muscle was then crushed transversely, 1-3 times, causing an injury 3-4 mm wide while maintaining the longitudinal continuity of the muscle (24, S6). In both cases, the incision was then sutured, and mice were monitored until recovery. For chemical

injury, anesthetized mice were injected intramuscularly with 25 μl of a 0.3 mg/ml solution of cardiotoxin (from *Naja mossambica mossambica*, Sigma) (24, S6).

Construction of human cDNA clones

Full-length cDNA clones for human cardiac *MYH6* (catalogue number SC309209; NCBI reference number NM_002471; aa 1-1940), *MYH7* (catalogue number SC125249; NCBI reference number NM_000257; aa 1-1936) and human *ACTN2* (catalogue number SC110819, NCBI reference number NM_001103.1, aa 1-4181) were purchased from OriGene Technologies. The human cardiac TnI (troponin I type 3 cardiac; TNNI3; NCBI reference number NM_000363; aa 1- 211) gene was cloned by RT-PCR using the following primers: Forward: 5'-TTGCACTCGTCTAGATGTCCTCGGGGAGTCTCAAGC-3' and Reverse: 5'-TACCACGCGTCTAGAAGCTCAGAGAGAAGCTTTATT-3'. Overlapping fragments of the S1, S2 and LMM domains of human *MYH6* were amplified by PCR using the primers: S1 forward 5'-TTGCACTCGAGAATTCCGAGATGACCGATG CCCAGATGG-3', reverse 5'-TACCACGCGTGCGGCCGCTCACAGCGTCTCTTTGATG CG-3' (aa 1-865); S2 forward 5'-TTGCACGTCGACACCATGGCCTTCATGGGGGTCA AG-3', reverse 5'-TACCACTGCGGCCGCTCACGCCTTGCCCTCCTCCTCCAG-3' (aa 822-1327); and LMM forward 5'-TTGCACGTCGACAACATGGAGCAGATCATCAAGG CC-3', reverse 5'-TACCACGCGTGCGGCCGCAGGTTCCCGAGGCAGTGTCAC-3' (aa 1237-1940). All cDNAs were subcloned into pCMVTNT vector (Promega).

Radioimmunoprecipitation assays

Human cardiac proteins were *in vitro* translated and [^{35}S]-labeled from cDNA clones with TnT quick coupled transcription/translation kit (Promega). Radioactive proteins were precipitated with trichloroacetic acid and RIA reactions contained 400,000 counts

per minute (cpm) for full-length α-or β-MyHC; 50,000 cpm for both α-MyHC fragments and Actn2; and 20,000 cpm for cTnI. For α-MyHC, β-MyHC, and cTnI, RIA was performed in 50 µl of immunoprecipitation (IP) buffer containing 20 mM Tris-HCl pH 7.4, 150 mM NaCl, 1% (v/v) Triton X-100, and 10 µg/ml aprotinin (Sigma); for Actn2, 0.06 mM $CaCl_2$, 1 mM $MgCl_2$, 1.6 mM KCl were added to the IP buffer; and for α-MyHC fragments, 0.5% NP-40 was used instead of Triton X-100 in IP buffer. Human serum was then added to a final dilution of either 1:5 (for α-or β-MyHC) or 1:25 (for α-MyHC fragments, cTnI, and Actn2). The samples were then incubated in 1.5 ml microcentrifuge tubes at room temperature for 2 h prior to overnight incubation at 4°C with constant shaking. 50 µl of protein A/G (50% A/8% G) Sepharose 4 Fast Flow beads (GE Healthcare) were then added to the microcentrifuge tubes and incubation continued for 1 h at 4°C. The protein A/G Sepharose-antibody complexes were collected by centrifugation, washed with IP buffer, and immunoprecipitated radioactivity was measured in a LS 6500 scintillation counter (Beckman Coulter). The RIAs for α-MyHC fragments, Actn2, and cTnI were carried out in a 96 well Unifilter plates (Whatman). 50 µl of protein A/G (50% A/8% G) Sepharose 4 Fast Flow beads and overnight incubated antigen-antibody complexes were added to each well and incubated for 1 h at 4°C. The protein A/G Sepharose-antibody complexes were centrifuged and washed with IP buffer at 4°C. The beads were then resuspended in scintillation fluid (Ultima Gold F, Perkin Elmer), and the immunoprecipitated radioactivity was measured in an I450 MicroBeta scintillation counter (Perkin-Elmer). The autoantibody index was calculated as follows: cpm immunoprecipitated by patient serum divided by mean cpm immunoprecipitated by all healthy control sera (S7). All sera samples were tested in duplicates. The cutoff value for each autoantibody assay was calculated using the mean antibody index + 3 SD of the healthy control subjects.

Cardiac MRI

The MRI study consisted of a 2-day imaging session. A GE systems 1.5 T MRI system was used to image the myocardium. On day 1, a T2* weighted gradient recall echo was performed and Ferumoxytol (Feraheme, AMAG Pharmaceuticals) was administered intravenously at 4 mg Fe/Kg (at a concentration of 30 mg/ml) at a rate of 1 ml/sec. After 24 h (day 2), the subject returned to have the second T2* weighted gradient recall echo MRI scan to detect Ferumoxytol-enhanced evidence of macrophage-mediated inflammation in the myocardium. Image analysis was performed using specialized software, General Electric CineTool version 3.5.

Statistics

Continuous variables are presented as means (± SD), and categorical variables as percentages. Comparisons between categorical and continuous variables were evaluated with Fisher's exact test and Student's *t*-test, respectively. Data were analyzed using GraphPad Prism 5 software (La Jolla, CA). A P value < 0.05 was considered statistically significant.

Supplementary Figures and Legends

Figures S1

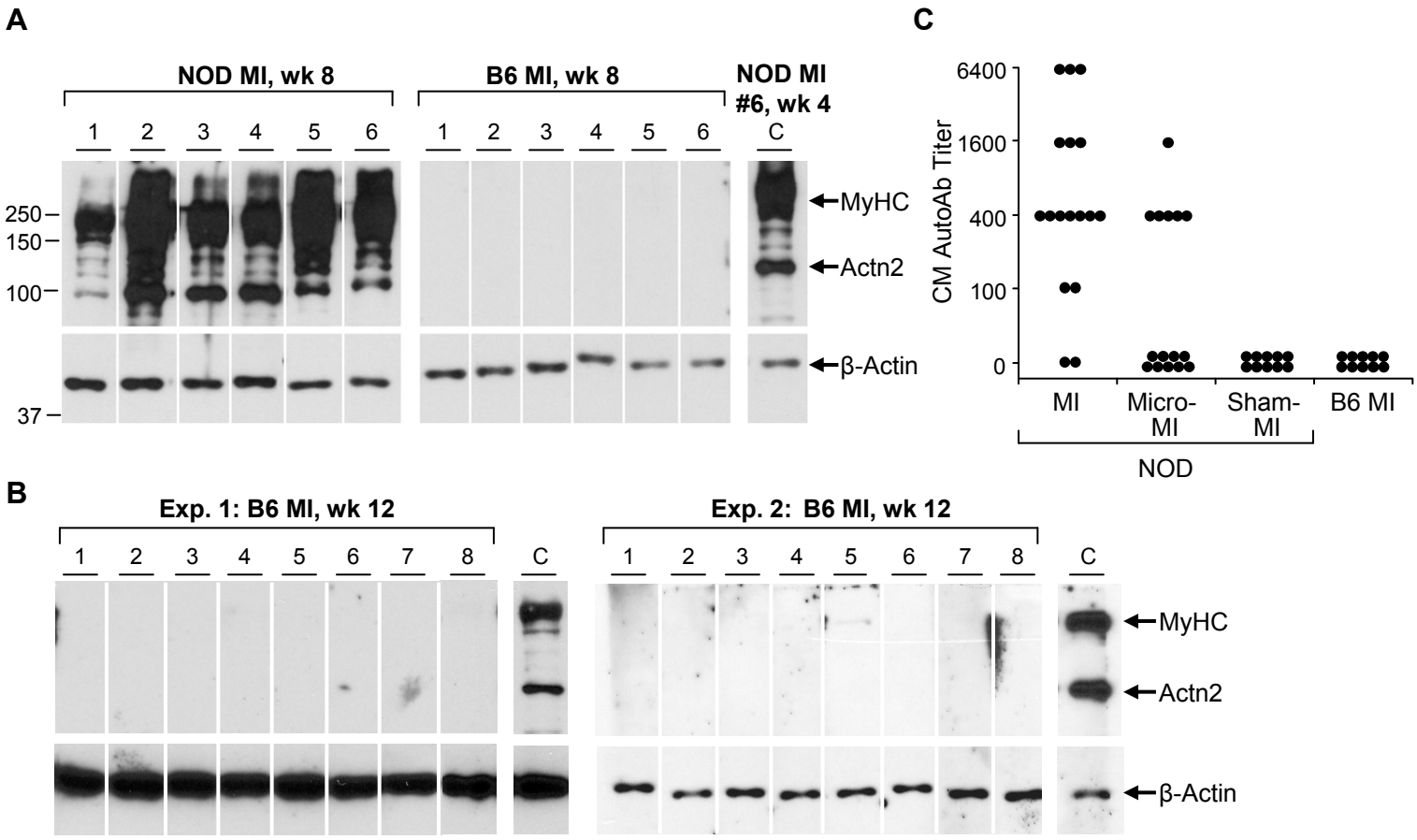


Fig. S1. Cardiac autoantibody production in NOD MI, NOD micro-MI, NOD sham-MI and B6 MI mice. (A) Representative immunoblots containing normal mouse heart extracts probed with sera from 8 wk post-MI NOD mice (n=6), 8 wk post-MI B6 control mice (n=6), and for comparison, sera from NOD MI mouse #6 obtained 4 wk post-MI. Data are representative of five independent experiments. (B) Immunoblots probed with sera from 12 wk post-MI B6 mice (n=8 mice/group). Results from 2 independent MI experiments (Exp.) are shown. (C). Titers and prevalence of autoantibodies to cardiac myosin (CM) as measured by ELISA in representative NOD MI mice (n=17), NOD micro-infarcted (Micro-MI) mice (n=15), NOD sham-MI mice (n=10) or B6 MI mice (n=10).

Figures S2

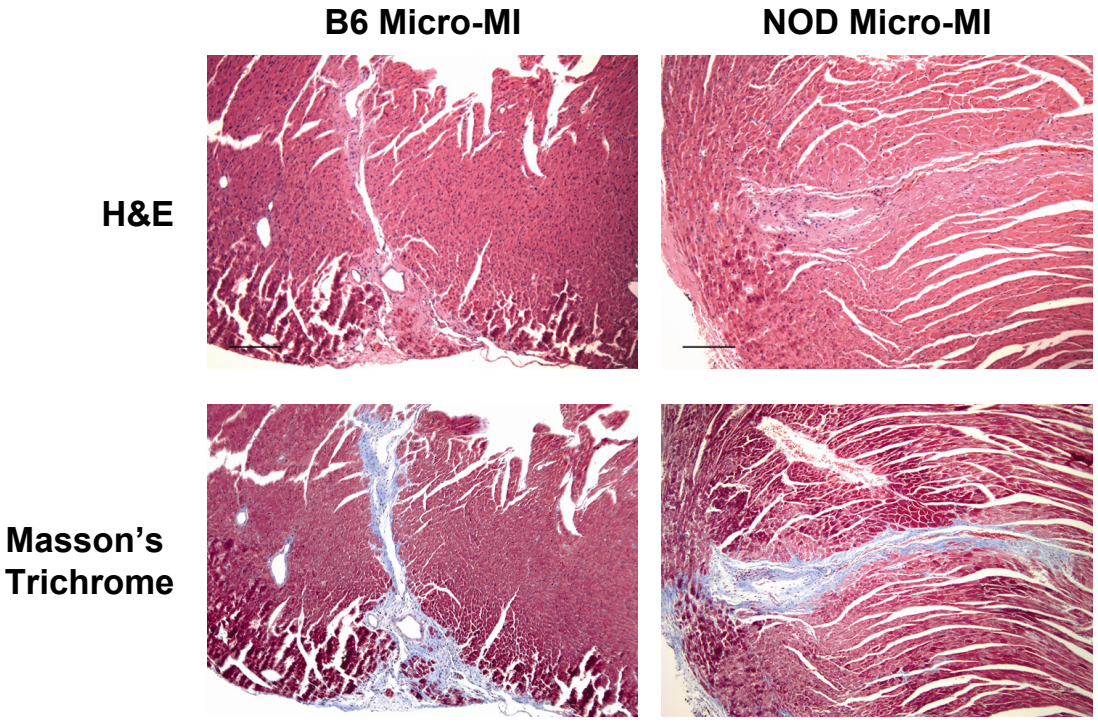


Fig. S2. Histology of NOD and B6 mouse hearts after microinfarction. Heart sections from representative NOD and B6 mice 4 wk after microinfarction (Micro-MI), stained with H&E and Masson's trichrome, showing discrete regions of fibrosis (blue). Scale bar: 250 μm.

Figures S3

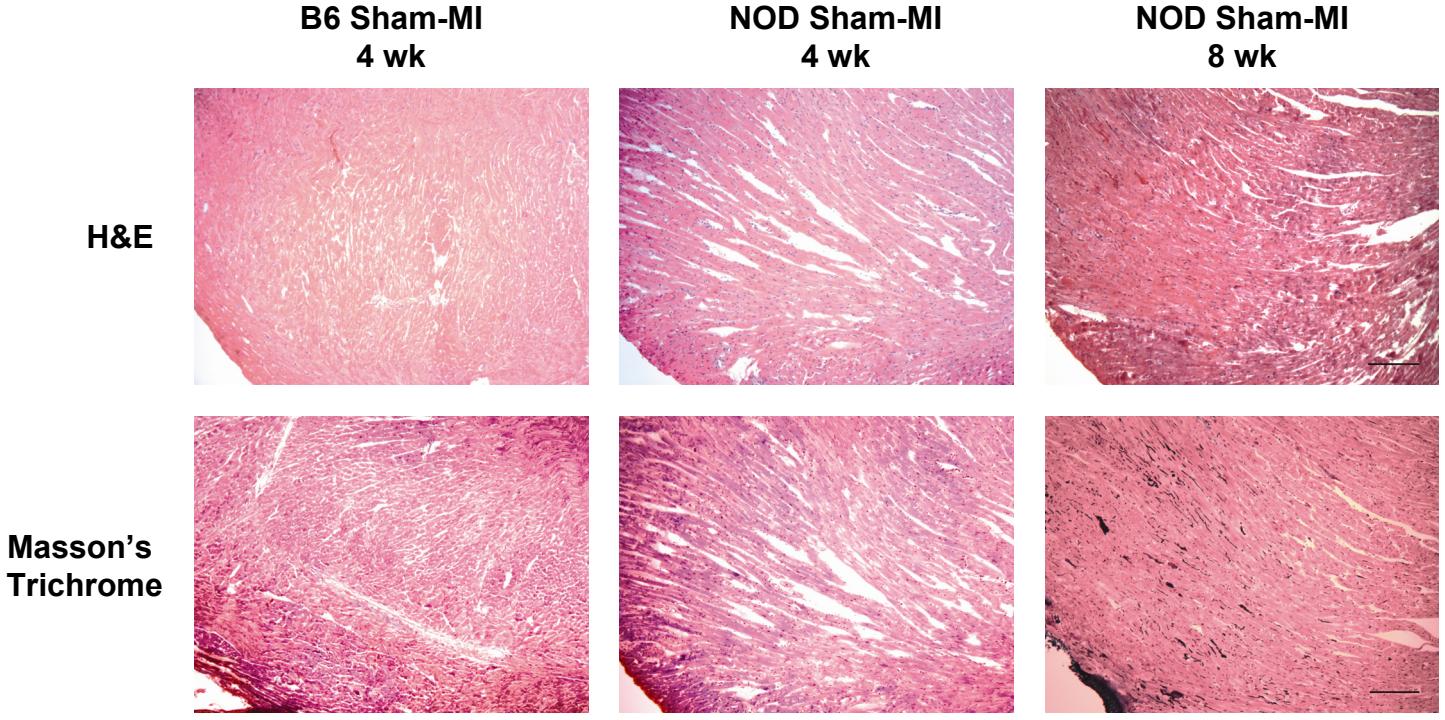


Fig. S3. Histology of NOD and B6 mouse hearts after sham-infarction. H&E and Masson's trichrome staining of heart sections from representative NOD and B6 mice 4 wk after sham-MI, and a NOD mouse 8 wk after sham-MI. Scale bar: 250 μm.

Figures S4

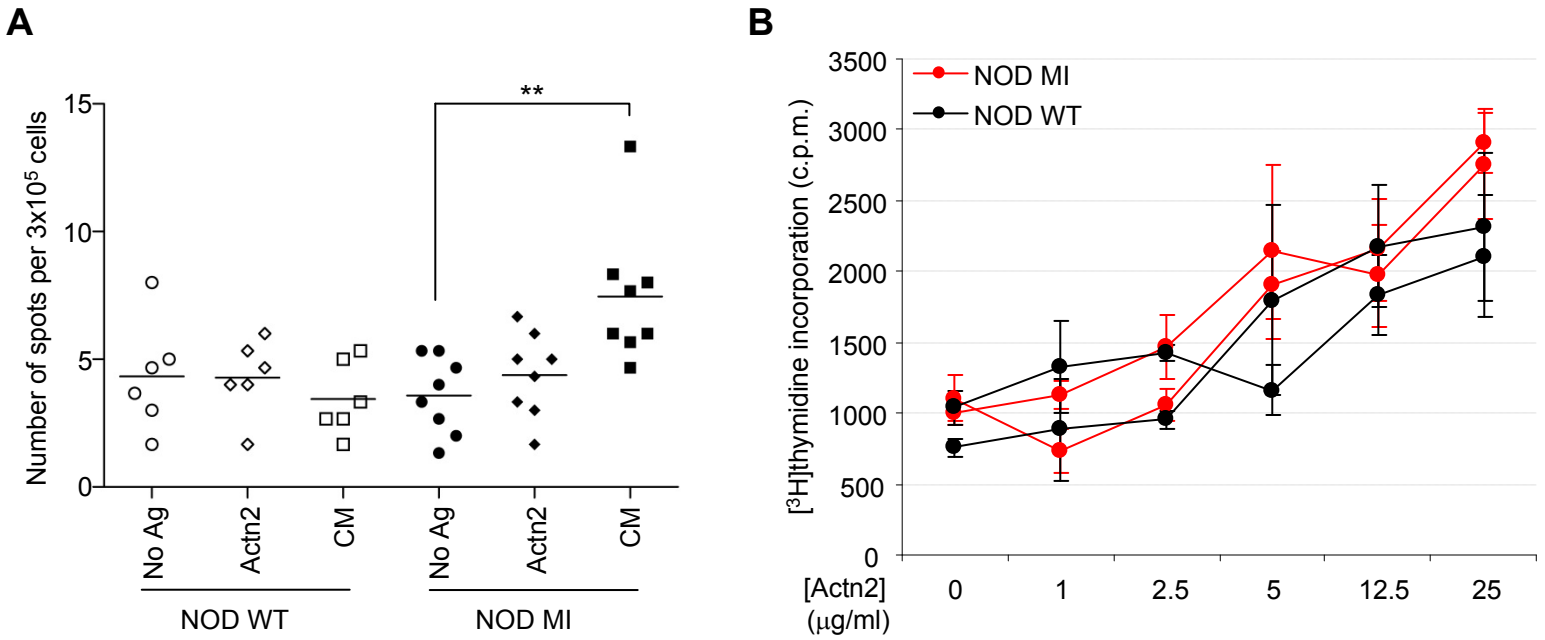


Fig. S4. Analysis of T-cell responses to Actn2 in post-MI NOD mice. Actn2-specific responses of splenocytes from 4 wk post-MI NOD mice were measured by IFN-γ ELISPOT (**A**) and proliferation (**B**) assays. Unmanipulated, age-matched NOD (NOD WT) mice were used as controls. (**A**) ELISPOT assays were performed as shown in Fig. 3. Mouse cardiac myosin (CM) served as a positive control antigen for Actn2 ELISPOT assays. Data are representative of three independent experiments. (**B**) Splenocytes were tested with titrated mouse Actn2. Data represent mean ± SD of responses measured in triplicate; ***P*=0.0032.

Figures S5

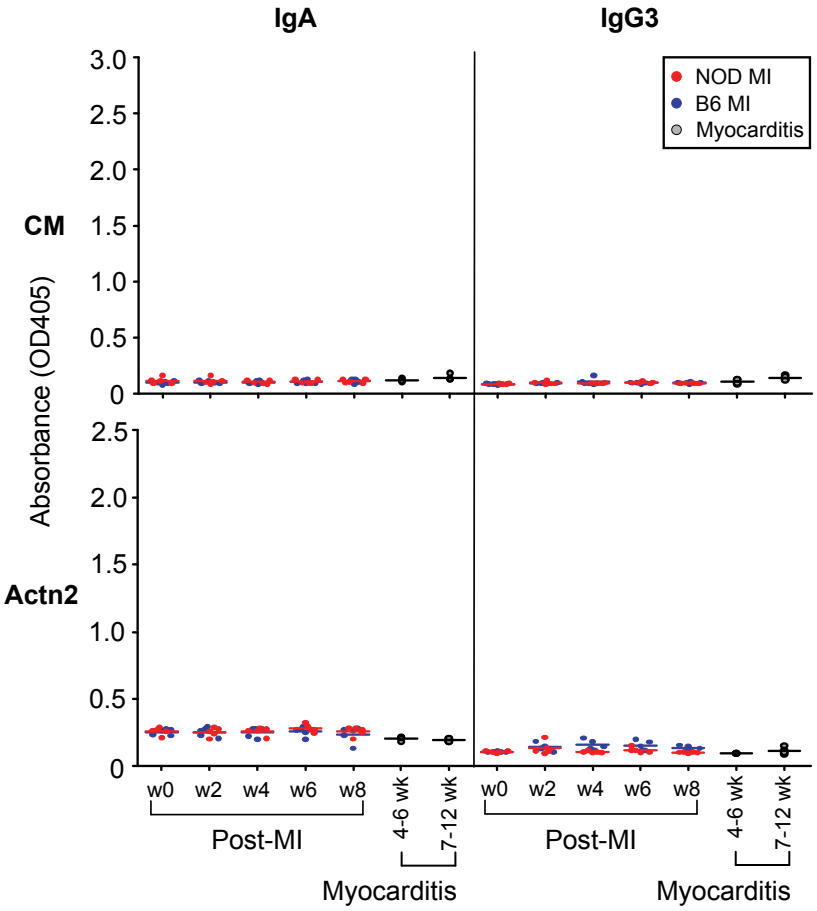


Fig. S5. Analysis of IgA and IgG3 autoantibodies to CM and Actn2 in post-MI NOD and B6 mice. Bi-weekly serial sera from post-MI NOD and post-MI B6 mice (n=5 mice/group), as shown in Fig. 3C, were analyzed by ELISA for IgA and IgG3 autoantibodies specific to CM and Actn2. w0=pre-MI bleed; w=wk post-MI. Longitudinal sera from DQ8^{+}NOD ('Myocarditis') mice (n=5) taken between ages 4-6 wk and at 7-12 wk, were analyzed side-by-side for comparison.

Figures S6

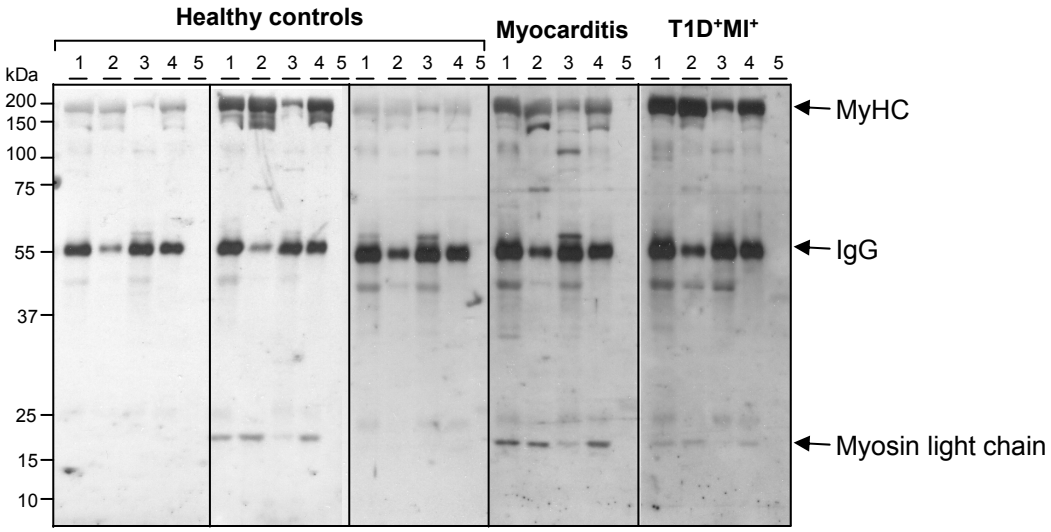
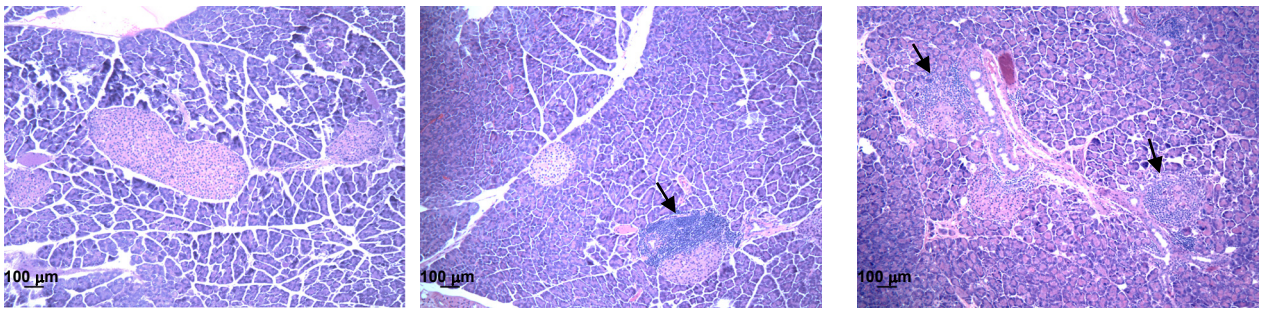


Fig. S6. Analysis of cardiac autoantibodies in humans by Western blotting. Western blots contained 2.5 μg/lane each of: human left ventricle myofibrillar extract (lane 1); human skeletal muscle myofibrillar extract (lane 2); human ventricle SDS lysate (lane 3); or 0.25 μg/lane each of: purified human ventricle cardiac myosin (lane 4), purified human cardiac troponin I/cardiac troponin T (lane 5). The blots were probed with serum from three consecutive healthy control subjects ("Healthy controls"), myocarditis patient, M-1 ("Myocarditis"), and post-MI T1D patient, T1D-16 ("T1D^{+}MI^{+}"), as described in **Table 1**. The positions of myosin heavy chain (MyHC), myosin light chain and IgG are as indicated. Control or patient sera and peroxidase conjugated secondary antibody were used at 1:1,000 and 1:10,000 dilutions, respectively.

Figures S7

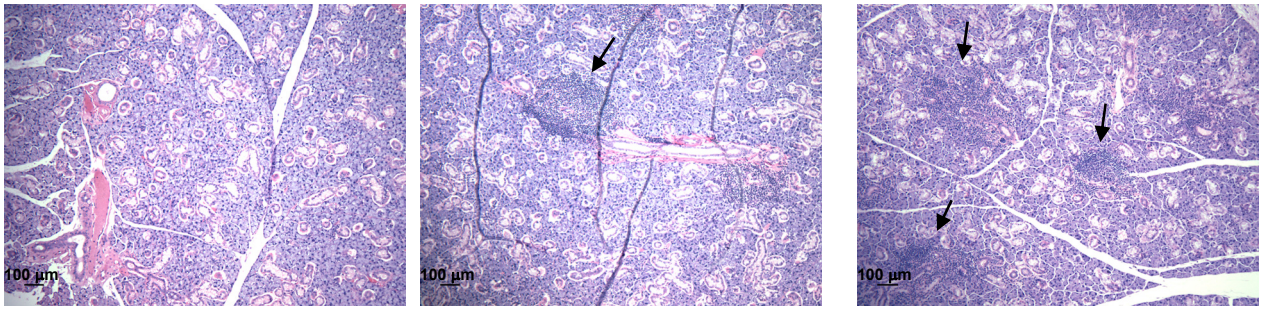
A Pancreas (Insulitis)

Absent (score 0); MI #336 | Mild-mod (score 1); MI #349 | Severe (score 2); Sham-MI #335



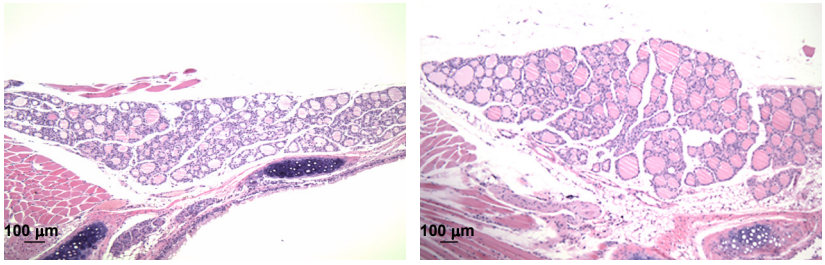
B Salivary gland (sialitis)

Absent (score 0); MI #350 | Mild-mod (score 1); Sham-MI #332 | Severe (score 2); Sham-MI #346



C Thyroid gland (thyroiditis)

Absent (score 0); MI #346 | Absent (score 0); MI #349



D.

Group	Mouse ID	Histological score		
		Pancreas	Salivary	Thyroid
NOD	332	1	1	0
Sham-MI	335	2	1	0
	346	1	2	0
	348	1	1	0
NOD MI	333	1	1	0
	334	2	1	0
	336	0	0	0
	344	2	1	0
	347	2	0	0
	349	1	2	0
	350	1	0	0
	377	2	1	0

Fig. S7. Insulitis, sialitis and thyroiditis in post-MI versus sham-MI NOD mice. 7-wk-old NOD mice underwent MI (n=8) or sham-MI (n=4) surgeries and 4 wk later, pancreata, submandibular and thyroid glands were collected. H&E-stained tissue sections were assigned histological scores for lymphocytic infiltrates (D); representative histology from each scoring category is shown. Score 0 (normal): absence of lymphocytic infiltrates. For pancreatic insulitis lesions (A, Pancreas), score 1 (mild-moderate): lymphocytic infiltrates in the periphery or invading less than 50% of the islets (middle panel, arrow); score 2 (severe): lymphocytic infiltrates invading more than 50% of the islets (right panel, arrows). For sialitis (B, Salivary gland), score 1 (mild-moderate): < 8 inflammatory foci per whole tissue section (middle panel, arrow); score 2 (severe): ≥ 8 inflammatory foci per section (right panel, arrows). Mice with at least one inflammatory lesion in the pancreas or islets were considered affected. None of these mice showed histological evidence of thyroiditis (C and D).

Supplementary Tables

Table S1

				HLA Alleles			
ID	Sex (M/F)	Age (y)	Post-MI (y)	DRB1-Allele 1	DQB1-Allele 1	DRB1-Allele 2	DQB1-Allele 2
TID-1	F	68	u	3	0201	4	0302
TID-2	F	56	7	1	0501	4	0302
TID-3	F	49	1.3	3	0201	3	0201
TID-4	M	60	8	4	0302	4	0302
TID-5	F	39	2	3	0201	4	0302
TID-6	M	59	4	3	0201	3	0201
TID-7	F	67	5	3	0201	3	0201
TID-8	M	61	6	3	0201	4	0302
TID-9	M	69	8	4	0301	4	0302
TID-10	F	57	5	1	0501	4	0302
TID-11	F	61	0.3	3	0201	15	0502
TID-12	M	52	u	3	0201	4	0302
TID-13	M	19	5	3	0201	4	0302
TID-14	F	46	8	1	0501	8	0501
TID-15	F	66	u	1	0501	4	0302
TID-16	M	59	3	11	0603	4	0302
TID-17	M	55	3	7	0202	14	0503
TID-18	F	54	0.5	17	0201	9	0303
T2D-1	M	55	6	7	0202	13	0603
T2D-2	F	68	u	3	0201	14	0503
T2D-3	M	63	9	15	0602	15	0602
T2D-4	M	63	10	7	0202	11	0301
T2D-5	M	57	0.9	13	0603	11	0301
T2D-6	M	45	11	3	0201	13	0609
T2D-7	F	61	7	4	0301	11	0301
T2D-8	M	80	5	7	0202	4	0302
T2D-9	M	57	20	7	0202	13	0603
T2D-10	M	60	15	1	0501	13	0604
T2D-11	M	36	5	3	0201	1	0501
T2D-12	M	64	12	4	0301	4	0301
T2D-13	M	56	0.3	7	0202	15	0602
T2D-14	F	62	13	1	0501	1	0501
T2D-15	M	60	0.08	15	0602	11	0301
T2D-16	M	61	6	1	0501	15	0602
T2D-17	F	54	17	14	0503	4	0302
T2D-18	M	59	4	7	0303	9	0303
T2D-19	F	78	0.8	1	0501	15	0602
T2D-20	F	59	11	1	0501	8	0301

Table S1. Characteristics of the T1D and T2D ischemic heart disease cohorts. HLA typing was done as described in Methods. Post-MI, timing of sample from MI in years (y); u, timing of MI unknown.

Table S2

Mouse mTECs

Gene name	Gene symbol	Probe name	WT signal	KO signal
actinin alpha 2	Actn2	160570_at	0.63	0.87
myosin, heavy polypeptide 6, cardiac muscle, alpha	Myh6	101071_at	2.83	2.73
myosin, heavy polypeptide 7, cardiac muscle, beta	Myh7	98616_f_at	19.50	46.63

Mouse eTACs

Gene name	Gene symbol	Probe name	WT signal	KO signal
actinin alpha 2	Actn2	1448327_at	2.8	2.2
myosin, heavy polypeptide 6, cardiac muscle, alpha	Myh6	1417729_at	7.1	6.8
myosin, heavy polypeptide 7, cardiac muscle, beta	Myh7	1448553_at	70.9	308.5

Table S2. Microarray data of expression of *Actn2*, *Myh6*, and *Myh7* genes in mTECs and eTACs from Aire$^{+/+}$and Aire$^{-/-}$ mice. These data were obtained from the NCBI GEO data repository, accession number GSE85 for mTECs and GSE12388 for eTACs.

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