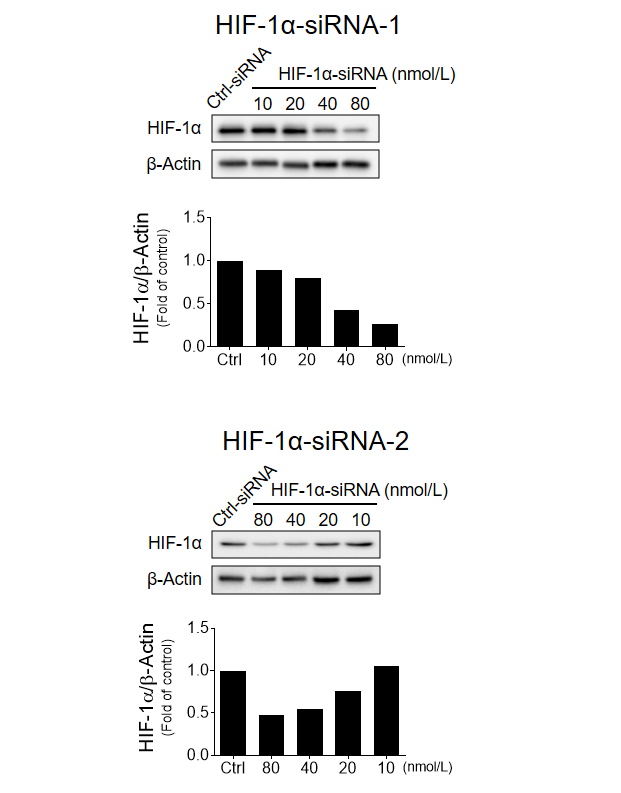
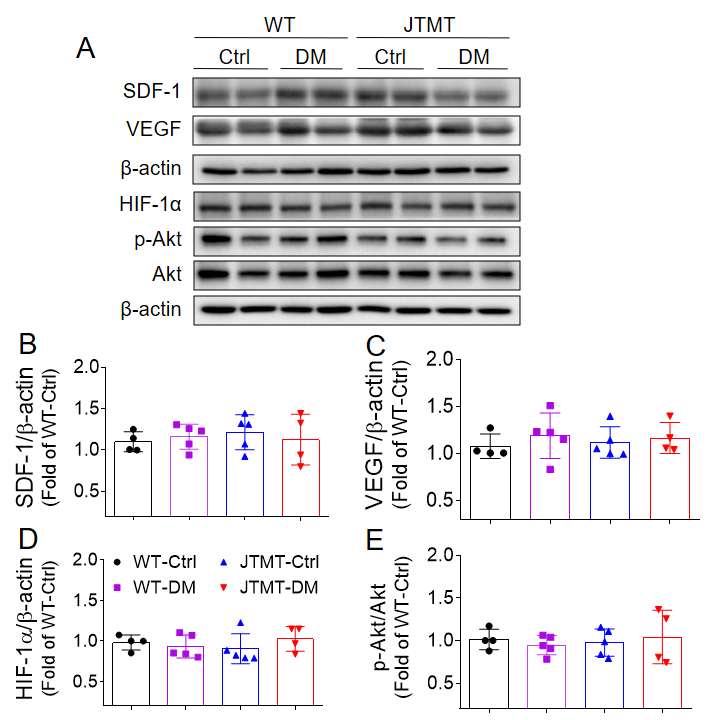


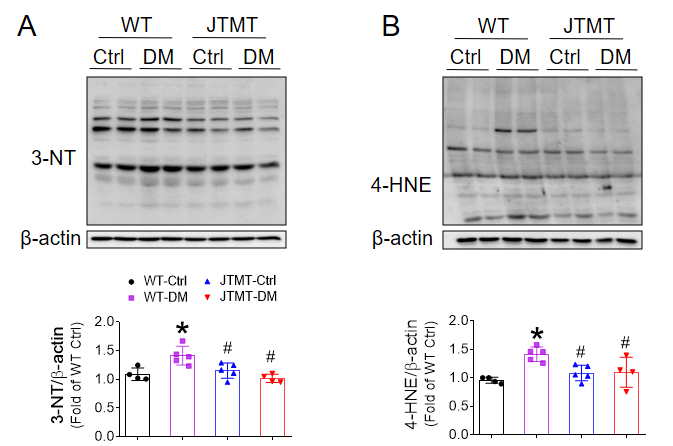
**Figure S1. Timeline of type 2 diabetes and diabetic hind limb ischemia (HLI) induction.** JTMT and WT male mice at age of 8-10 weeks were fed with high fat diet (HFD, Research Diets 12492, 60% kcal from fat) or normal diet (ND, Research Diets 12450B, 10% kcal from fat) for 23 weeks (**A**). Body weight was monitored every week (**B**) and blood glucose levels were monitored every other week (**C**). After 8 weeks on HFD, intraperitoneal glucose tolerance test (IPGTT) was performed to confirm the glucose intolerant status (**D, E**). After 15 weeks on HFD, HFD feeding mice with glucose intolerance were injected a single dose of streptozocin (STZ, 100mg/kg, Sigma, St. Louis, MO) in 0.1 mol/L sodium citrate buffer (pH 4.5) to induce insulin deficiency and hyperglycemia. Seven days after the injection of STZ, mice with blood glucose levels ≥ 250 mg/dL were considered diabetic (**C**). Mice feeding with ND were injected a single dose of 0.1 mol/L sodium citrate buffer (pH 4.5) as controls. Four weeks after STZ injection, the mice were used for HLI induction (**A**). Data shown in graphs represent the mean±SD. n≥9 mice per group. \* P<0.05, vs respective controls of WT and JTMT. Ctrl, control; DM, type 2 diabetes mellitus.



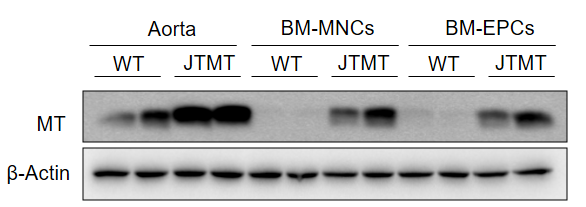
**Figure S2. Optimizing the dose of hypoxia-inducible factor 1α (HIF-1α) siRNA.** To knockdown HIF-1α expression in early bone marrow endothelial progenitor cells (BM-EPCs) from JTMT mice, two different specific siRNAs (HIF-1α-siRNA-1 and HIF-1α-siRNA-2) against mouse HIF-1α, alone with Silencer Select Negative Control were transfected into EPCs. HIF-1α-siRNAs dose-dependently interfered HIF-1α expression detected by Western blot assay. β-actin was used as loading control. Accordingly, 80 nmol/L was chosen for *ex vivo* studies.



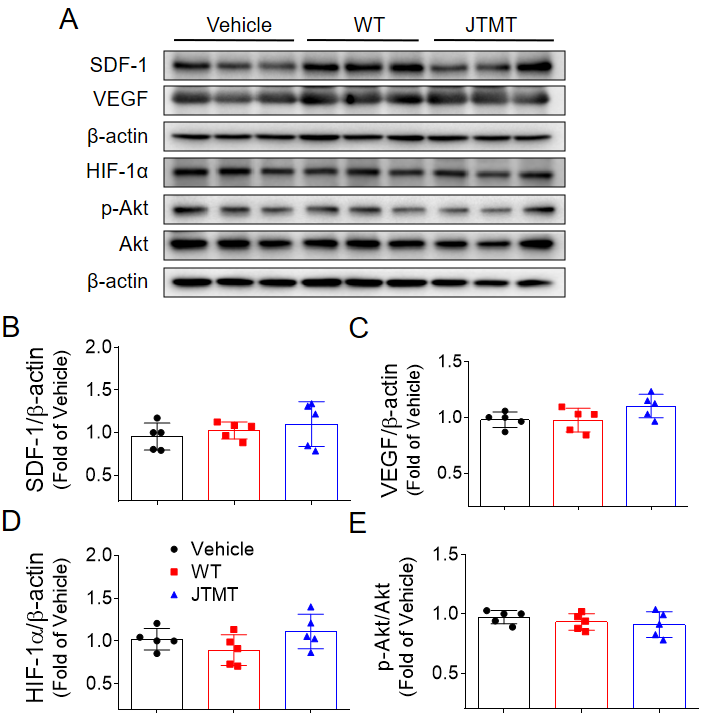
**Figure S3. The expression of pro-angiogenic factors in the contralateral non-ischemic gastrocnemius muscle in WT and JTMT mice.** Type 2 diabetes was induced as described in Figure 1. At day 3 after HLI surgery, the expression of stromal cell-derived factor 1 (SDF-1, **A,** **B**), vascular endothelial growth factor (VEGF, **A, C**) and hypoxia-inducible factor 1α (HIF-1α, **A,** **D**), and phosphorylation of protein kinase B (Akt, **A,** **E**) in the contralateral non-ischemic gastrocnemius muscle were detected by Western blot, and β-actin was used as loading control. Data shown in graphs represent the mean±SD. n≥4 mice per group. Ctrl, control; DM, diabetes mellitus.



**Figure S4. Endothelial MT overexpression alleviates oxidative stress in diabetic HLI.** Type 2 diabetes was induced as described in Figure 1. At day 3 after HLI surgery, the gastrocnemius muscle lysis was used to evaluate the levels of oxidative damage markers 3-nitroryrosine (3-NT, **A**) and 4-hydroxynonenal (4-HNE, **B**) by Western blot. β-actin was used as loading control. Data shown in graphs represent the mean±SD. n≥4 mice per group. \* P<0.05, vs WT-Ctrl; # P<0.05, vs WT-DM.



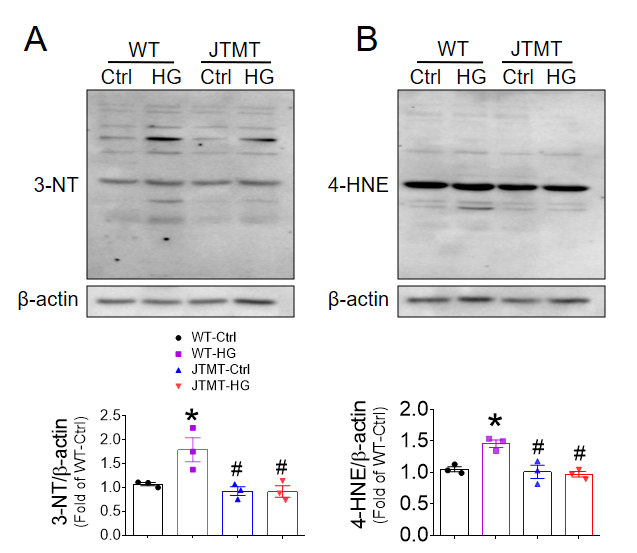
**Figure S5.** **Expression of MT in different tissues.** The expression of MT in aorta, bone marrow mononuclear cells (BM-MNCs) and BM-endothelial progenitor cells (EPCs) from WT and JTMT mice was detected by Western blot.



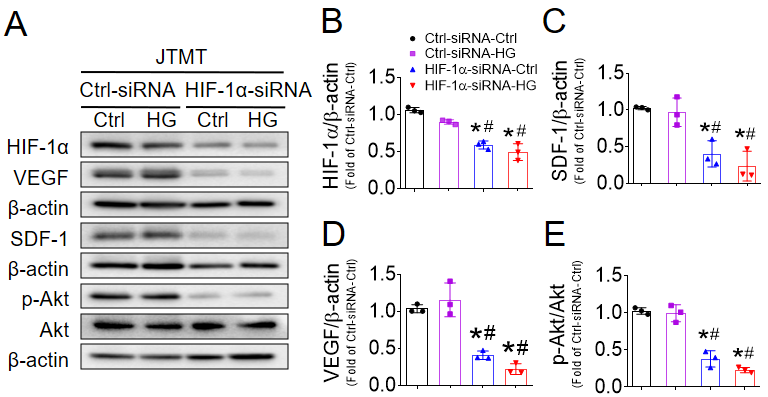
**Figure S6. The expression of pro-angiogenic factors in the contralateral non-ischemic gastrocnemius muscle in db/db mice infused with WT-MNCs and JTMT-MNCs.** BM-MNCs transplantation was performed as described in Figure 3. At day 7 after HLI surgery, the expression of stromal cell-derived factor 1 (SDF-1, **A,** **B**), vascular endothelial growth factor (VEGF, **A, C**) and hypoxia-inducible factor 1α (HIF-1α, **A,** **D**), and phosphorylation of protein kinase B (Akt, **A,** **E**) in the contralateral non-ischemic gastrocnemius muscle were detected by Western blot, and β-actin was used as loading control. Data shown in graphs represent the mean±SD. N=5 mice per group.



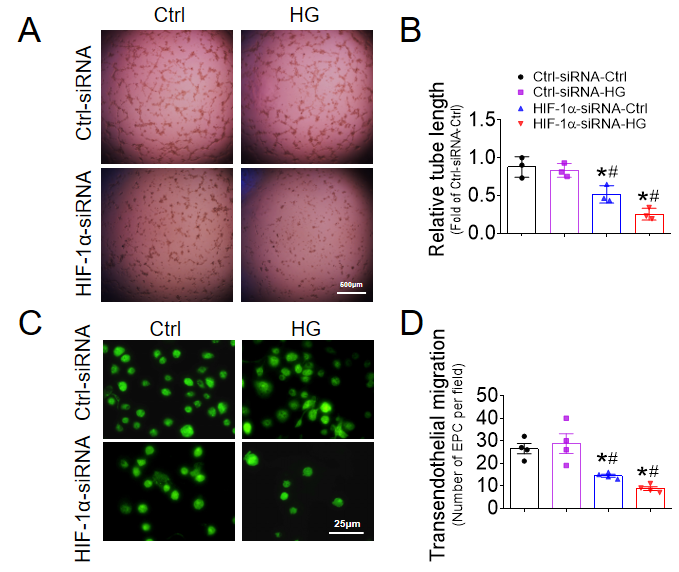
**Figure S7.** **MT overexpressing bone marrow-derived mononuclear cells (BM-MNCs) transplantation alleviates oxidative stress in db/db diabetic mice with HLI.** BM-MNCs transplantation was performed as described in Figure 3. At day 7 after HLI surgery, the gastrocnemius muscle lysis was used to evaluate the levels of oxidative damage markers 3-NT (**A**) and 4-HNE (**B**) by Western blot. β-actin was used as loading control. Data shown in graphs represent the mean±SD. n=5 mice per group. \* P<0.05, vs Vehicle; # P<0.05, vs WT.



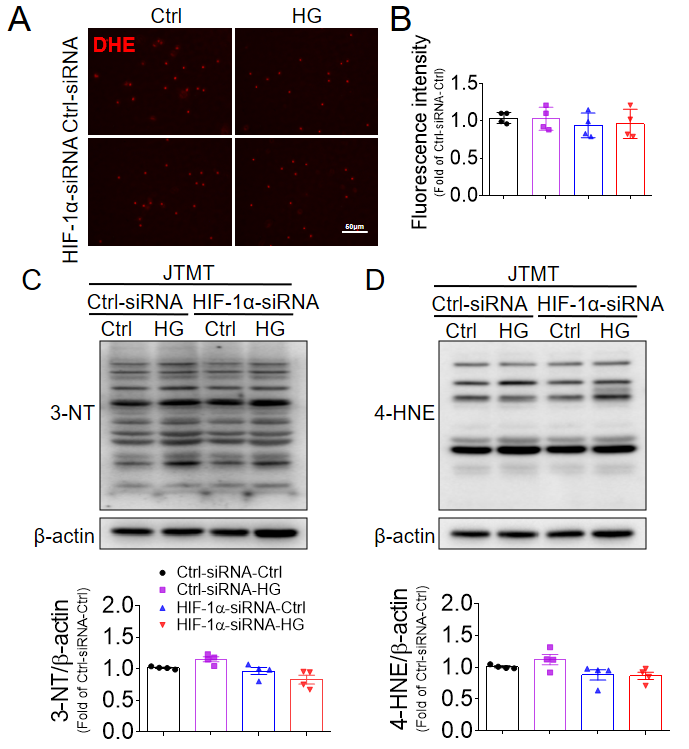
**Figure S8.** **Endothelial MT overexpression protects EPCs from high glucose (HG) and hypoxia-induced oxidative stress.** BM EPCs from WT and JTMT mice were exposed to HG (25 mmol/L) and hypoxia for 24 h, the equivalent concentration of mannitol was used as osmotic control (Ctrl). The oxidative damage was evaluated by Western blot assay of 3-NT (**A**) and 4-HNE expression (**B**). β-actin was used as loading control. Three independent experiments were performed. Data shown in graphs represent the mean±SD. \* P<0.05, vs WT-Ctrl; # P<0.05, vs WT-HG.



**Figure S9. Knockdown of HIF-1α abolishes MT overexpression protecting EPCs from HG and hypoxia-impaired HIF-1α/SDF-1/Akt signaling.** BM EPCs from JTMT mice were transfected a second specific siRNA (Figure S2) against HIF-1α for 48 h, the Silencer Select Negative Control was used as control siRNA (Ctrl-siRNA). Then the transfected EPCs were exposed to HG (25 mmol/L) and hypoxia for additional 24 h, the equivalent concentration of mannitol was used as osmotic control (Ctrl). The expression of hypoxia-inducible factor 1α (HIF-1α, **A, B**), stromal cell-derived factor 1 (SDF-1, **A, C**), vascular endothelial growth factor (VEGF, **A, D**), and phosphorylation of protein kinase B (Akt, **A, E**) was tested by Western blot. β-actin was used as loading control. Three independent experiments were performed. Data shown in graphs represent the mean±SD. \* P<0.05, vs Ctrl-siRNA-Ctrl; # P<0.05, vs Ctrl-siRNA-HG.



**Figure S10. Knockdown of HIF-1α abolishes MT overexpression protecting EPCs against HG and hypoxia-induced EPC dysfunction.** BM-EPCs from JTMT mice were transfected a second specific siRNA (Figure S2) against hypoxia-inducible factor 1α (HIF-1α) for 48 h, the Silencer Select Negative Control was used as control siRNA (Ctrl-siRNA). Then the transfected EPCs were exposed to HG (25 mmol/L) and hypoxia for additional 24 h, the equivalent concentration of mannitol was used as osmotic control (Ctrl). The angiogenic function was evaluated by tube formation assay (**A, B**). The migration capability was evaluated by transendothelial migration assay (**C**, **D**). At least three independent experiments were performed. Data shown in graphs represent the mean±SD. \* P<0.05, vs Ctrl-siRNA-Ctrl; # P<0.05, vs Ctrl-siRNA-HG.



**Figure S11. Knockdown of HIF-1α does not affect MT overexpressing EPCs resistance to HG and hypoxia-induced oxidative stress.** BM-EPCs from JTMT mice were transfected a second specific siRNA (Figure S2) against HIF-1α for 48 h, the Silencer Select Negative Control was used as control siRNA (Ctrl-siRNA). Then the transfected EPCs were exposed to HG (25 mmol/L) and hypoxia for additional 24 h, the equivalent concentration of mannitol was used as osmotic control (Ctrl). The oxidative damage was evaluated by dihydroethidium (DHE) stain of superoxide production (**A**, **B**) and Western blot assay of 3-NT (**C**) and 4-HNE (**D**) expression. Four independent experiments were performed. Data shown in graphs represent the mean±SD.

**Table S1. Human subject information**

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| --- | --- | --- | --- |
| **Description** | **Health Subjects**  **(n=6, mean ± SD)** | **Type 2 Diabetes**  **(n=6, mean ± SD)** | **P value** |
| **Age (years)** | 52.75 ± 3.467 | 51.33 ± 3.473 | P=0.3281 |
| **Sex, male/female (%)** | 3/3 (50%) | 3/3 (50%) |  |
| **Height (cm)** | 158.67 ± 3.601 | 159.08 ± 7.477 | P=0.8635 |
| **Weight (kg)** | 56.375 ± 5.398 | 67.917 ± 4.757 | P<0.0001 |
| **BMI (kg/m2)** | 22.17 ± 1.814 | 27.03 ± 1.602 | P<0.0001 |
| **Systolic blood pressure (mmHg)** | 108.17 ± 9.666 | 133.92 ± 9.070 | P<0.0001 |
| **Diastolic blood pressure (mmHg)** | 68.33 ± 7.608 | 93.75 ± 9.006 | P<0.0001 |
| **HbA1C (%)** | 4.18 ± 0.652 | 10.41 ±1.500 | P<0.0001 |
| **HbA1C (mmol/mol)** | 22 ± 7.1 | 90 ±16.4 | P<0.0001 |
| **Fasting blood glucose (mmol/L)** | 5.43 ± 0.624 | 15.86 ± 4.228 | P<0.0001 |
| **Triglyceride (mmol/L)** | 0.93 ± 0.255 | 3.12 ± 0.868 | P<0.0001 |
| **Total Cholesterol (mmol/L)** | 3.90 ± 0.604 | 5.63 ± 1.040 | P<0.0001 |
| **LDL-Cholesterol (mmol/L)** | 2.16 ± 0.497 | 3.70 ± 0.824 | P<0.0001 |
| **HDL-Cholesterol (mmol/L)** | 1.35 ± 0.243 | 0.84 ± 0.193 | P<0.0001 |

BMI, body mass index; HbA1c, hemoglobin A1C; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

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