Cite this as: Jing GUO, Jihong ZHENG, Ruixia LI, Jindong YAO, He ZHANG, Xu WANG, Chao ZHANG, 2025. Single-cell transcriptome analysis reveals abnormal angiogenesis and placentation by loss of imprinted glutaminyl-peptide cyclotransferase. *J Zhejiang Univ-Sci B (Biomed & Biotechnol)*, 26(6):589-608
https://doi.org/10.1631/jzus.B2400099

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Single-cell transcriptome analysis reveals abnormal angiogenesis and placentation by loss of imprinted glutaminyl-peptide cyclotransferase

Key words: *Qpct*$^{-/-}$ mice; Placenta; Single cell sequencing; Overgrowth; Angiogenesis

Introduction: *Qpct* and Placental Development

Imprinted Genes: ~200 identified in mice; key for feto-placental growth (*H19, Igf2*).

Placental Angiogenesis: Essential for feto-maternal interaction (*Ccl3, Egr1*).

***Qpct* Gene**: Located on chromosome 17; maternally expressed; involved in early embryonic development.

Single-Cell Technologies:
• scRNA-seq: Identifies cell subtypes and explores tissue heterogeneity.
• snRNA-seq: Effective for tissues hard to dissociate into single cells, overcomes limitations of scRNA-seq.

Objective: Investigate the impact of *Qpct* deletion on placental angiogenesis by generating *Qpct* knockout mice, and using immunohistochemistry and single-cell sequencing to examine changes in the placenta and embryo.

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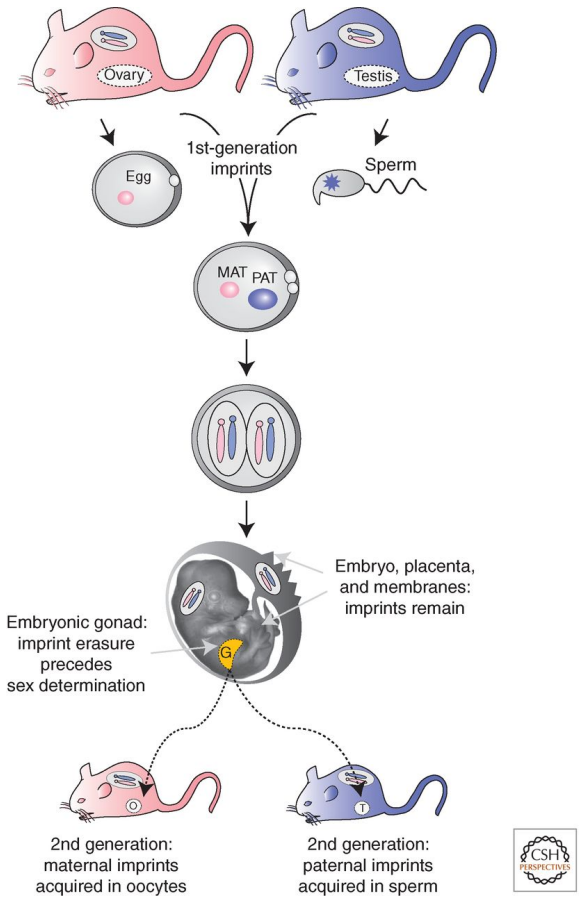
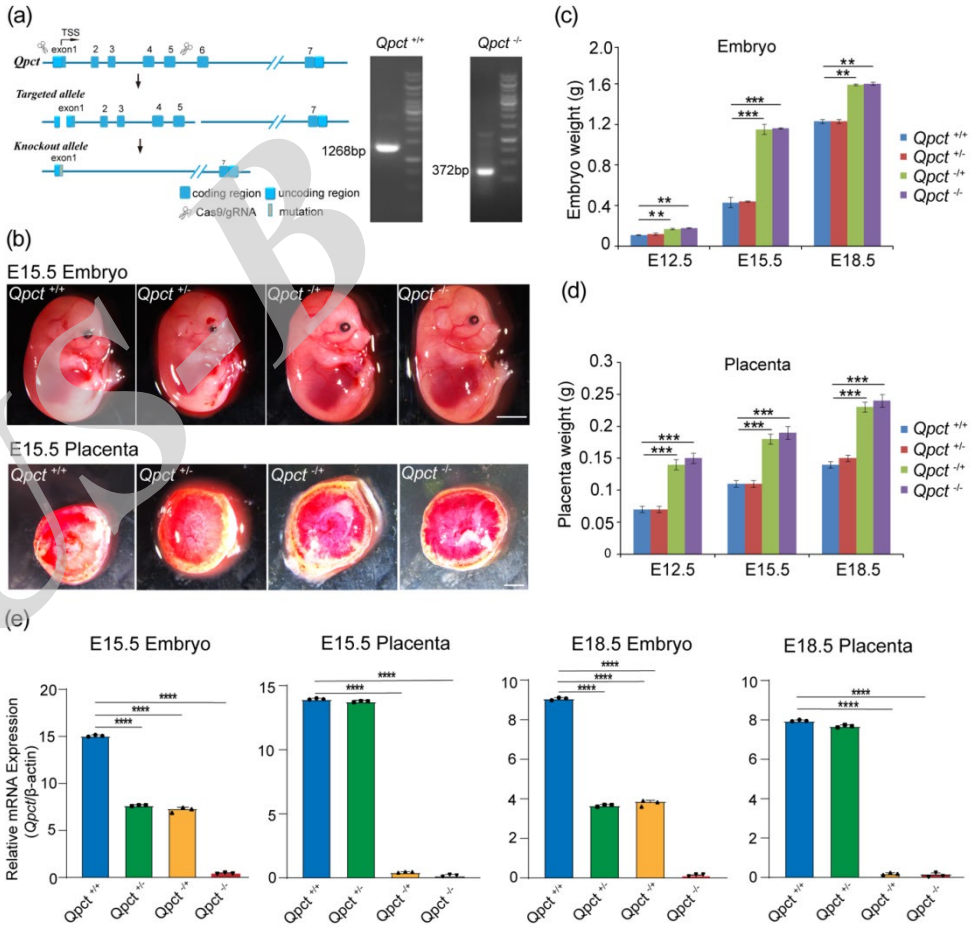


Barlow DP, Bartolomei MS. Genomic imprinting in mammals, 2014, Cold Spring Harb Perspect Biol.

Result: Embryonic and placental overgrowth in *Qpct*-knockout conceptuses

(a) *Qpct* knockout mice were successfully generated.
(b) Embryo and placenta sizes significantly increased in *Qpct*$^{-/+}$ and *Qpct*$^{-/-}$ mice at E15.5.
(c, d) Embryo and placental weights were higher in *Qpct*$^{-/+}$ and *Qpct*$^{-/-}$ mice at E12.5, E15.5 and E18.5.
(e) *Qpct* expression was reduced or absent in *Qpct* knockout embryos and placentas.



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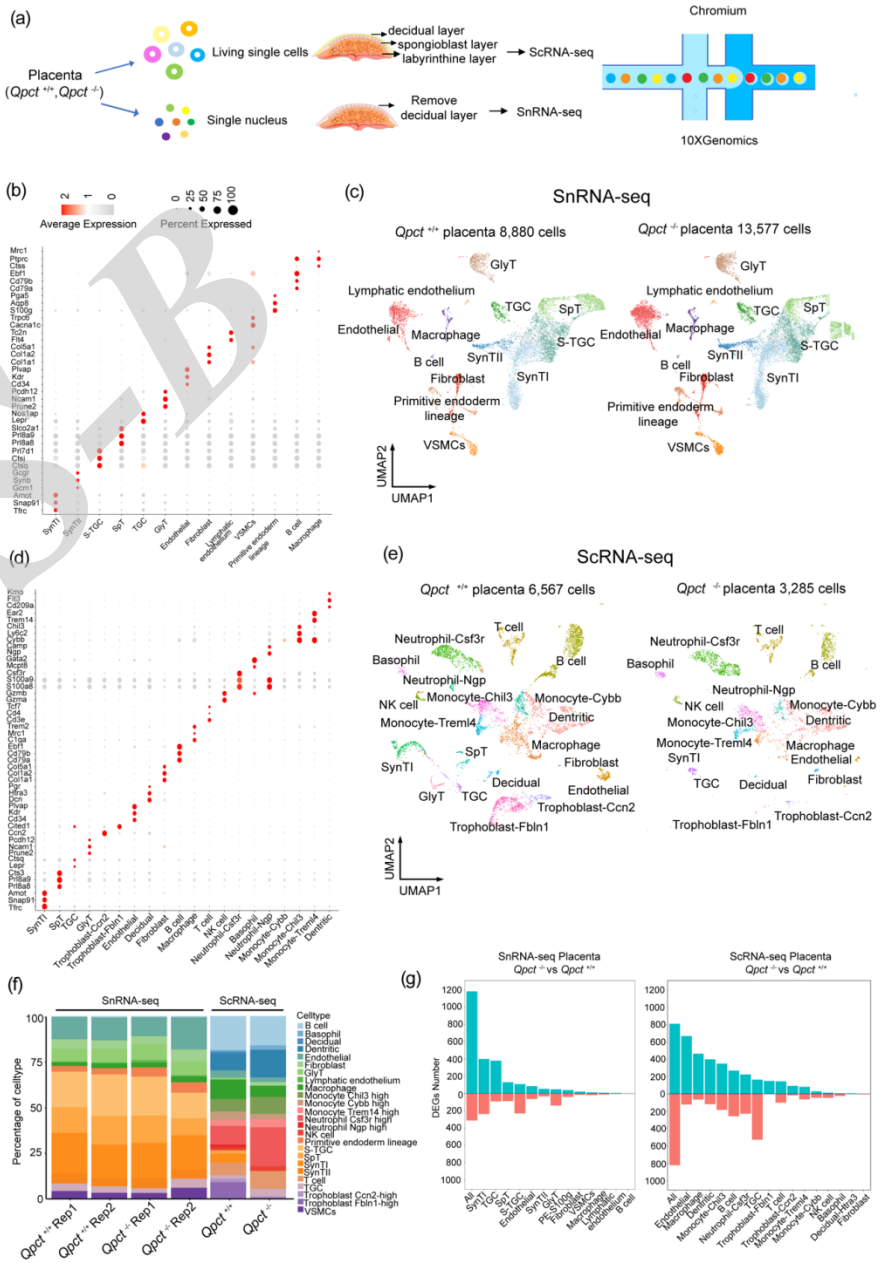
Result: Single-cell analysis revealed transcriptional and cell-type differences between *Qpct*$^{+/+}$ and *Qpct*$^{-/-}$ placentae

(a) Experimental design showing scRNA-seq and snRNA-seq approaches to analyze placental cells in *Qpct*$^{+/+}$ and *Qpct*$^{-/-}$ mice.
(b-f) scRNA-seq revealed decreased trophoblast and SynT cells and increased immune cells in *Qpct*$^{-/-}$ placentas, while snRNA-seq showed stable SynT proportions but detected fewer immune cells.
(g) Differential gene expression analysis shows SynT cells have more DEGs in snRNA-seq, while immune cells show more DEGs in scRNA-seq in *Qpct*$^{-/-}$ placentas.



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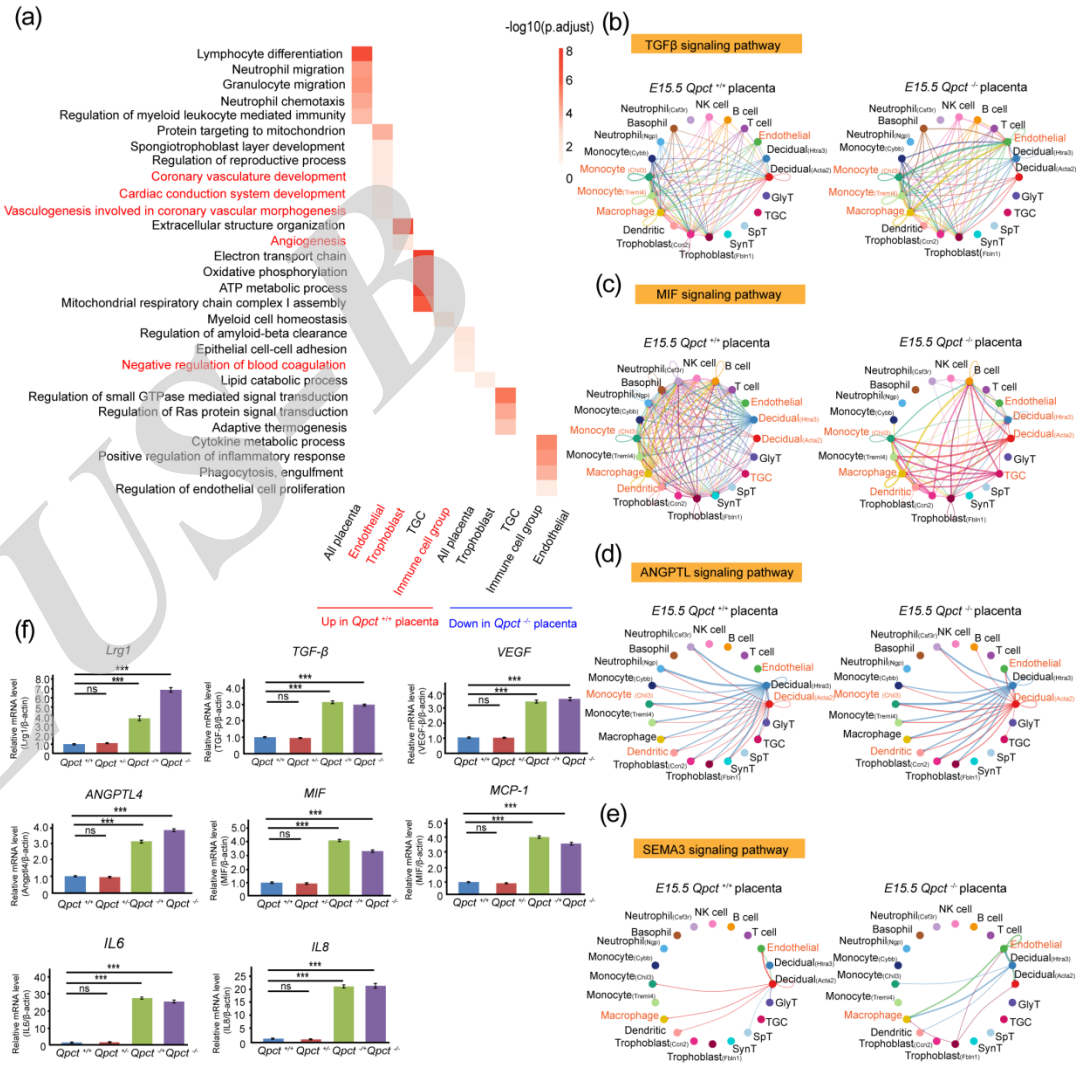
Result: Cell type-specific cell communication increased in promoting the angiogenesis signaling pathway in E15.5 mouse *Qpct*$^{-/-}$ placentae

(a) Upregulated genes in *Qpct*$^{-/-}$ placentae relate to angiogenesis and mitochondrial function.
(b) Enhanced TGF-β signaling in endothelial-immune cells.
(c) MIF signaling boosts trophoblast-immune cell interaction.
(d) ANGPTL signaling between endothelial and decidual cells.
(e) SEMA3 signaling increases endothelial and macrophage communication.
(f) Upregulated promoted angiogenesis genes in placentae of four genotypes at E15.5.



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Summary

***Qpct* Knockout Enhances Angiogenesis**: Increased angiogenesis-related genes and blood vessel count in *Qpct*$^{-/-}$ placentae.

Immune Cell Increase: Higher immune cell proportions in *Qpct*$^{-/-}$ placentae suggest a role in angiogenesis.

Supports Parental Conflict Hypothesis: *Qpct*$^{-/-}$ embryos and placentae show increased growth, consistent with the hypothesis.

Angiogenesis Pathways Activated: Upregulation of key angiogenic pathway in *Qpct*$^{-/-}$ placentae.

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