Metformin administration protects deltoid tendon damage through activation of Notch signaling

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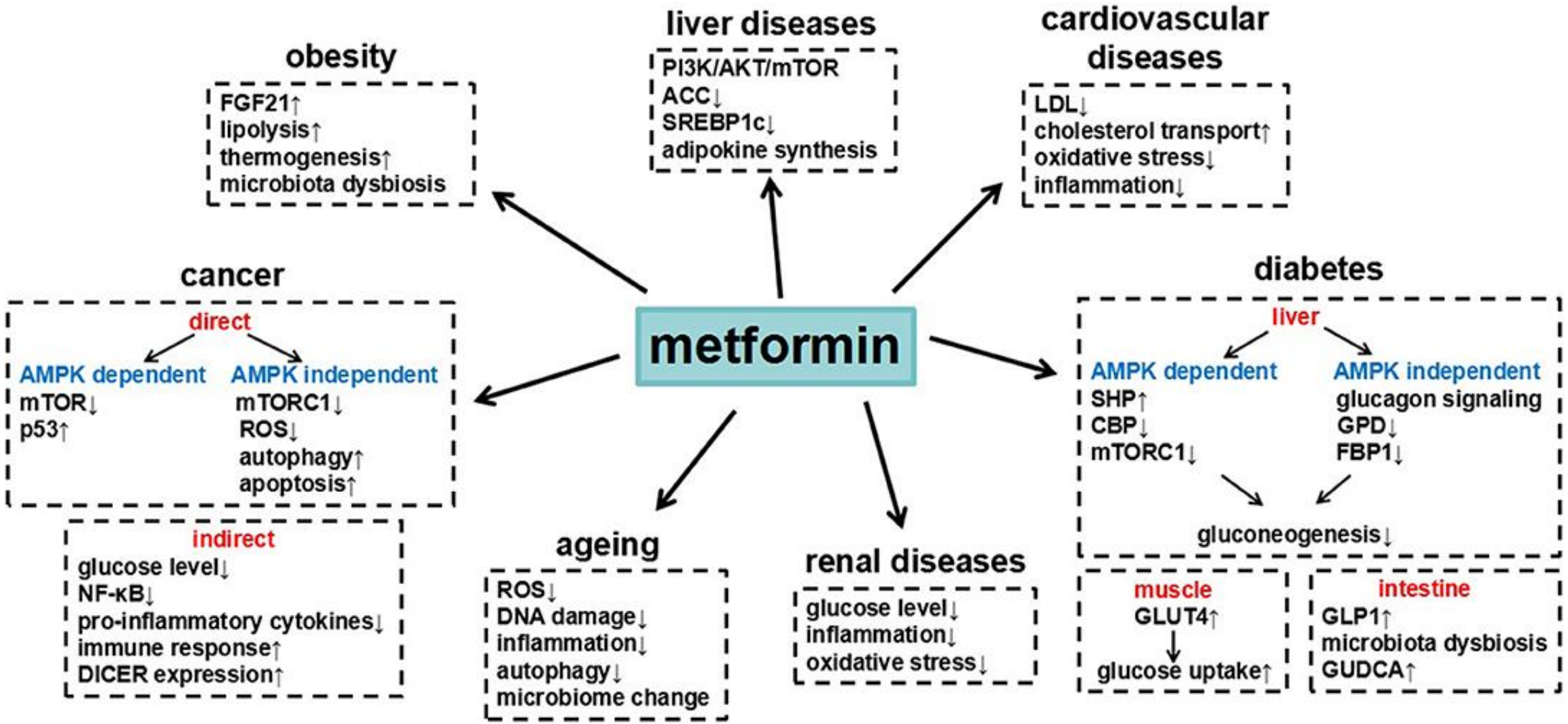
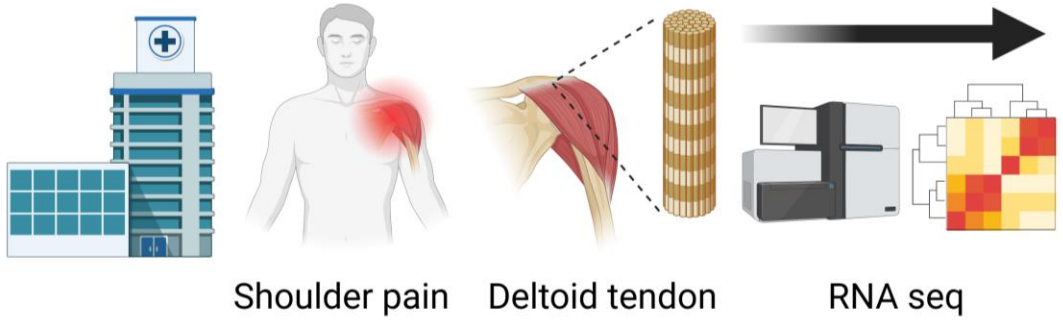
Introduction



Lv Z, Guo Y. Front Endocrinol (Lausanne). 2020.

Highlights



Deltoid tendon from T2DM patients

- Disconnected tendon fibers
- Impaired ECM and cell adhesion related pathways
- High level of *MMP3*
- Low level of *HES1*

Increased risk of tendon surgery

Tenogenic differentiation + Metformin

- Tenogenic marker *TNMD* ↑
- Notch activation ↑

Db/Db + Metformin

- Hyperglycemia control ↑
- *Notch* and *Hes1* in tendon ↑

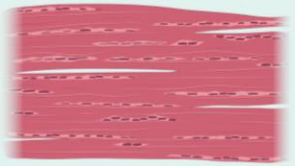
STZ-induced T2D + Metformin

- Insulin sensitivity ↑
- HES1 in tendon ↑

Aging + Metformin

- *MMP3* in tendon ↓
- *HES1* in tendon ↑

T2DM patients with Metformin



- Normal structure
- Altered expression of genes inintegral component of plasma membrane
- Low level of *MMP3*
- High level of *HES1*

Reduced risk of tendon surgery

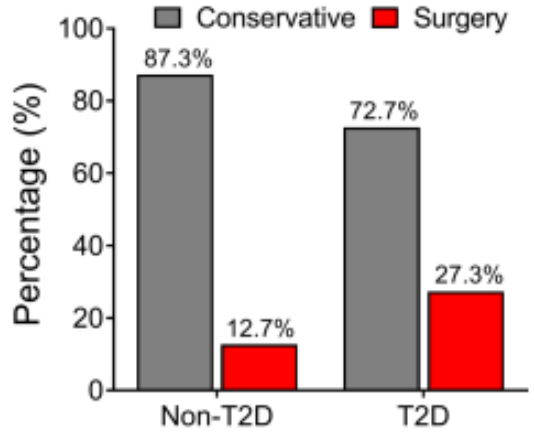
RESULTS AND DISCUSSION

(A)

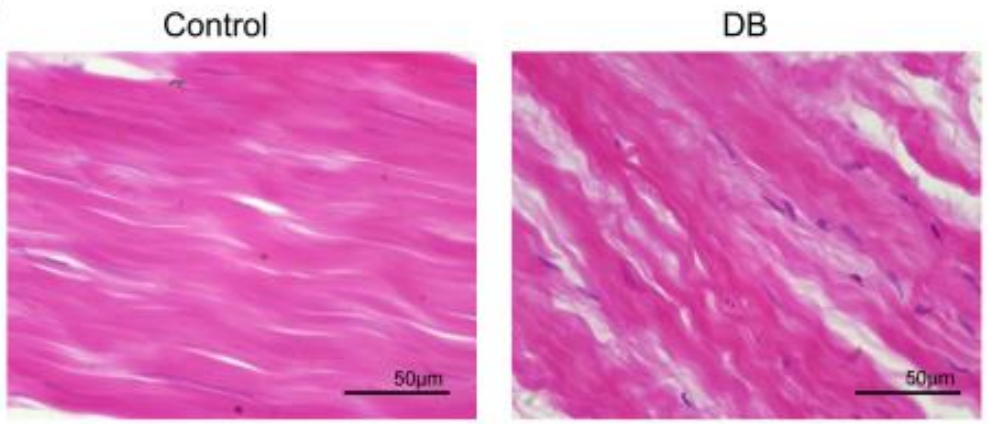
Statistical analysis of patients with shoulder pain in Department of shoulder and elbow surgery, Center for Orthopedic Surgery, The Third Affiliated Hospital of Southern Medical University from 2021-2023

Treatments	Conservative	Tendon surgery	Total
Shoulder pain	3,875	606	4,481
Type 2 diabetes	178	67	245
Chi-square test: *P* = 7.6497E-11			

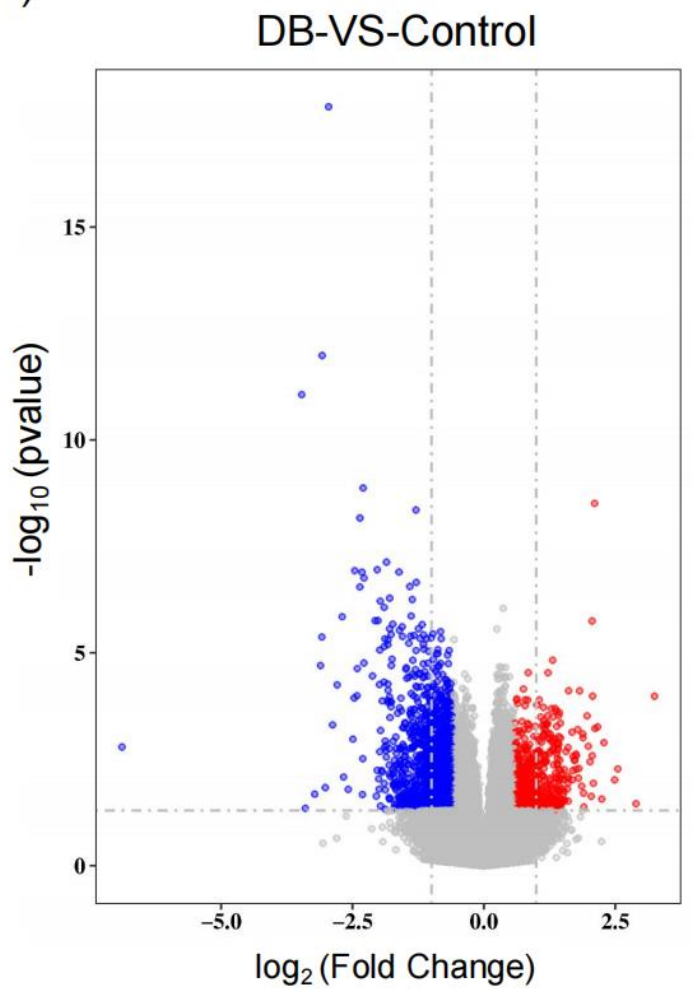
(B)



(C)

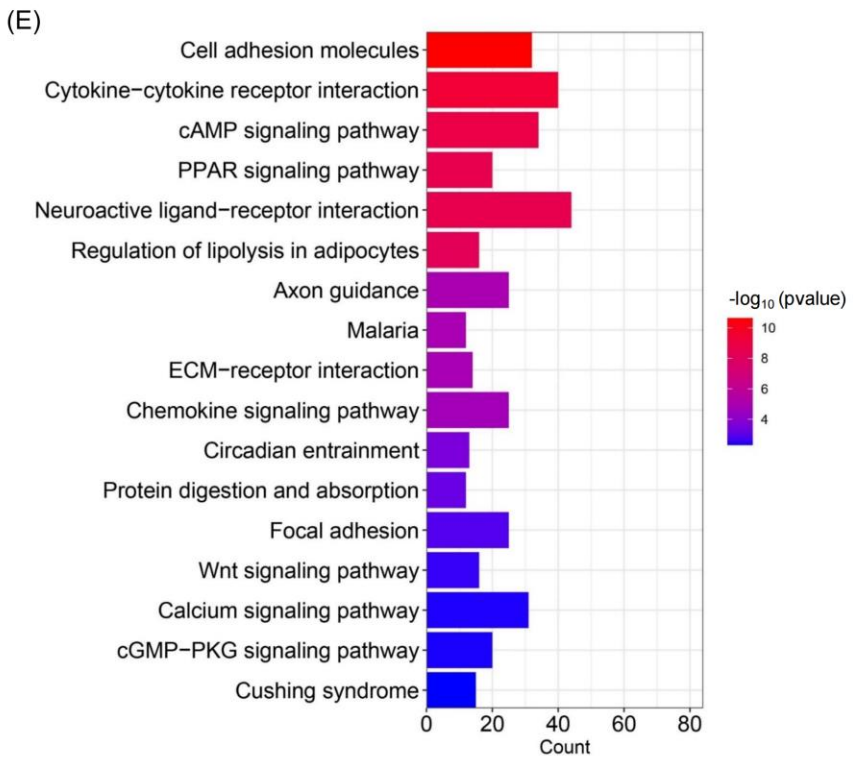


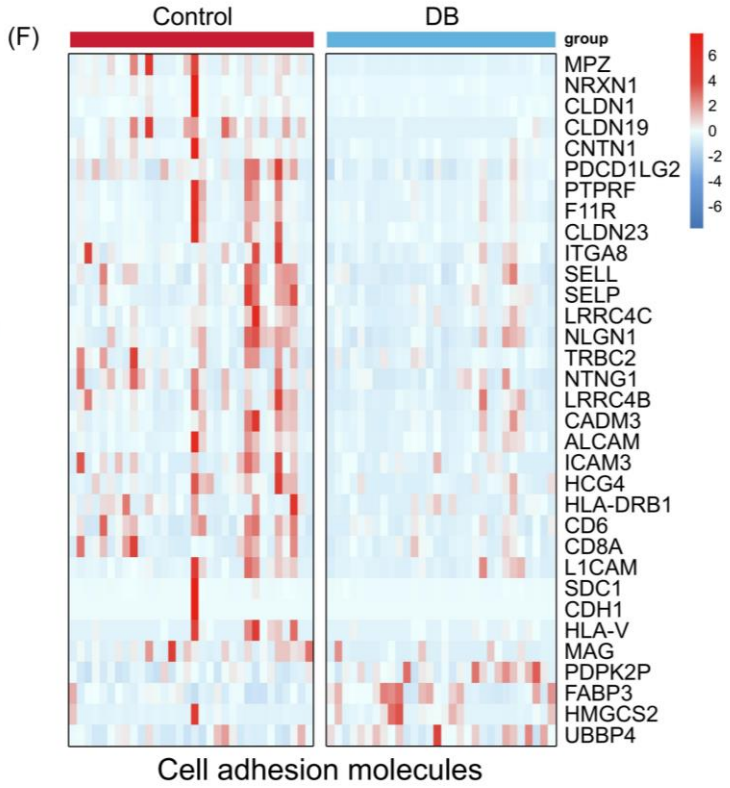
(D)

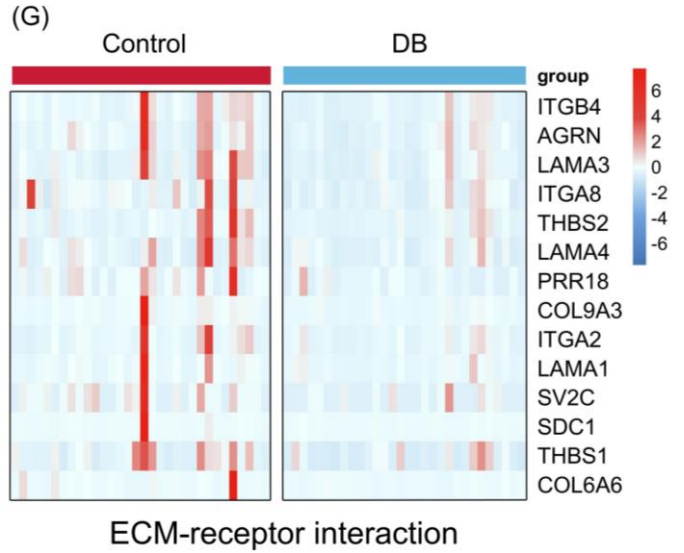


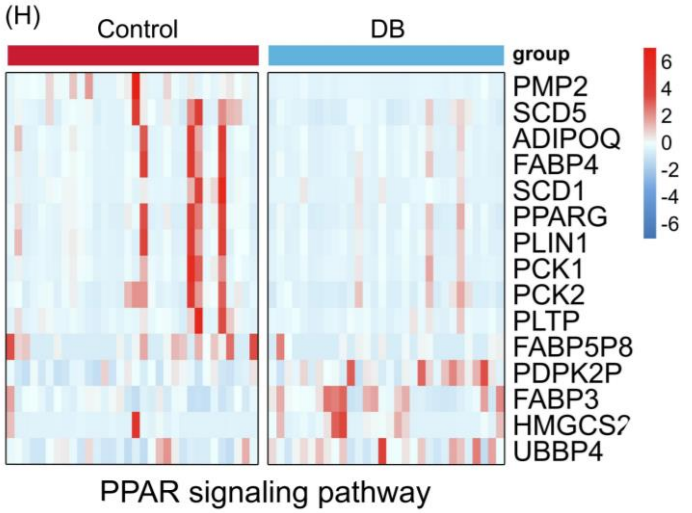
(A) Statistical analysis of patients with shoulder pain.
(B) Percentage of non-T2DM and T2DM patients with conservative treatment or undergo tendon surgery.
(C) Relative image of H&E staining using deltoid tendons from non-T2DM and T2DM patients.
(D) Volcano plot of the RNA-seq results from Control and DB groups, n = 32 and 30, respectively.

RESULTS AND DISCUSSION









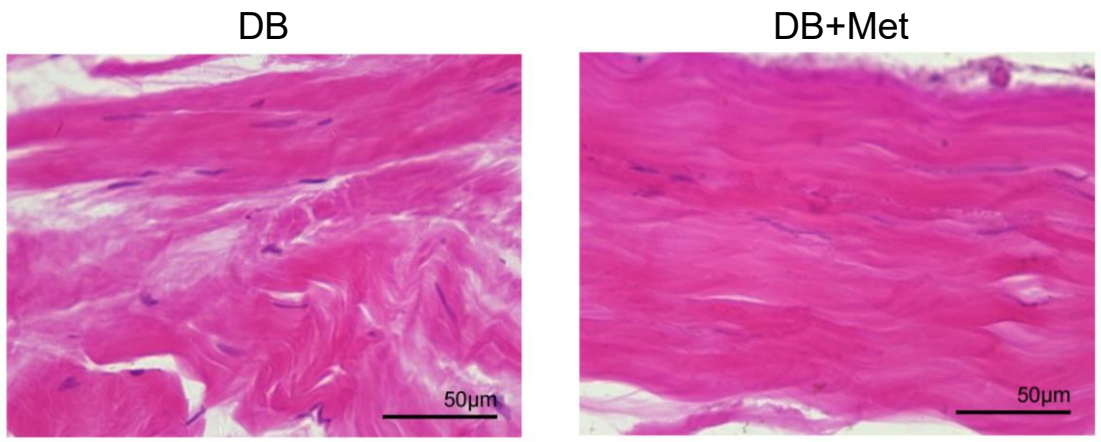
(E) KEGG analysis of deltoid tendon DEGs.
(F-H) Heatmap of DEGs from Control vs DB that enriched in Cell adhesion molecules (F), ECM-receptor interaction (G), and PPAR signaling (H) pathways.

RESULTS AND DISCUSSION

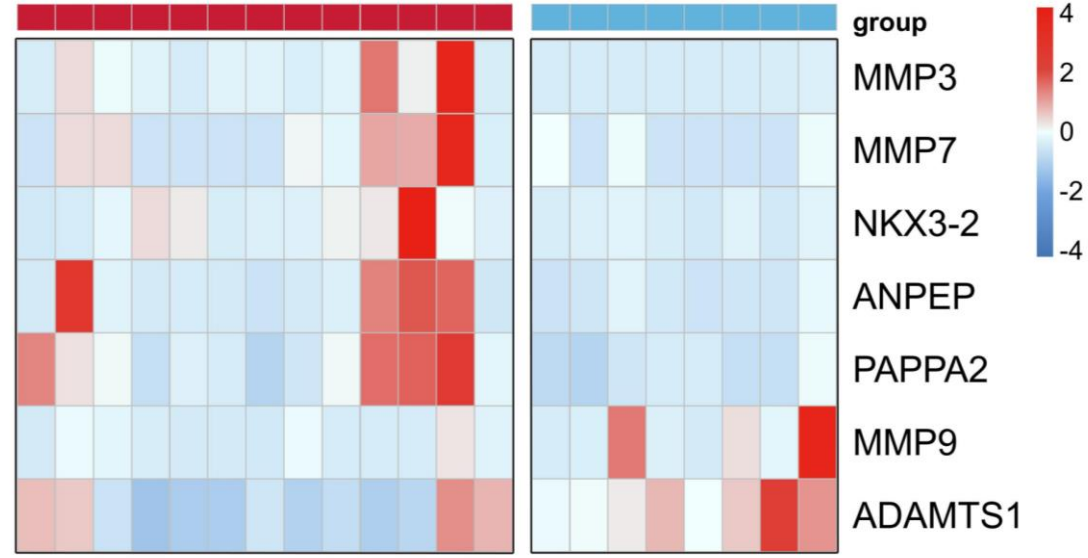
(I) Statistical analysis of T2D patients with shoulder pain in Department of shoulder and elbow surgery, Center for Orthopedic Surgery, The Third Affiliated Hospital of Southern Medical University from 2021-2023

Treatments	Conservative	Tendon surgery	Total
T2D with Metformin	77	21	98
Other medication	68	41	109
Chi-square test: $P = 0.011$			

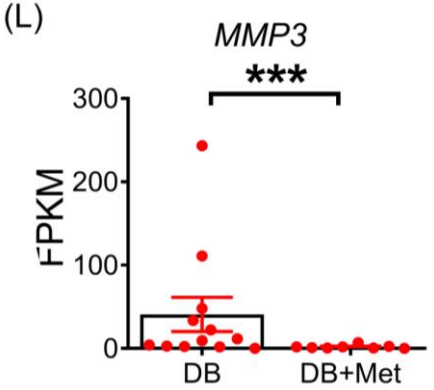
(J)



(K)

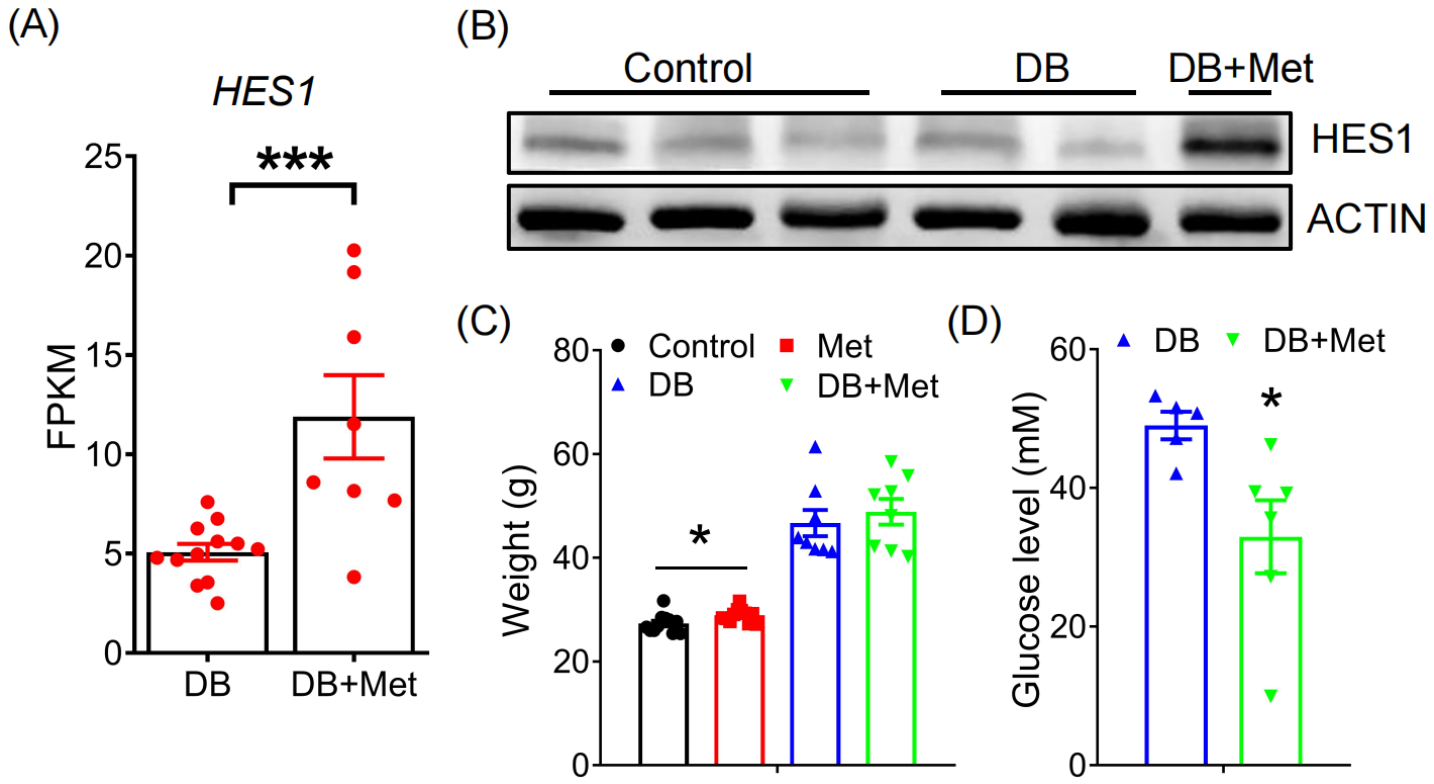


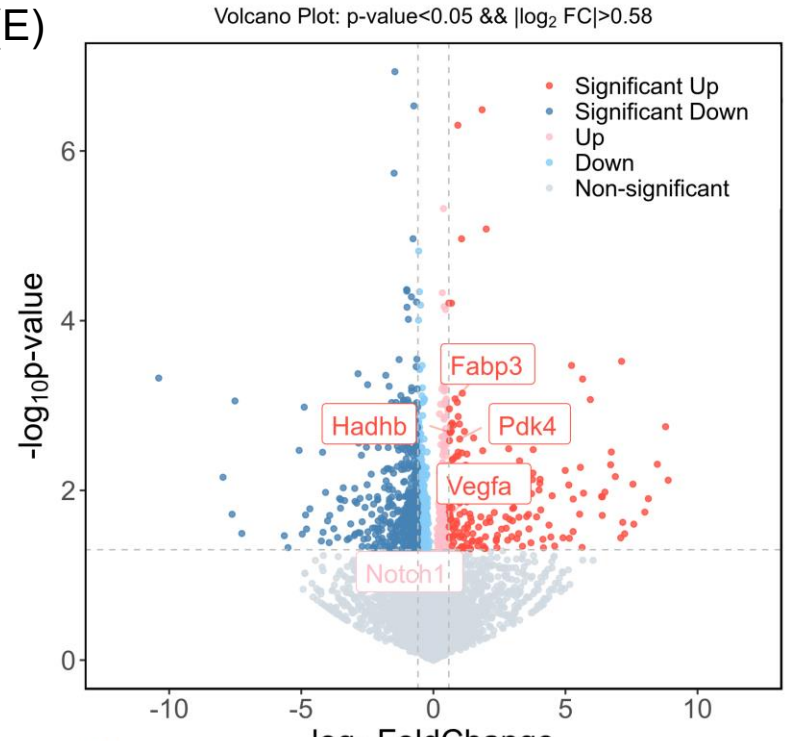
(L)

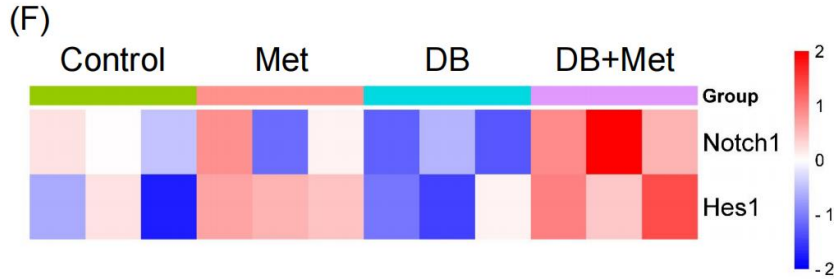


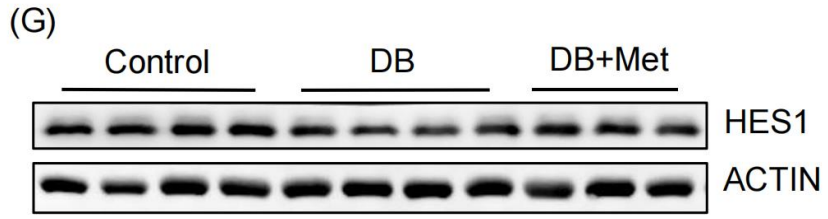
(I) Statistical analysis of T2DM patients with shoulder pain taking metformin or other medications.
(J) Relative image of H&E staining using deltoid tendons from T2DM patients and T2DM patients with metformin.
(K) Heatmap of the expression of genes in ECM-receptor interaction pathway.
(L) Relative mRNA levels of MMP3 from DB and DB+Met groups, n = 13 and 8, respectively.

RESULTS AND DISCUSSION



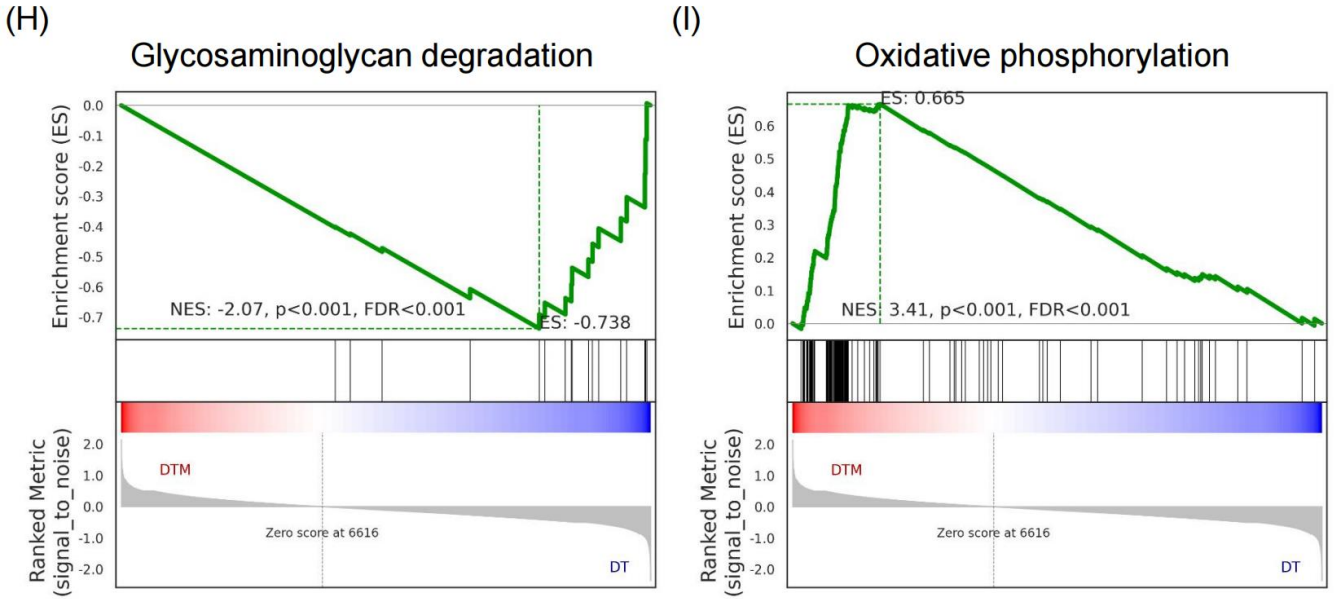


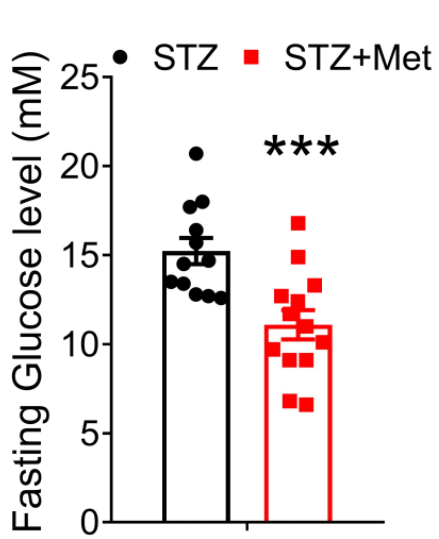


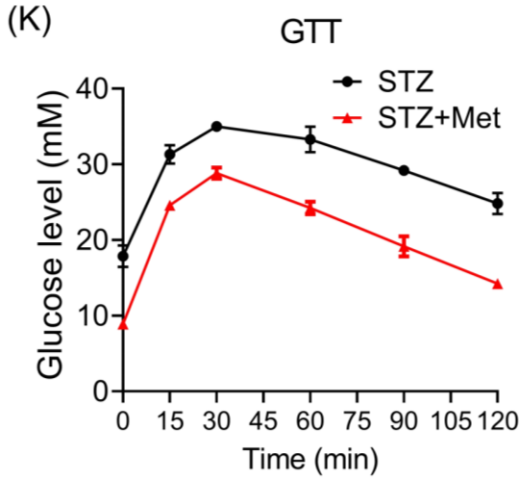


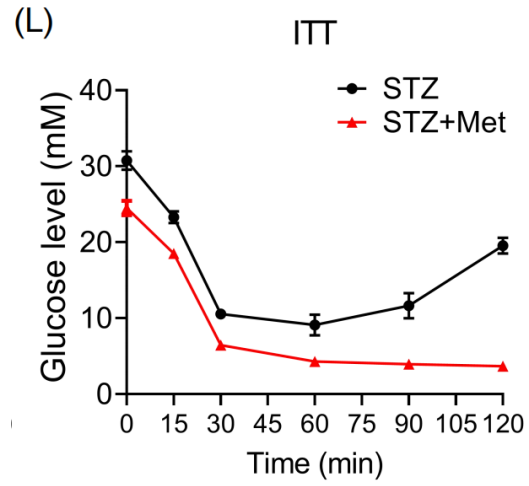
(A) Relative mRNA levels of HES1 expression in T2DM patients (n = 13) vs Met-treated T2DM patients (n = 8). (B) HES1 protein levels in deltoid tendons of Control, T2DM, and Met-treated T2DM groups. (C) Body weight of WT and DB/DB mice after 3-month of metformin treatment from WT and DB/DB groups. (D) Serum glucose levels of DB/DB mice with or without metformi n = 5 and 6, respectively. (E) Volcano plot analysis of tendon transcriptomes in DB/DB mice vs Met-treated DB/DB mice, n = 4. (F) Heatmap of Notch1 and Hes1 expressions in mouse deltoid tendon from WT, WT+Met, DB and DB+Met groups, n = 4. (G) Western blot analysis of HES1 protein levels in deltoid tendon from WT, DB and DB+Met groups.

RESULTS AND DISCUSSION

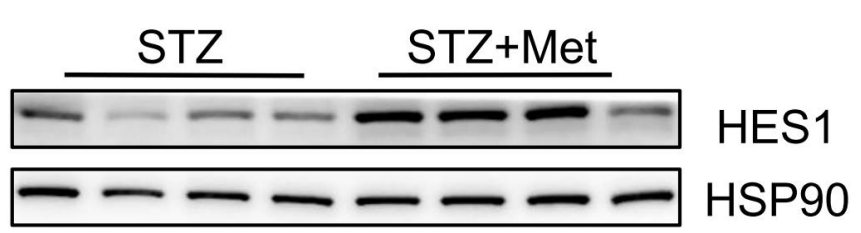




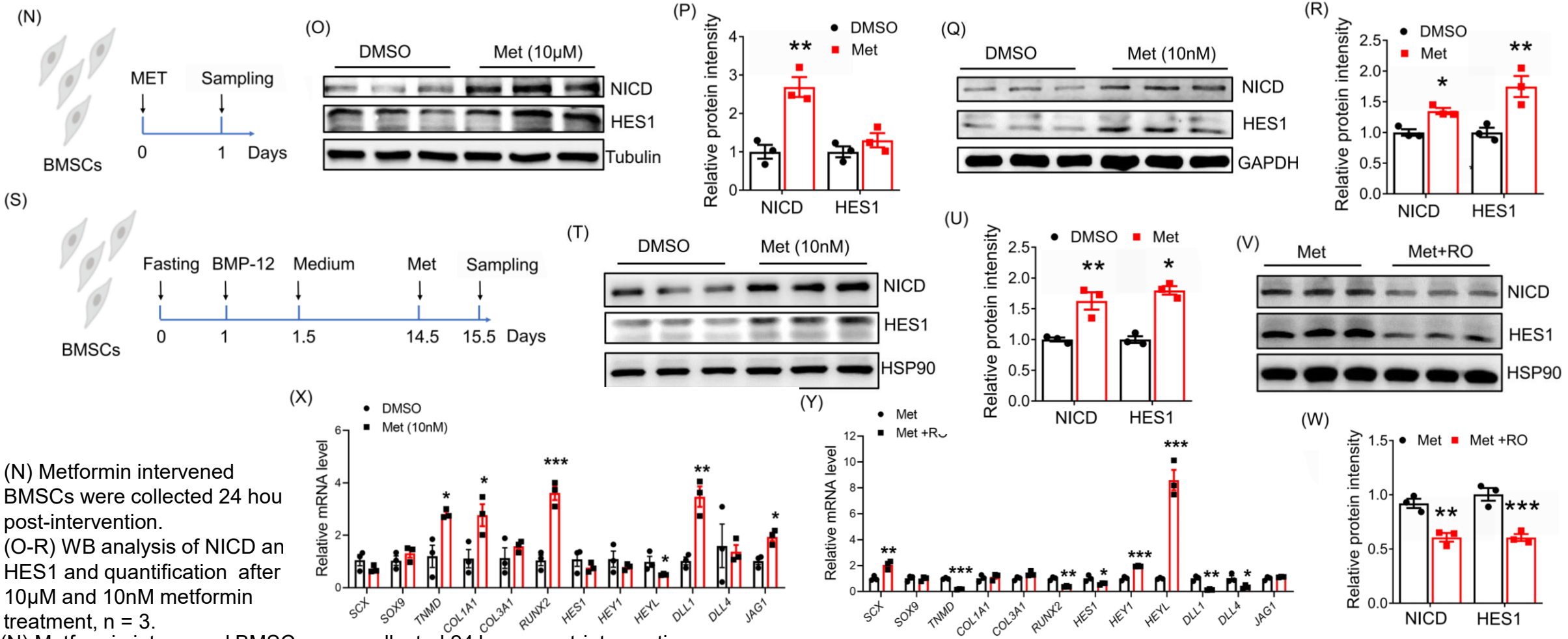




(H, I) Gene Set Enrichment Analysis (GSEA) of DEGs from Control and Met-treated DB/DB mice.
(J) Fasting blood glucose in streptozotocin (STZ)-induced T2DM mice, n = 13.
(K) Glucose tolerance tests (GTT) in STZ-T2DM mice, n = 5.
(L) Insulin tolerance tests (ITT) in STZ-T2DM mice, n = 5.
(M) HES1 protein levels in tendon of Control and STZ-induced T2DM mice, n = 4.



RESULTS AND DISCUSSION



(N) Metformin intervened BMSCs were collected 24 hou post-intervention.
(O-R) WB analysis of NICD an HES1 and quantification after 10μM and 10nM metformin treatment, n = 3.

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(O-R) WB analysis of NICD and HES1 and quantification after 10μM and 10nM metformin treatment, n = 3.
(S) A scheme showing metformin treatment on BMSCs after induction of tenogenic differentiation. Differentiated BMSCs were collected after sequential treatment: 24-hour nutrient deprivation, followed by 12-hour BMP-12 exposure, culture in normal media until day 14.5, 24-hour Met administration, and final sample collection.
(T, U) WB of NICD and HES1 and quantification after 10nM metformin treatment in tenogenic differentiated BMSCs.
(V, W) WB of NICD and HES1 and quantification after 10nM metformin treatment in tenogenic differentiated BMSCs with or without notch inhibitor RO4929097.
(X) Relative mRNA expressions of SCX, SOX9, TNMD, COL1A1, COL3A1, RUNX2, HES1, HEY1, HEYL, DLL1, DLL4, JAG1 in BMSCs from DMSO or Met groups, n = 3. (Y) Relative mRNA expressions of the aforementioned genes in BMSCs from Met or RO4929097 groups, n = 3.

Summary

- T2DM results in significant deltoid tendon damage and a higher risk of tendon surgery, attributed to abnormal tendon structure and impaired ECM and cell adhesion.
- T2DM patients treated with metformin for hyperglycemia control had a reduced risk of tendon surgery, along with the downregulation of the key tendon damage-related gene *MMP3* and the upregulation of the Notch signaling gene *HES1*.
- Cell culture, T2DM mice and aged monkey models were also applied to confirm that metformin treatments upregulated Notch signaling in tendons.
- Metformin directly protects tendons from injury by activating Notch signaling.

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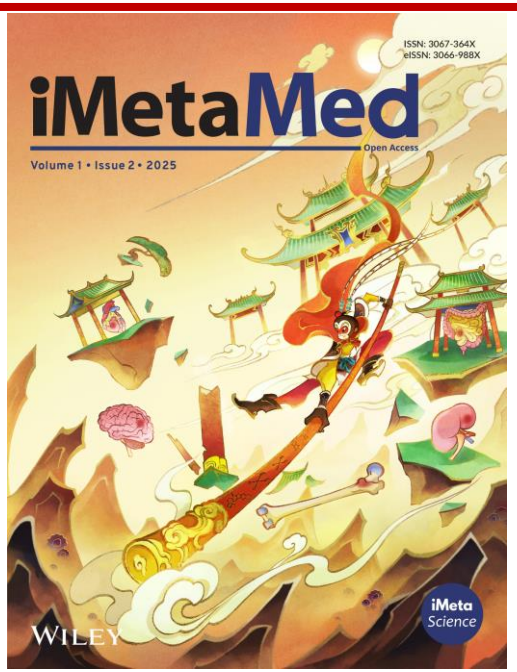

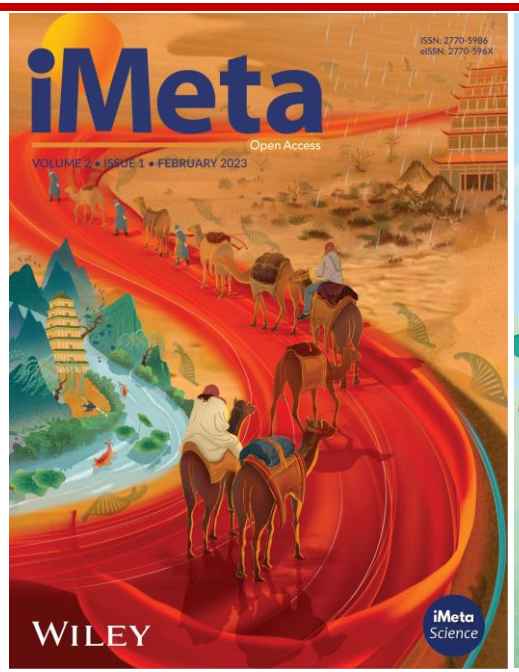

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