scRiskCell: A single-cell framework for quantifying islet risk cells and their adaptive dynamics in type 2 diabetes

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Introduction

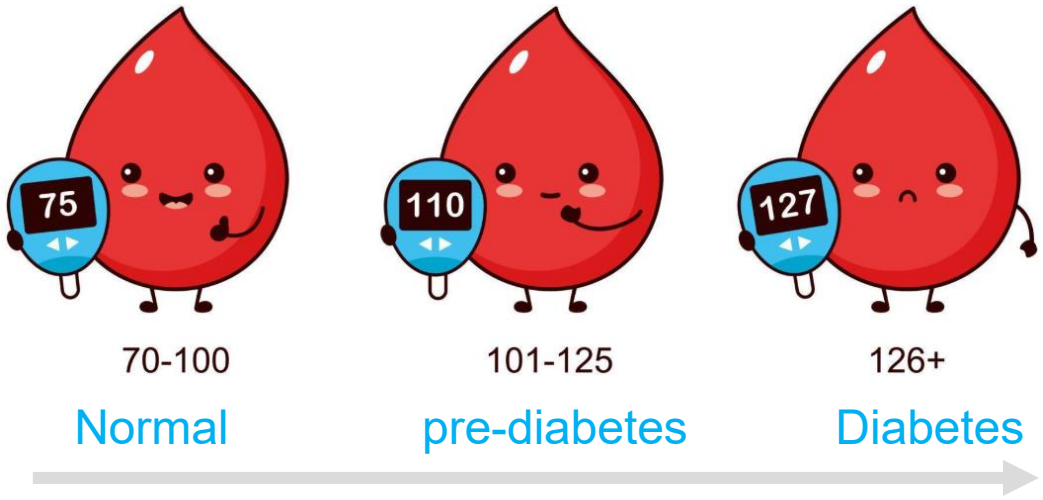

Figure 1. Diabetic progression trajectory.

American Diabetes Association Professional Practice, Committee, *Diabetes Care* 2024

- Type 2 diabetes (T2D) is a chronic progressive metabolic disorder characterized by impaired insulin secretion. The disease typically progresses through distinct stages: normal glucose tolerance→prediabetes(preT2D)→T2D.

- While research on diabetes has significantly advanced our understanding of the disease, the specific mechanisms driving preT2D progression remain poorly understood.

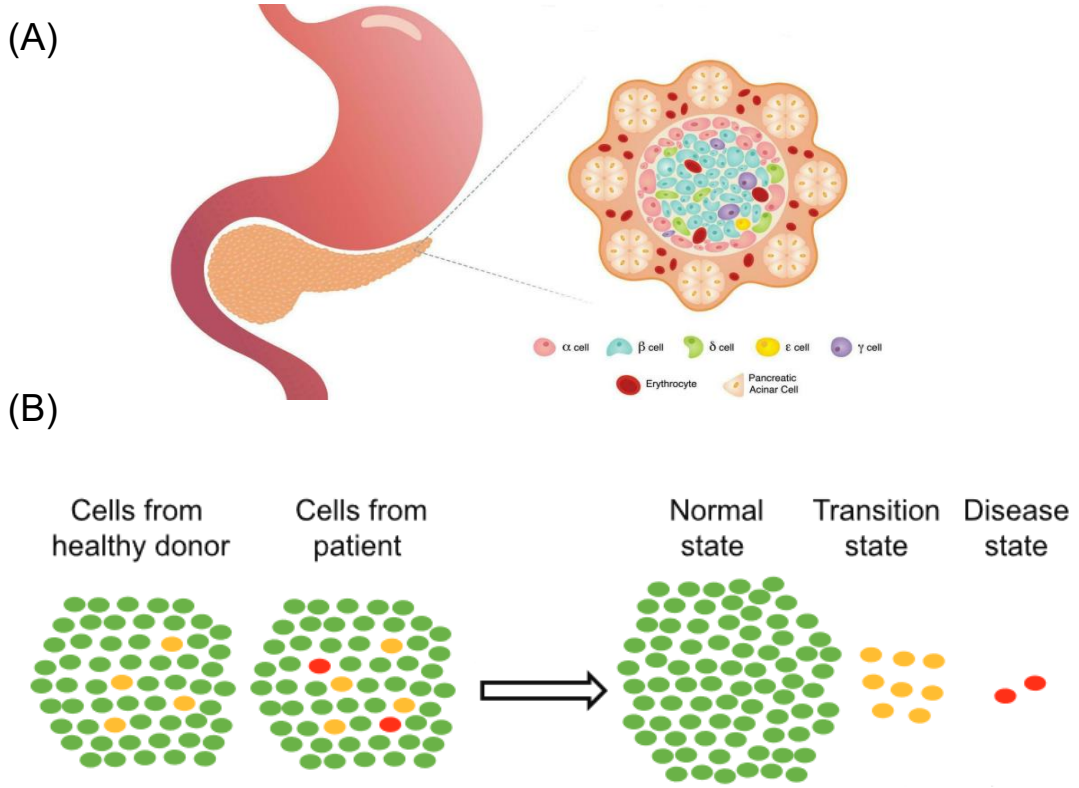

Figure 2. Cellular heterogeneity of the human pancreas.

Li et al., *Cell reports* 2019

- Pancreatic cells may exhibit a co-existence of ‘healthy’ and ‘diseased’ populations. However, the dynamic changes of this risk-associated heterogeneity during disease progression remain unclear.

Overview of scRiskCell

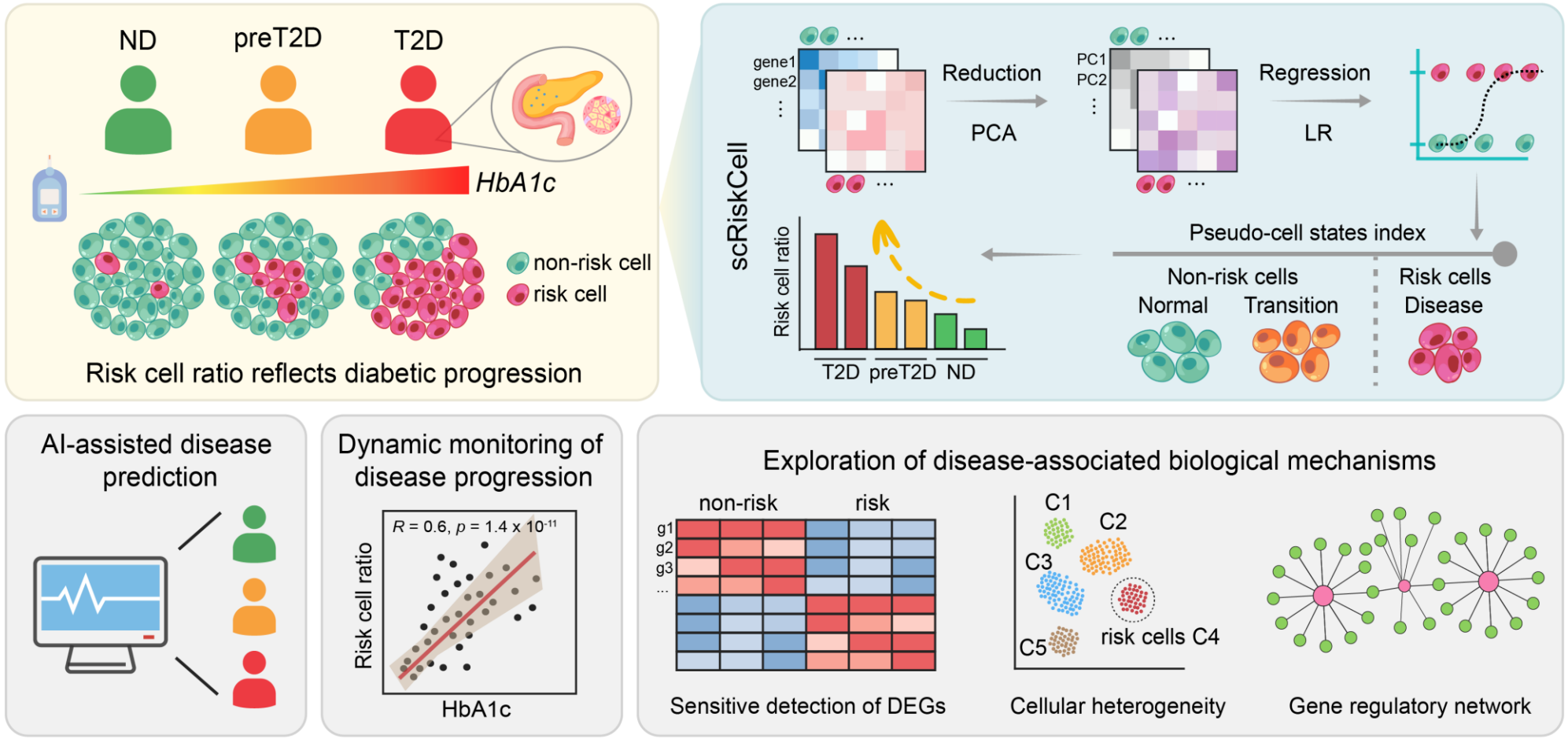

Figure 3. Overview of the scRiskCell for identifying risk cells by integrating islet single-cell profiles across the normal-prediabetes-diabetes continuum.

Islet cell atlas reveals key dynamics of T2D progression

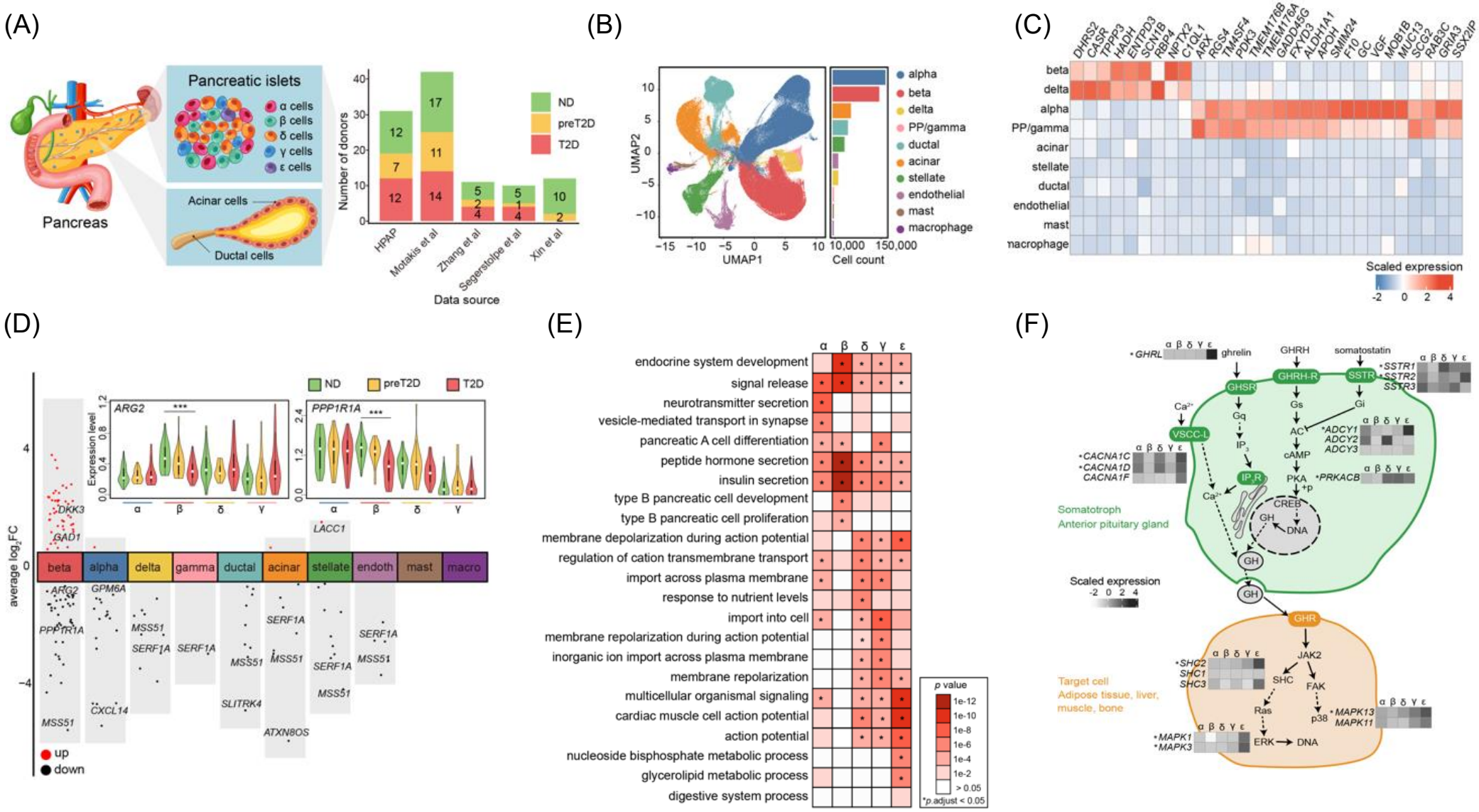

Figure 4. Meta-analysis of human islet data across the normoglycemia-prediabetes-diabetes continuum.

scRiskCell reveals cell-type-specific risk profiles

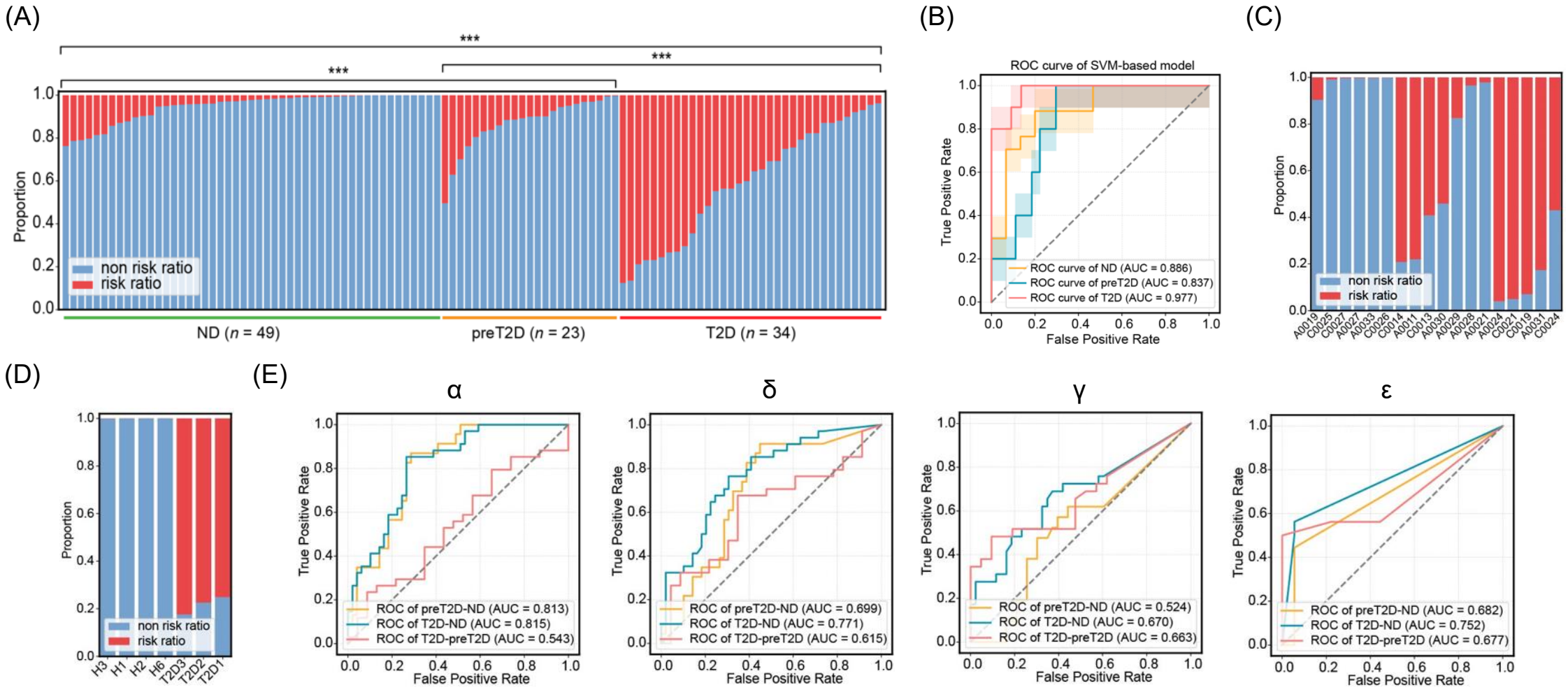

Figure 5. Cross-cohort validation of scRiskCell for precise identification of cell-type-specific risk cells.

Risk β cell proportion reflects key clinical parameters

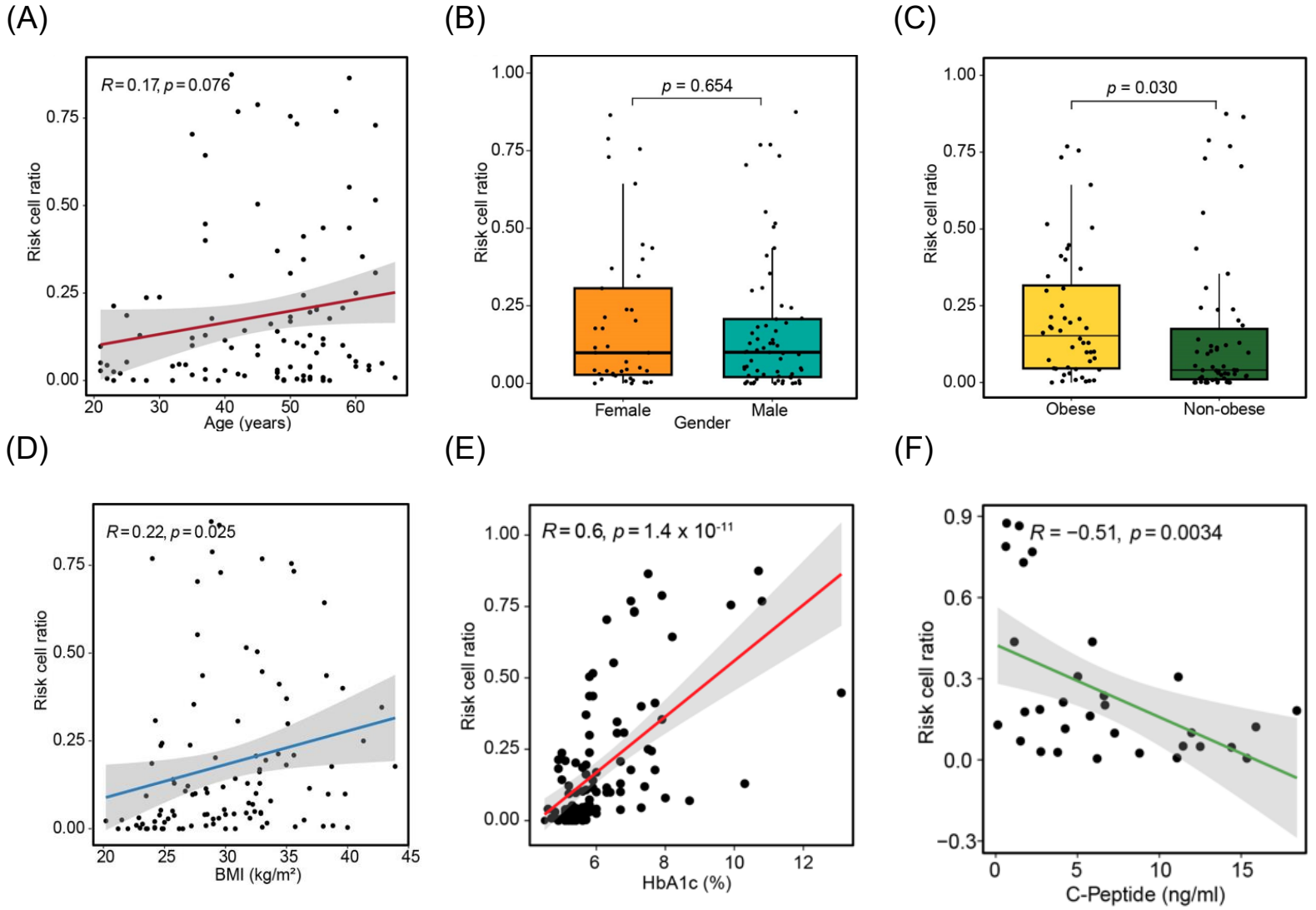

Figure 6. Risk β cell dynamics predict progressive glycemic deterioration and β cell dysfunction during diabetes progression.

Risk β cells exhibit T2D-associated molecular signatures

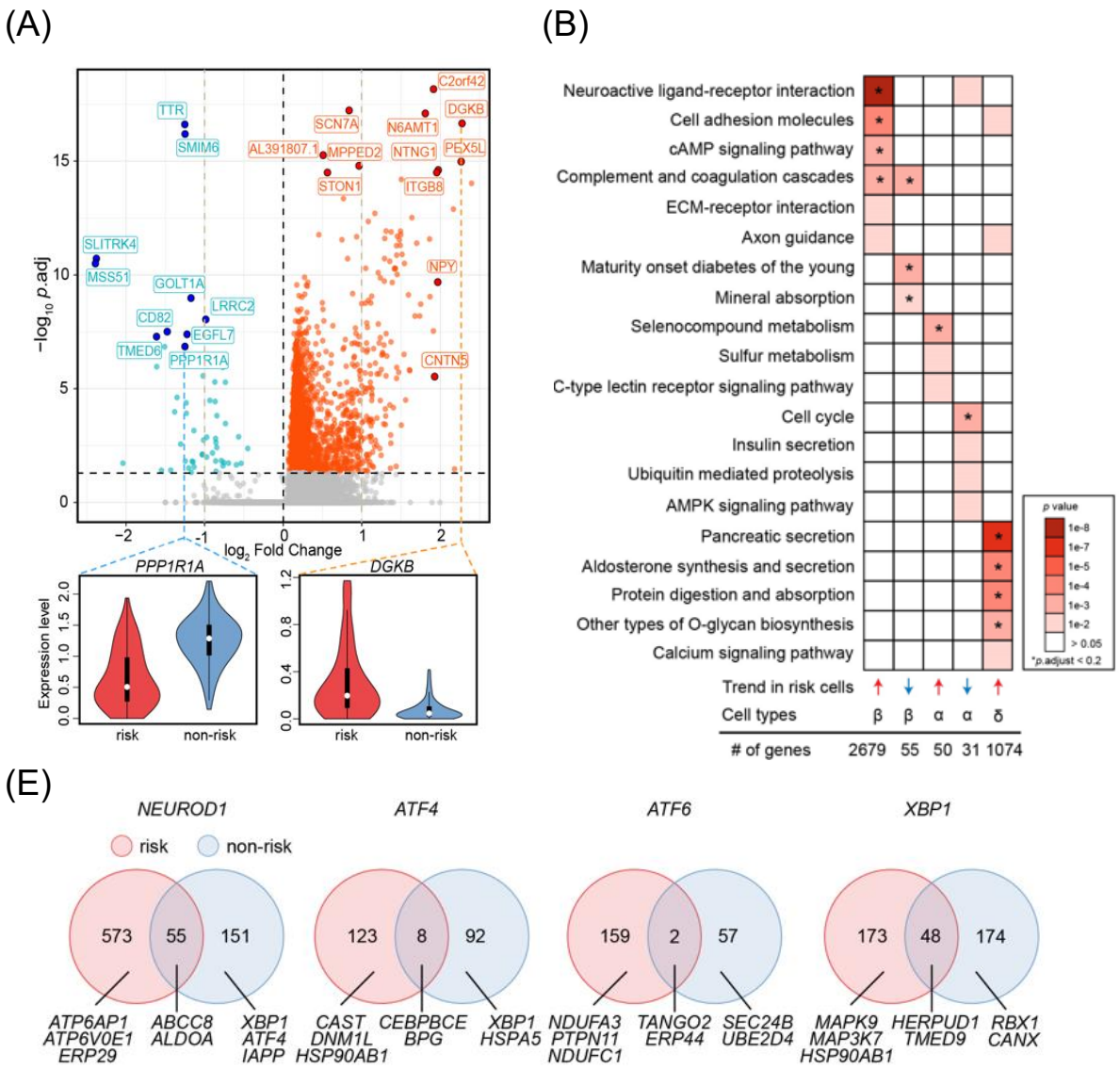

Figure 7. Risk β cells reveal disease-associated molecular signatures and gene regulatory networks.

Dynamic clustering of risk β cells during T2D progression

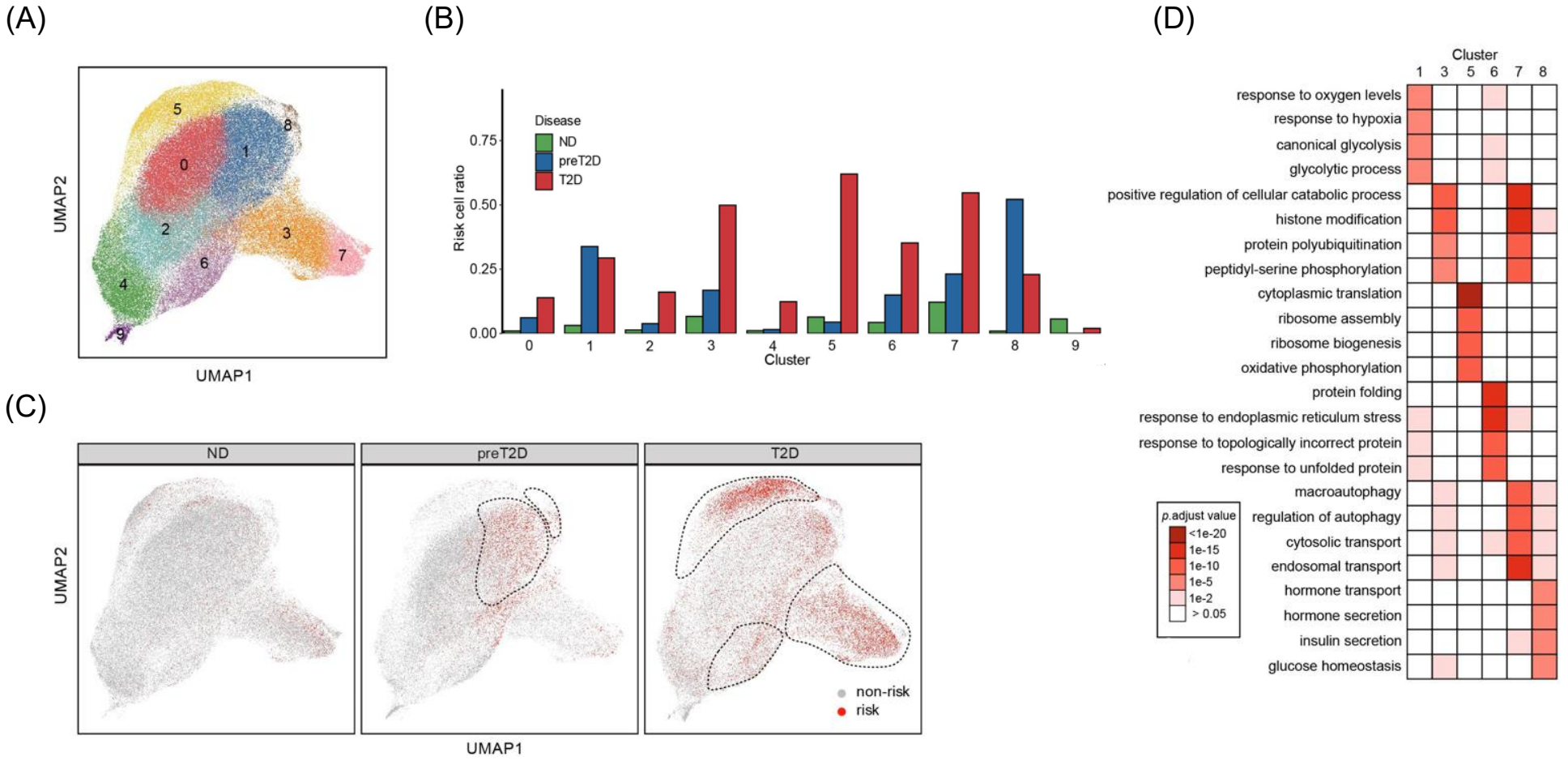

Figure 8. Dynamic clustering patterns of risk β cell subtypes during T2D progression.

Summary

- We developed scRiskCell, an interpretable computational framework that identifies cell-type-specific risk cells using large-scale human islet single-cell expression profiles;
- Risk cell signatures delineate T2D progression trajectories, with its changes strongly correlating to individual glycemic fluctuations and islet β cell dysfunction;
- scRiskCell generalizes well across independent cohorts, detecting rare risk cells including low-abundance ε-cells;
- scRiskCell deciphers the regulatory mechanisms and dynamics of islet dysfunction during diabetogenesis, offering new insights for early detection of T2D.

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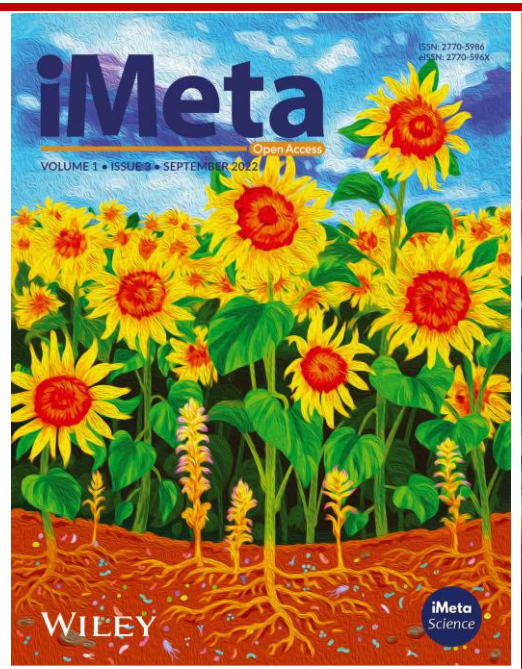

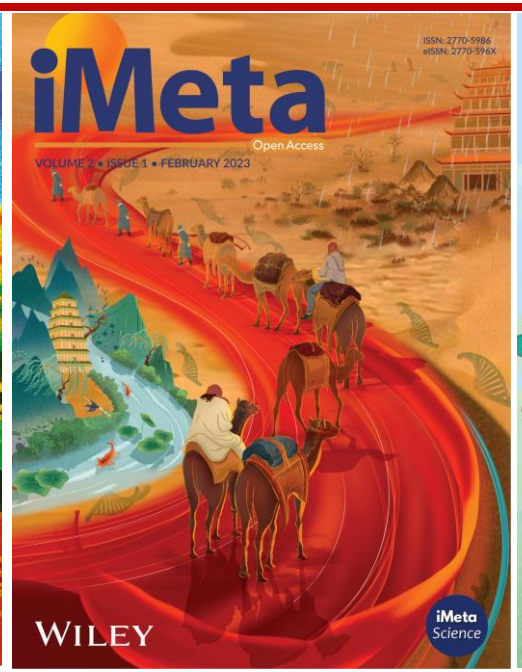

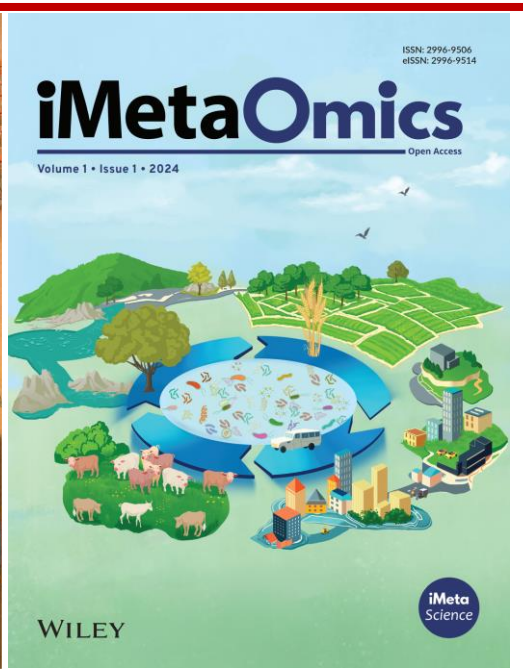

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