Targeting Recipient-derived macrophage Xbp-1 protects early kidney allotransplant function by promoting renal cell regeneration through the downregulation of Klf4.

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Introduction
The IRE1α/XBP1 pathway is part of the unfolded protein response (UPR), a cellular stress response related to the endoplasmic reticulum (ER). The UPR is activated in response to an accumulation of unfolded or misfolded proteins in the ER. IRE1α/XBP1 pathway has been shown to play a role in developing various diseases, including kidney disease, and has been reported to regulate inflammatory responses in macrophages. However, the role of IRE1α/Xbp1 in macrophage in kidney transplantation has not been researched. This study aims to find the role of macrophage-derived IRE1α/Xbp-1 ER stress pathway in tubular epithelial cell regeneration after kidney transplantation.

Methods
The impact of transplant ischemia-reperfusion injury (IRI) on the ER stress response was examined. We used conditional Knockout mice lacking Xbp-1 in myeloid cells to investigate macrophage Xbp-1’s role in modulating kidney graft epithelial cell regeneration in kidney transplantation and epithelial IRI models. A clinically relevant mouse kidney transplantation model was used in this research, and a new epithelial cell cold ischemic-reperfusion injury model was established.

Results
Figure 2| Conditional Knockout of Xbp1 in Myeloid cells helps recovery of graft function at the early stage after kidney transplantation. a, Generation of the conditional Knockout mice lacking Xbp-1. b, Upregulation of Xbp-1 upstream genes and Downregulation of both types of Xbp-1 after kidney transplantation in the Xbp1 KO group. c, Downregulation of kidney injury biomarkers in the Xbp1 KO group. d, Better graft function in the Xbp1 KO group 24 Hours and 3 Days post-transplantation. e, HE staining of WT and Xbp1 showing worse kidney injury in WT mice 24 hours post-transplantation. f, Kidney regeneration marker MCM2 staining.

Figure 3| Kidney regeneration panel after transplantation. a, Kidney regeneration panel in WT at early stage after transplantation. b, Kidney regeneration panel in WT and Xbp1 KO mice 24 hours post transplantation.

Conclusion
Recipient-derived macrophage Xbp-1 protects early kidney allotransplant function by the downregulation of Klf4 to promote renal epithelial cell regeneration. Donor-derived macrophage IRE1α-XBP1 pathway can be explored as a potential future therapeutic target against IRI of graft.