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Rescue of cardiac function in obese type-2 diabetic mice by transfer of a human longevity gene

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Elisa Avolio, Anita C Thomas, Zexu Dang, Ashton Faulkner, Yue Gu, Antonio P Beltrami, Albino Carrizzo, Anna Maciag, Elena Ciaglia, Anna Ferrario, Antonio Damato, Gaia Spinetti, Carmine Vecchione, Annibale A Puca, Paolo Madeddu

University of Bristol, Bristol Medical School, United Kingdom (EA, ACT, ZD, AF, YG, PM); University of Udine, Department of Pathology, Italy (APB); IRCCS Neuromed, Department of Vascular Physiopathology, Pozzilli, Italy (AC, AD, CV); IRCCS Multimedica, Cardiovascular Department, Milan, Italy (AM, AF, GS); Department of Medicine, University of Salerno, Baronissi, Italy (EC, APP)

Background: Healthy longevity is the result of the interaction between favourable environment and unique genetic makeup. We showed that horizontal transfer of a longevity-associated gene variant (LAV-BPIFB4) improves endothelial function and accelerates the recovery from ischemia.

Purpose: To determine if the benefit of LAV-BPIFB4 gene therapy can be extended to diabetic cardiomyopathy.

Methods and results: We confirmed that human diabetic patients with heart failure (n=13) show a decreased cardiac expression of BPIFB4 compared with healthy subjects (n=10). Obese db/db mice received a systemic injection of adeno-associated viral vector (AAV9)-LAV-BPIFB4, AAV9-wild type (WT)-BPIFB4 (both 100 µL at 1×10^{12} GC/mL) or vehicle before the onset of cardiomyopathy, and were euthanised four weeks later for histological, metabolic and transcriptional analyses. Echocardiographic evaluation (n=8/group), performed at baseline and after gene therapy, showed that LAV-BPIFB4 treatment, despite not resolving hyperglycaemia, improved left ventricular function compared with the other groups. Histological analyses of the hearts (n=5 to 10/group) revealed that LAV-BPIFB4 reduced myocardial fibrosis and increased angiogenesis compared with vehicle and WT-hearts; moreover, LAV increased the expression of the alpha-isoform of the cardiac myosin heavy chain, which is associated with a superior cardiomyocyte contractility. Interestingly, LAV-BPIFB4 treatment induced an increase in cardiac SDF1 expression compared with WT and vehicle, despite the mechanism linking the two events is still unknown. The oral administration of the CXCR4 antagonist AMD-070, given at 2 mg/kg/day for four weeks, abolished several of the beneficial effects exerted by the LAV-BPIFB4 therapy in the obese diabetic mice, as assessed by echocardiography and histology (n=7/group).

At the molecular level, next-generation RNA sequencing (n=3 to 4 /group) showed 8 genes were differentially expressed by LAV-BPIFB4-hearts compared with vehicle-hearts. These genes are associated with mitochondrial and metabolic functions. Among them, changes in the UCP3, HMGCS2, CS, ATPB and TOMM20 expression were also validated at the protein level by western blotting. Lipidomics using ultrahigh-performance liquid chromatography-mass spectrometry (n=6 or 7/group) showed 63 metabolites differentially expressed by LAV-BPIFB4- compared with vehicle-hearts, with only 3 (two cardiolipins and one glycerophospholipid) returning close to the non-diabetic phenotype following LAV-BPIFB4 treatment.

Conclusions: This study newly shows the possibility of transferring the benefit of salutary polymorphic gene variants to protect the cardiovascular system from metabolic pressure. Rather than combating pathogenic mechanisms, the strategy activates alternative pathways overriding disease risk factors.