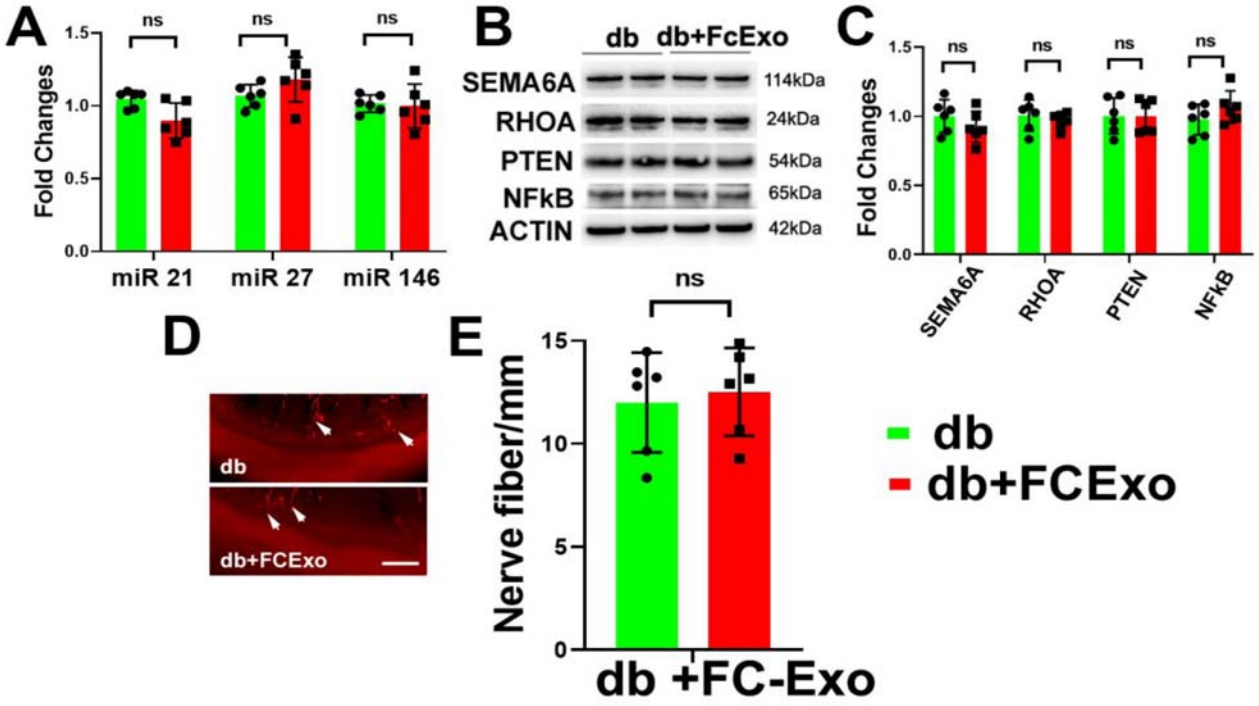
SUPPLEMENTARY DATA

Supplementary Figure 1. Fibroblast-Exos do not alter miRs and their target proteins in the sciatic nerve tissue and do not increase IENF density in diabetic mice. Panel A shows quantitative RT-PCR data of miR-21, -27a, and -146a levels in sciatic nerve tissue in diabetic mice treated with saline (db, green), and diabetic mice treated with FC-Exos (db+FCExo, red). n=6 mice/group. Panel B and C show representative Western blot image (B) and quantitative data (C) of protein levels of SEMA6A, RhoA, PTEN and pNF-kB in sciatic nerve tissues of diabetic mice treated with saline (db, green), or with FC-Exos (db+FCExo, red). n=6 mice/group. Fold changes=Fold changes normalized to control. Panel D shows representative images of PGP immunoreactive intraepidermal nerve fibers (red, arrows) in the hind plantar paw skin from diabetic mice treated with saline (db) or with FC-Exos (db+FCExos). Histogram (E) represents the quantitative data of the nerve fiber density under various conditions. Bar=50μm. n=6 mice/group. "ns" indicates not significant (p>0.05).



SUPPLEMENTARY DATA

Supplementary Table 1. miRNA primers used in real-time RT-PCR

miRNAs	**Mature miRNA sequence**
hsa-miR-21-5p	UAGCUUAUCAGACUGAUGUUGA
hsa-miR-27a-3p	UUCACAGUGGCUAAGUUCCGC
hsa-miR-146a-5p	UGAGAACUGAAUUCCAUGGGUU
U6 snRNA	GTGCTCGCTTCGGCAGCACATATACTAAAATTGGAACGATACAGAGAA GATTAGCATGGCCCCTGCGCAAGGATGACACGCAAATTCGTGAAGCGT TCCATATTTT

SUPPLEMENTARY DATA

Supplementary Table 2. Antibodies used for Western Blots

Antibody name	**Company and catalog number**	**concentration**
Anti-Alix	Cell Signaling, 2171	1:500
Anti-CD63	Santa Cruz, sc15363	1:500
Anti-HSP70	Abcam, ab31010	1500
Anti-SEMA6A	Abcam, ab154938	1:500
Anti-RhoA	Santa Cruz, sc418	1:500
Anti-pNFkB	Cell Signaling,3033	1:500
Anti-Pten	Cell Signaling, 9559	1:250
Anti-β action	Abcam, ab6276	1:5000

SUPPLEMENTARY DATA

Supplementary Table 3. Effect of SC-Exos on Triglycerides and Total Cholesterol

	Triglycerides		Total Cholesterol	
	Plasma (mg/dl)	**Liver (mg/g liver)**	**Plasma (mg/dl)**	**Liver (mg/g liver)**
dm-saline	58.9±17.1	21.7±0.7	85.6±12.6	3.1±0.1
db-saline	92.4±39.6	29.2±4.4*	130.0±29.2*	4.0±0.4*
db-SC-Exo	69.4±22.2	24.9±1.5	125.8±12.7	3.5±0.3

*p<0.05 versus dm+saline group. #p<0.05 versus db+saline group. n=7 mice/group for plasma analysis and n=4 mice/group for liver tissue analysis.

SUPPLEMENTARY DATA

SUPPLEMENTARY MATERIAL

Liposome preparation

In order to mimic the exosomal lipid layer, we have prepared liposome based on three major fatty acids that are found in exosomal lipid analysis. Liposomes were generated by means of the thin-film hydration technique (1). Briefly, to a 4 mL vial was added 1,2-dipalmitoyl-*sn*-glycero-3-phosphocholine (14.0 mg, 19 μmol), 1,2-distearoyl-*sn*-glycero-3-phosphocholine (4.0 mg, 5 μmol), 1,2-dioleoyl-*sn*-glycero-3-phosphocholine (4.0 mg, 5 μmol), cholesterol (8.0 mg, 2.1 μmol), and chloroform (1 mL) to produce a clear, colorless solution. Solvent was then removed under reduced pressure to form a visible film on the bottom of the vial. The hydration solution, PBS (1.15 mL) and vial containing the lipid thin film were placed in a water bath at 60 °C for 30 min, and then the hydration solution was added to the vial containing the thin film. The resulting white suspension was stirred at 60 °C for 1 hour. Extrusion of the suspension was accomplished using a mini-extruder and heating block (Avanti Polar Lipids, Alabaster, AL, USA) heated to 60 °C (4 passes through a 0.2 μm polycarbonate filter followed by 15 passes through a 0.1 μm polycarbonate filter). After extrusion, the suspension was allowed to cool to ambient temperature. Liposome samples were prepared for light scattering experiments by diluting liposome suspensions in phosphate-buffered saline (PBS, 1:10, 29 mM Na2HPO4, 46 mM NaH2PO4, 57 mM NaCl, and 2.1 mM KCl). Dynamic light scattering (DLS) data were obtained using a Malvern Zetasizer Nano-ZS instrument (ZEN3600) operating with a 633 nm wavelength laser. Dust was removed from samples by filtering through 0.2 μm hydrophilic filters (Millex–LG, SLLGR04NL). The size distribution of the prepared liposome was determined by DLS and their mean diameter was approximately 134 nm which is within the size range of exosomes (2; 3).

References:

1. Ekanger LA, Ali MM, Allen MJ: Oxidation-responsive Eu(2+/3+)-liposomal contrast agent for dual-mode magnetic resonance imaging. Chem Commun (Camb) 2014;50:14835-14838

2. Villarroya-Beltri C, Gutierrez-Vazquez C, Sanchez-Cabo F, Perez-Hernandez D, Vazquez J, Martin-Cofreces N, Martinez-Herrera DJ, Pascual-Montano A, Mittelbrunn M, Sanchez-Madrid F: Sumoylated hnRNPA2B1 controls the sorting of miRNAs into exosomes through binding to specific motifs. Nature communications 2013;4:2980

3. Xin H, Katakowski M, Wang F, Qian JY, Liu XS, Ali MM, Buller B, Zhang ZG, Chopp M: MicroRNA cluster miR-17-92 Cluster in Exosomes Enhance Neuroplasticity and Functional Recovery After Stroke in Rats. Stroke; a journal of cerebral circulation 2017;48:747-753