band structures, and misalignments of T-tubules with z-disk. We find that the neuregulin-1-ErbB3 signaling and the baroreceptor reflex response, which have been functionally associated, are both altered in the diabetic mice. We further demonstrate that ShcA interacts with Cav-1 and the costameric protein plasma membrane Ca2+/calmodulin-dependent ATPase (PMCA), and that its deletion leads to abnormal dystrophin signaling. Our studies demonstrate that ShcA modulates ErbB3/Neuregulin and Cav-1/dystrophin signaling, two crucial pathways for z-disk and costamere linkages in cardiomyocytes.

0213

**Gevokizumab, an IL1-beta modulating antibody exerts promising cardioprotecive effects against ischemia-reperfusion injury in diabetic rats.**

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**Aims:** Enhanced myocardial interleukin-1 beta (IL1-β) production is involved in ischemia/reperfusion (IR) induced left ventricular (LV) dysfunction. We tested neutralization of IL-1β as a potential therapeutic target for the treatment of IR induced LV dysfunction.

**Methods:** We assessed in diabetic (Goto Kakizaki, GK) rats the preventive effects of gevokizumab, a potent modulator of IL-1β, administered once a week, started 4 weeks prior to a 20 min of transient ischemia induced by left coronary artery occlusion and continued 90 days after IR, on LV remodeling/function (echocardiography) 7 and 90 days after IR, LV hemodynamics (LV catheterization), LV tissue perfusion (MRI) and LV collagen density (image analysis) were assessed 90 days after IR.

**Results:** IR induced early LV expansion followed by late LV dilatation, associated with LV dysfunction as well as after 90 days, reduced LV tissue perfusion and LV collagen accumulation. Gevokizumab limited both early LV expansion as well as late LV dilatation, associated with an improved LV function. Ninety days after IR, gevokizumab improved both LV systolic and LV diastolic functions, illustrated by the increase in LV end-systolic pressure volume relation, and the reductions in LV end-diastolic pressure and LV end-diastolic pressure volume relation. Moreover, long-term gevokizumab moderately increased LV tissue perfusion and significantly reduced LV collagen density.

**Conclusions:** Our results, obtained using a clinically relevant model of IR, suggest a therapeutic benefit of the IL-1β modulating antibody, gevokizumab, in myocardial IR injury.

LVDD: left ventricular diastolic diameters; LVFS:LV fractional shortening; LVESPVR and LVEDPVR: LV end-diastolic and end-systolic pressure volume relations. *p<0.05 vs GK; † p<0.05 vs GK IR

0190

**Early and delayed IL-1 beta antibody gevokizumab treatments prevent cardiac remodeling and reverse coronary endothelial dysfunction following myocardial infarction injury in Goto Kakizaki rats**

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**Aims:** Cardiac interleukin-1 beta (IL1-β) production is enhanced acutely after myocardial infarction and is involved in myocardial damages. We tested if early and delayed IL1-β modulations by IL-1β antibody, gevokizumab, prevent left ventricular (LV) remodeling and endothelial dysfunction induced by LV ischemia/reperfusion (IR) in diabetic rats.

**Methods:** Gevokizumab (Gevo; 10 mg/kg) was administered 1 hour (early) or 7 days (delayed) following reperfusion, after a 20 min of transient ischemia induced by LV artery occlusion and continued every week for 90 days. Delayed perindopril (1 mg/kg) was used as a positive control. LV remodeling and function were assessed (Echocardiography) at 7 and 90 days, LV hemodynamics (Millar catheterization) and relaxation of isolated coronary arteries to acetylcholine (Mulvany wiregraph) were evaluated at 90 days. Collagen density and leukocytes infiltration were evaluated (Histology) at 90 days.

**Results:** At 7 days, early Gevo limited the early LV expansion and reduction of FS induced by IR. At 90 days both of early and delayed Gevo as well as perindopril limited in a similar manner, the LV late dilatation, the reduction of FS and LV systolic and diastolic dysfunction induced by IR. At 90 days, GK coronary endothelium-dependent relaxation to acetylcholine was impaired by IR (59±13 vs.17±4%, p<0.05). Early, delayed Gevo and perindopril restored the (86±4, 92±2 and 98±1% respectively; p<0.05 vs GK+IR) coronary relaxation to acetylcholine. Early, delayed Gevo and perindopril significantly reduced collagen density and leukocytes infiltration at 90 days.

**Conclusions:** In a clinically relevant model of acute myocardial infarction, the IL-1β antibody gevokizumab started early or late after myocardial reperfusion exerts immediate and late cardiovascular protection.