

## Supplementary Figure legends

**Supplementary Figure 1. Plasma Metrnl content in mice and human.** (A) Serum Metrnl content of 16-week-old male C57BL/6 and *db/db* after wounded at 7 days or not, were detected using ELISA (n=5 mice per group). (B). Human serum Metrnl content in healthy control (n=10), DM (n=10) and DFU (n=14) were measured using ELISA. Data are mean  $\pm$  SD (n = 3 independent experiments). DM, diabetes mellitus; DFU: diabetic foot ulcer. \* $p < 0.05$ , compared with C57BL/6 group; # $p < 0.05$ , compared with C57BL/6-wound group.

**Supplementary Figure 2. Metrnl promotes proliferation, migration and/or tube formation in human primary keratinocytes and vascular endothelial cells.** (A-B) CCK-8 (A) and transwell assay (B) were conducted in human primary keratinocytes after rMet treatment (1  $\mu$ g/mL). (C-E) CCK-8 (C), transwell (D) and tube formation (E) assay were conducted after rMet treatment (1  $\mu$ g/mL) in human primary vascular endothelial cells (HUVECs). Data are mean  $\pm$  SD (n = 3 independent experiments). \* $p < 0.05$ , \*\* $p < 0.01$ , \*\*\* $p < 0.001$ , compared with Ctrl group.

**Supplementary Figure 3. Metrnl promotes wound healing in HFD/STZ mice.**

A. Timeline for *in vivo* experiments (n=24 mice per group). B. Fasting blood glucose of HFD/STZ mice before wound creation. C. Representative images and quantitative analysis of the wound areas treated with rMet hydrogel for 11 days in HFD/STZ mice. D. H&E staining of dorsal skin section on 7<sup>th</sup> and 11<sup>th</sup> day post-injury in HFD/STZ mice treated with or without rMet hydrogel. Scale bar =200  $\mu$ m. Data are mean  $\pm$  SD. n=6 mice per group at different points in time. Compared with Ctrl, \* $p < 0.05$ .

**Supplementary Figure 4. Metrnl accelerates wound healing in STZ mice.**

A. Timeline for *in vivo* experiments (n=24 mice per group). B. Fasting blood glucose of STZ mice before wound creation. C. Representative images and quantitative analysis of the wound with rMet hydrogel for 11 days in STZ mice. D-E. H&E (D) and Masson staining (E) of dorsal skin section at 7<sup>th</sup> and 11<sup>th</sup> day after post-injury in STZ mice treated with or without rMet hydrogel. Scale bar =100 and 200  $\mu$ m. F. Immunofluorescence staining of Ki67 (red) in the wound region at 7<sup>th</sup> day in STZ mice treated with or without rMet hydrogel. Scale bars, 50  $\mu$ m. Data are mean  $\pm$  SD.

n=6 mice per group at different points in time. Compared with Ctrl, \*\* $p < 0.01$ , \*\*\* $p < 0.001$ .

**Supplementary Figure 5. Metrnl recombinant protein (rMet) doesn't lead to obvious toxicity *in vitro* and *in vivo*.** (A-B) The cell viability of HaCat (A) and HUVECs cells (B) was measured using CCK-8 assay. (C-E) H&E staining of liver and kidney tissues (C) serum ALT (D) and creatinine (E) of C57BL/6 and *db/db* mice treated with or without Metrnl-hydrogels for 11 days. Data are mean  $\pm$  SD (n = 3 independent experiments). n=5 mice per group. \* $p < 0.05$ , \*\* $p < 0.01$ , \*\*\* $p < 0.001$ , compared with 0 ng/mL group.

**Supplementary Figure 6. Local application of Metrnl hydrogel doesn't alter glucose tolerance and increased insulin sensitivity in mice.** (A) Plasma Metrnl levels in STZ, HFD/STZ and *db/db* mice were detected using ELISA. (B, D, F) Mice were fasting for 8 h, subsequently 1.5 g/kg glucose were administrated intraperitoneally, and the blood glucose were determined at 0, 15 min, 30 min, 60 min and 120 min in STZ, HFD/STZ and *db/db* mice. (C, E, G). Mice were fasting for 8 h, subsequently insulin (0.5 U/kg body weight) was administrated intraperitoneally, and peripheral blood samples were collected to detected the blood glucose at 0, 15 min, 30 min, 60 min and 120 min in STZ, HFD/STZ and *db/db* mice. Data are mean  $\pm$  SD (n = 3 independent experiments). n=5 mice per group. IPGTT, intraperitoneal glucose tolerance test; ITT, insulin tolerance test.