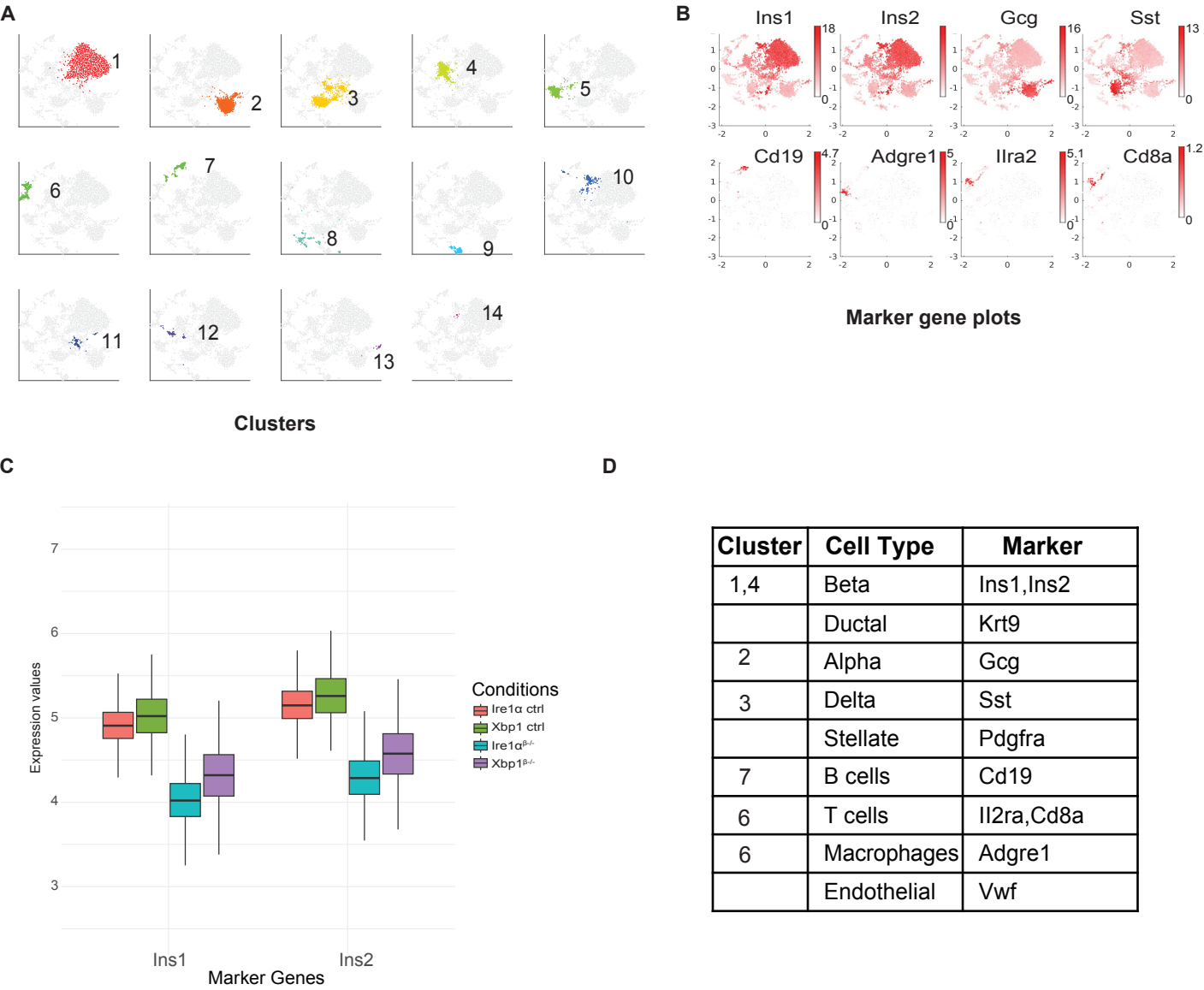


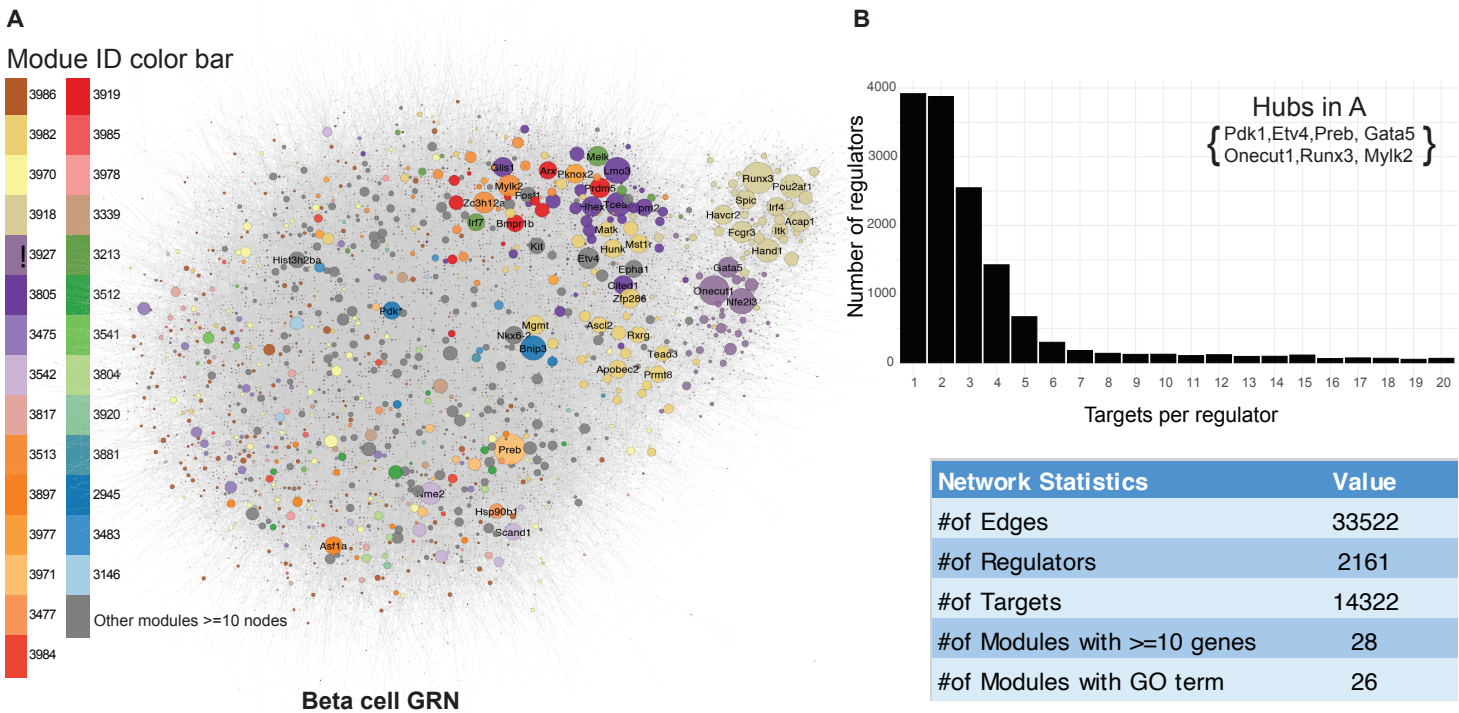
Supplementary Figures

Supplementary Figure 1.



Supplementary Figure. 1. Cell Type Annotation of scVI Clusters Using Marker Gene Expression. **A** Individual visualization of scVI clusters using scVI low-dimensional embedding. **B** Expression of marker genes. **C** Expression of *Ins1* and *Ins2* in β -cells per condition. **D** Table showing cell type annotation of the clusters based on the marker genes. Expression values are zero-mean normalized across all cells.

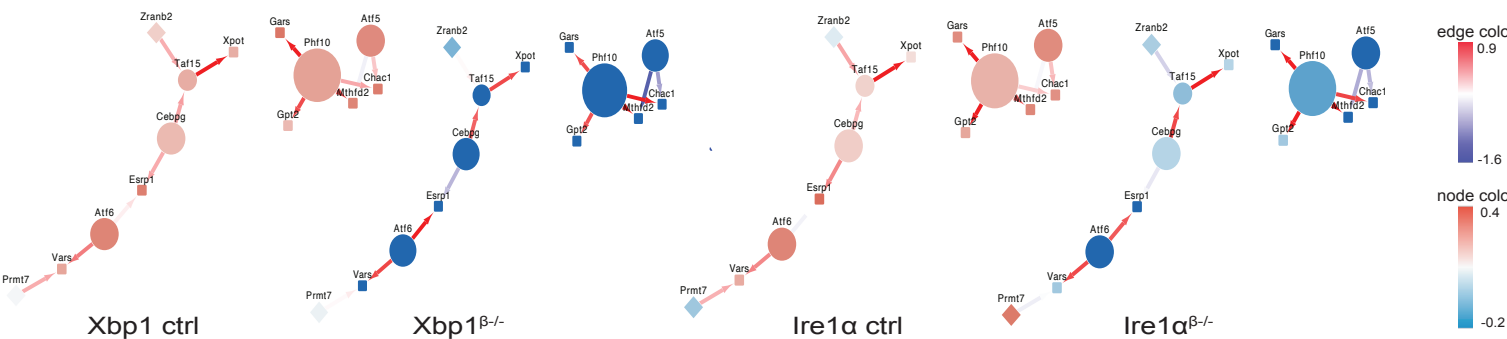
Supplementary Figure 2.



Supplementary Figure 3.

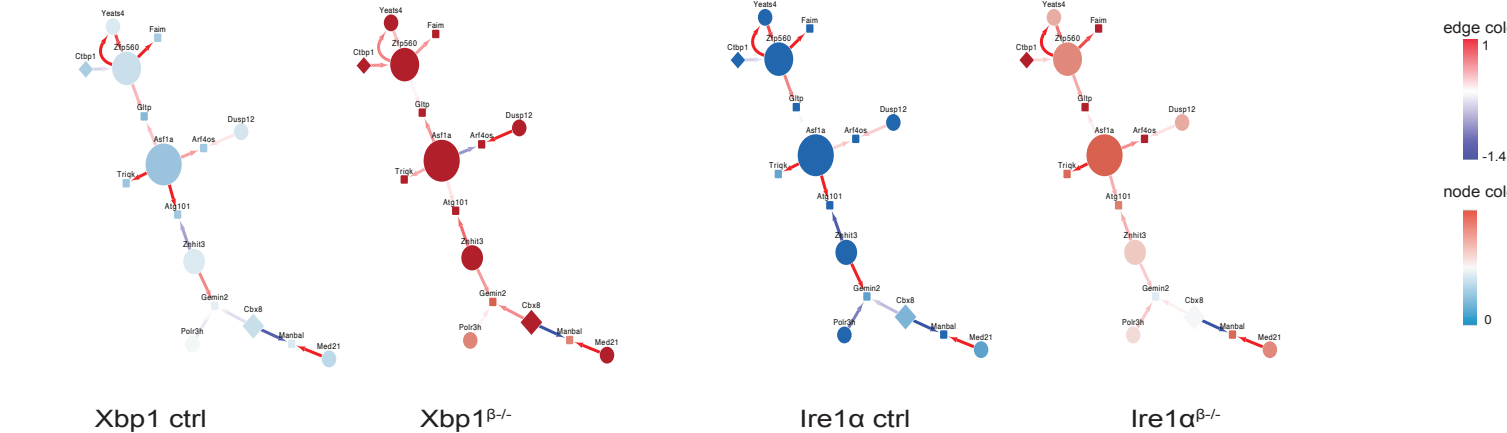
A

Shared Down pattern module 3339



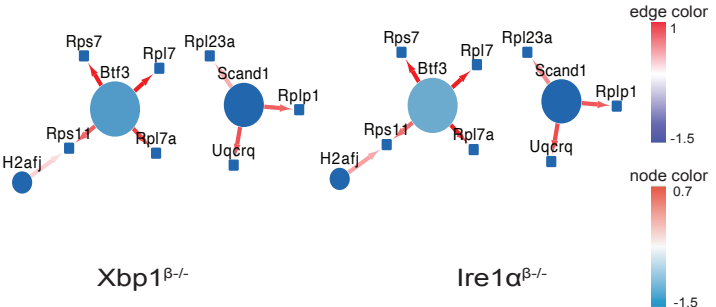
B

Shared Up pattern module 3897



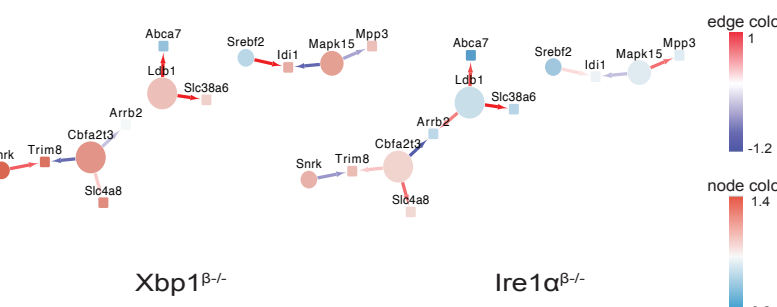
C

Xbp1^{β-/-} Up pattern module 3542



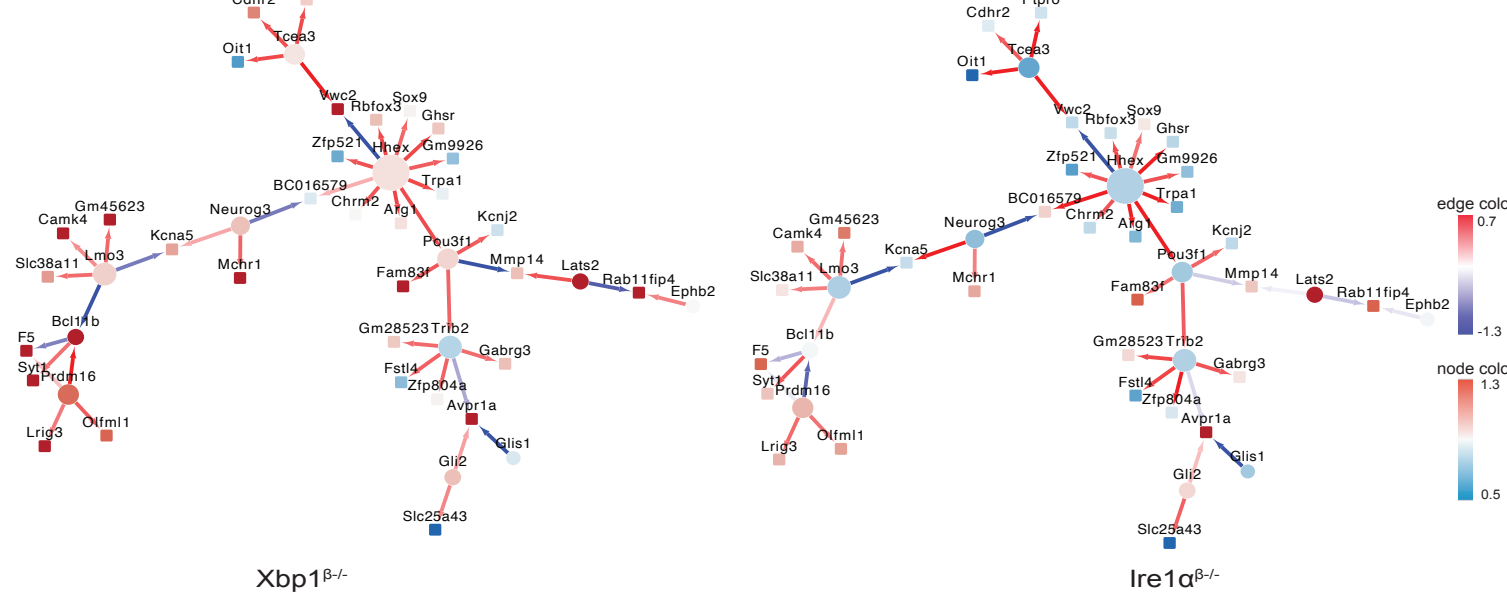
D

Xbp1^{β-/-} Up pattern module 3970



E

Xbp1^{β-/-} Up pattern module 3805

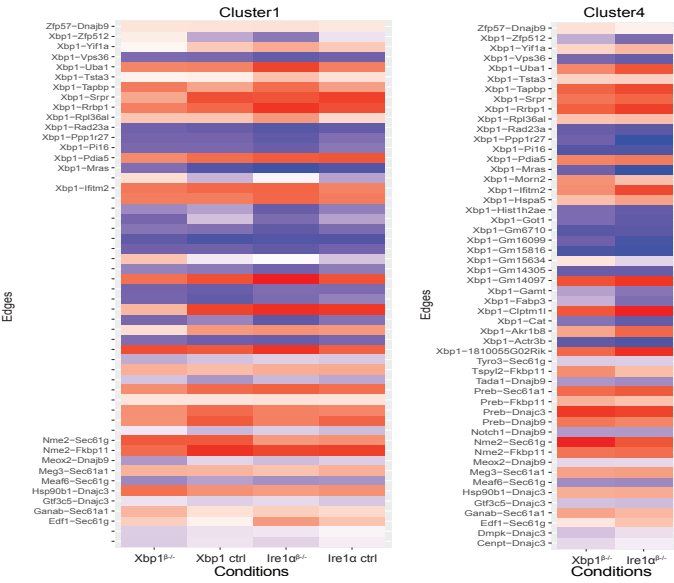


Supplementary Figure 3. Network wiring of regulatory connections inferred using MERLIN, for selected modules from each module patterns. A Shared-Down pattern module 3339, **B** Shared-Up pattern module 3897, **C** Xbp1^{β-/-} Up pattern module 3542, **D** Xbp1^{β-/-} Up pattern module 3970, **E** Xbp1^{β-/-} Up pattern module 3970. The edge color corresponds to z-score-normalized regression coefficient between the regulator and target connected by the edge (color scale set to 10th (blue) to 90th (red) percentile) estimated using the data from the specific genotype. Node color corresponds to the mean of zero-mean.

Supplementary Figure 4.

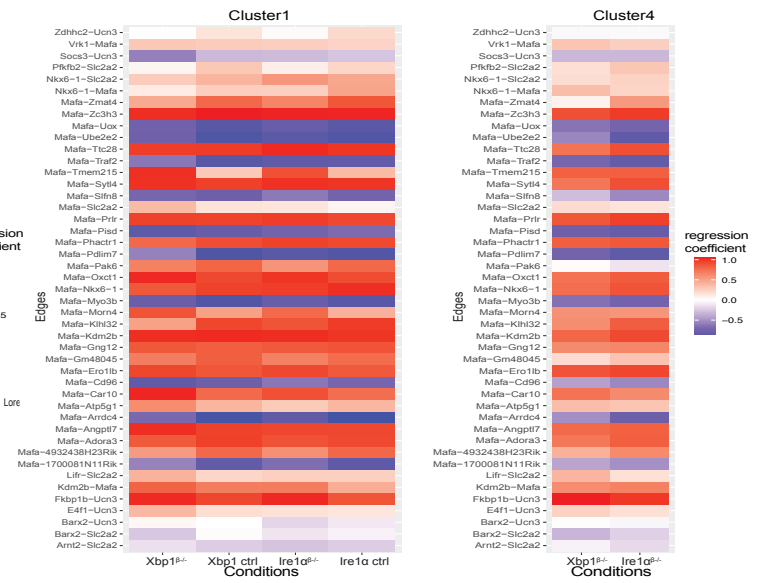
A

Edges with Xbp1 target genes



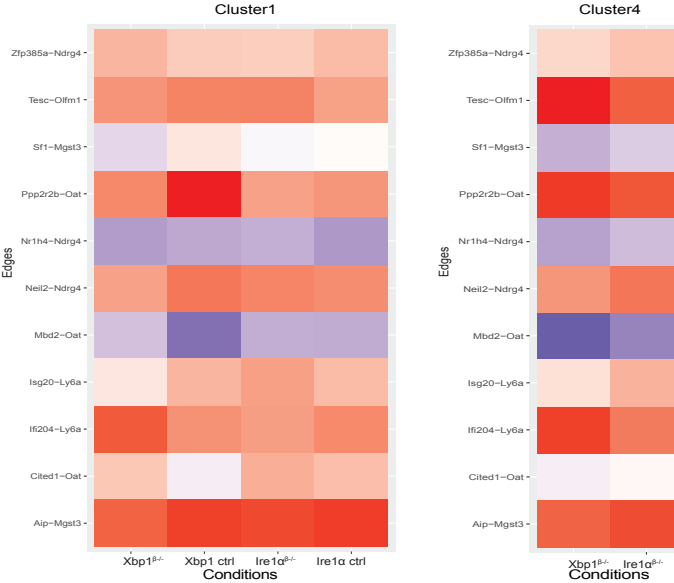
B

Edges with β -cell marker genes



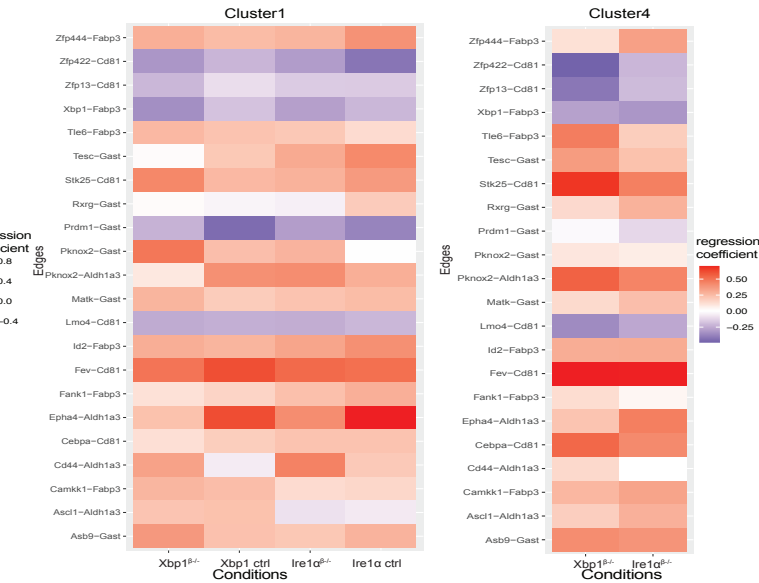
C

Edges with Disallowed genes



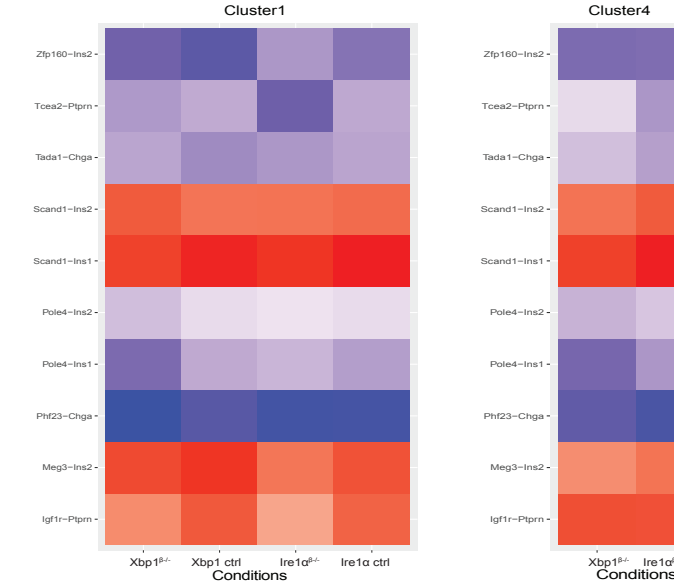
D

Edges with Dedifferentiation genes



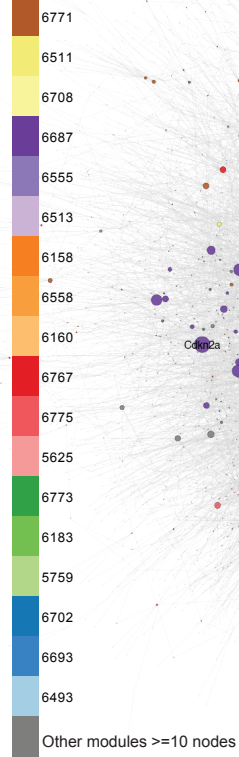
E

Edges with Autoantigen genes



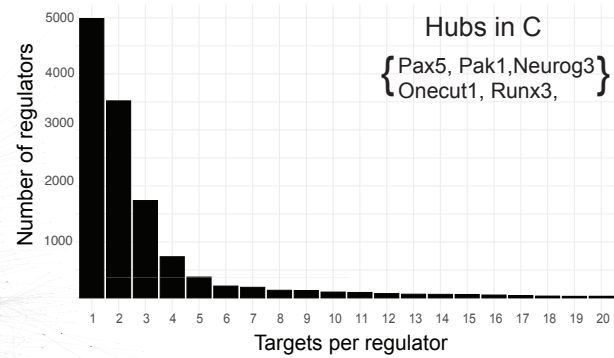
Supplementary Figure 4. Heatmaps showing regression coefficients in both β -cell cluster1 and cluster4 for edges involving genes (either as regulator or target) from Figure 3. A Xbp1 target genes, B β -cell marker genes, C disallowed genes, D dedifferentiation genes, E autoantigen genes panels.

A



Alpha cell GRN

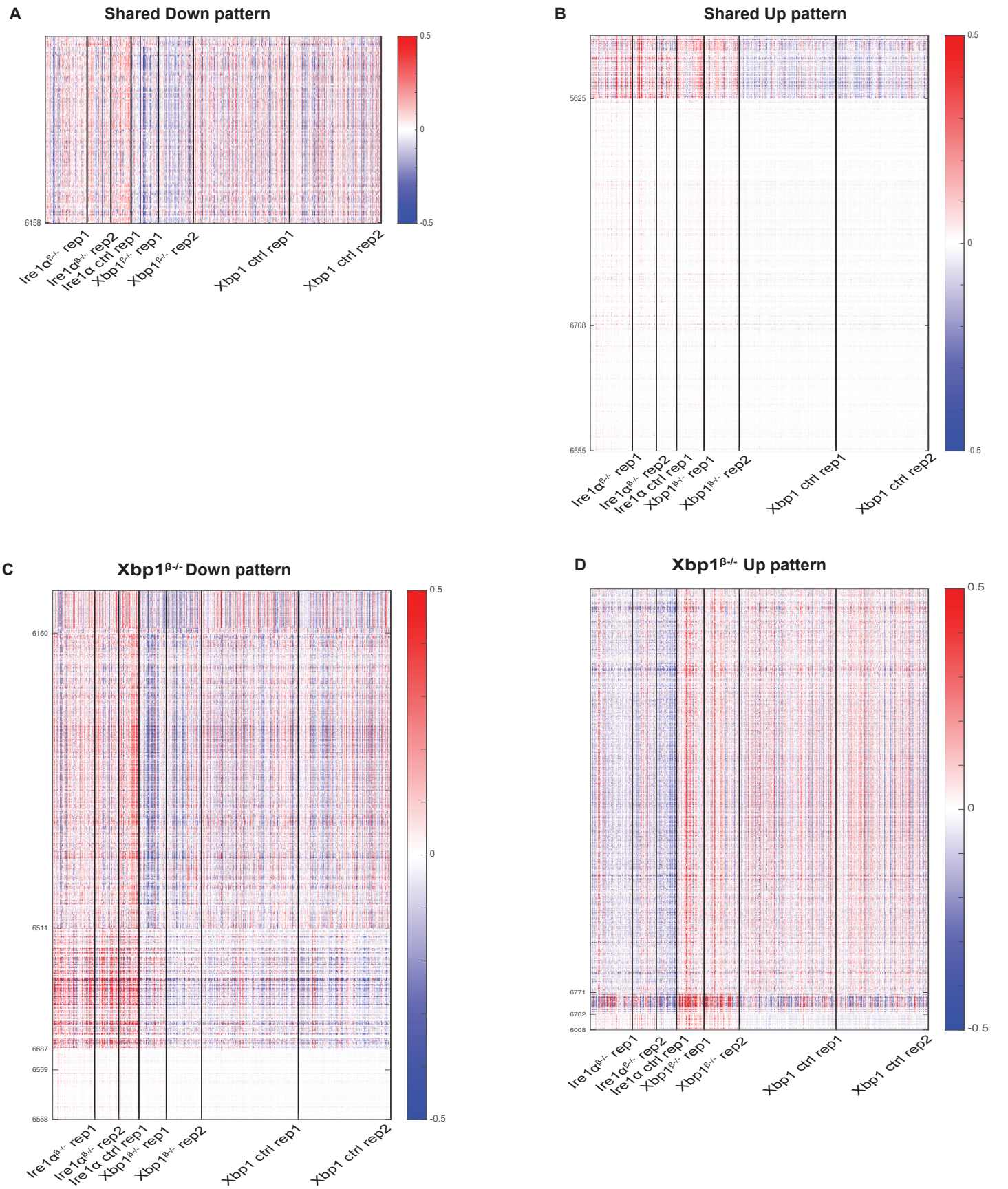
B



Network Statistics	Value
#of Edges	22922
#of Regulators	2136
#of Targets	12302
#of Modules with ≥ 10 genes	18
#of Modules with GO term	16

Supplementary Figure 5. Global Architecture of the Gene Regulatory Network (GRN) in α -Cells. **A** GRN for α -cells with 90% confidence. Nodes are colored by modules. Only modules with ≥ 10 genes are shown. Node size corresponds to outdegree. **B** Top panel: bar graph showing frequency of regulator with different number of total targets within GRN shown in **(A)**. Regulators with the greatest number of edges mentioned in bar graph. Bottom panel: Table showing the statistics associated with GRN in **(A)**.

Supplementary Figure 6.



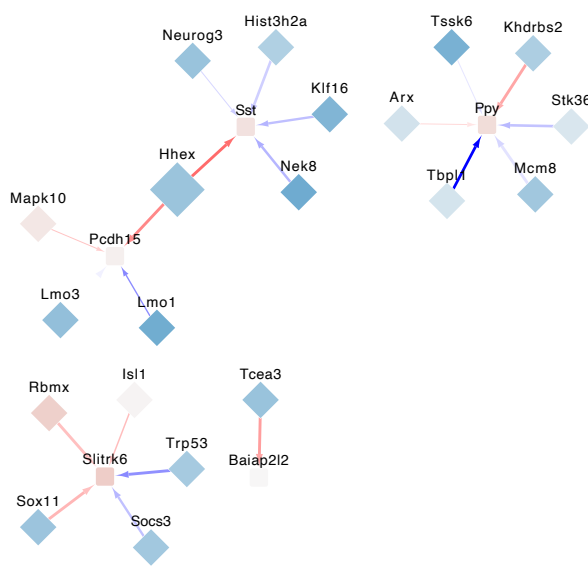
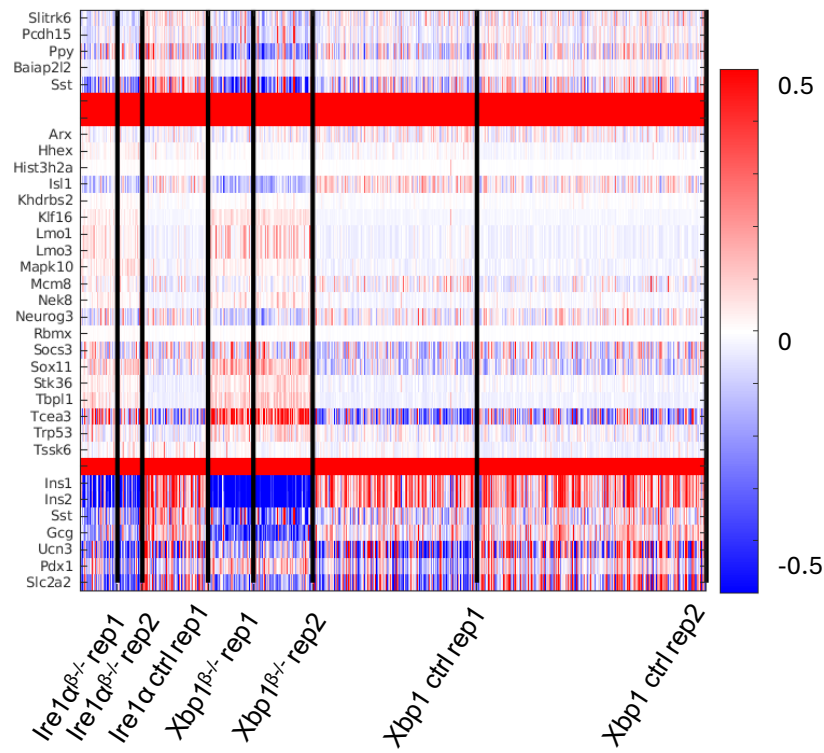
Supplementary Figure 6. MERLIN module analysis of α -cells. Heatmaps of modules with the **A** Shared-Up, **B** Shared-Down, **C** Xbp1 ^{β -/-} Up and **D** Xbp1 ^{β -/-} Down patterns. In each module, each row is a separate gene, and each module is separated by a vertical tick. Values are normalized to zero-mean. Each column is a separate cell grouped based on the genotype.

Supplementary Data Set

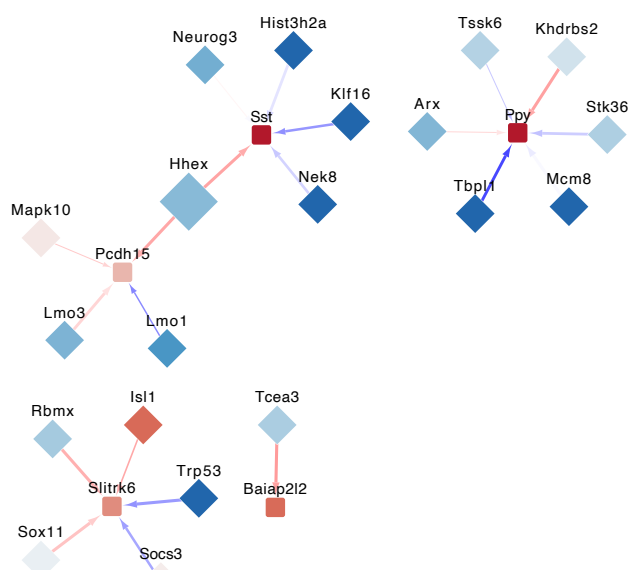
Heatmaps and full gene regulatory networks for selected modules

Full GRNs for selected modules. These networks are not filtered based on the difference between regression weights and edge weights are not z-score converted as in GRNs in **Figure 4** and **Supplementary Figure 3**. These networks contain all edges between module genes and enriched regulators of the modules. Edges between non-enriched regulators and module genes are also shown.

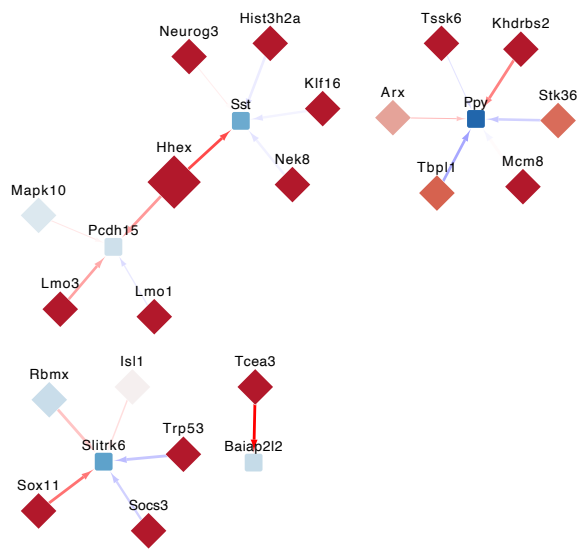
Shared Down: Module 3781



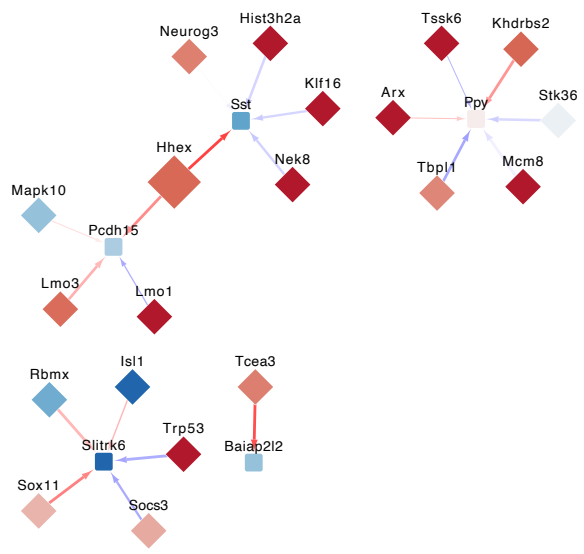
Xbp1ctrl



Ire1a ctrl

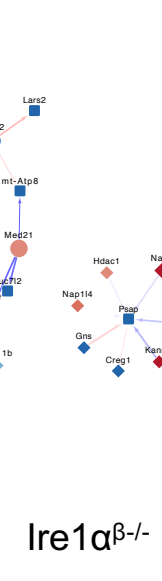
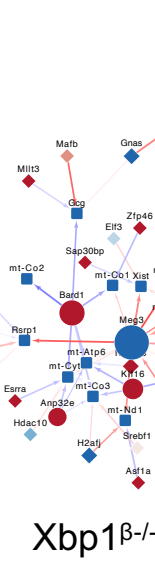
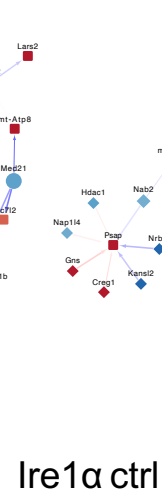
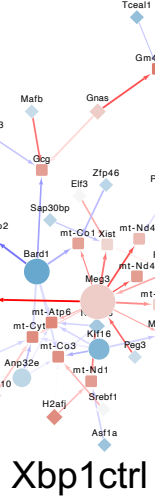
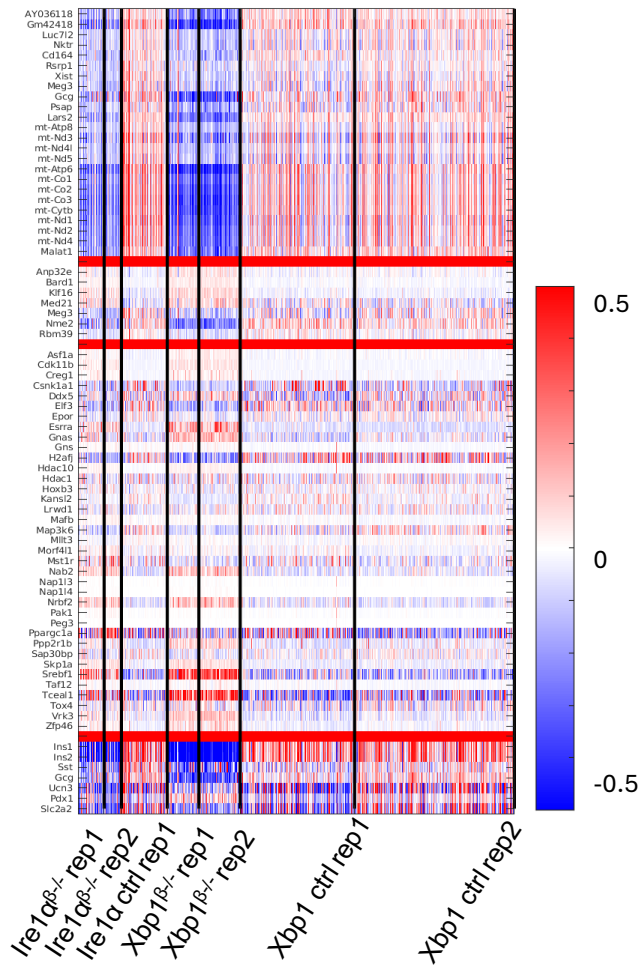


Xbp1 $\beta^{-/-}$



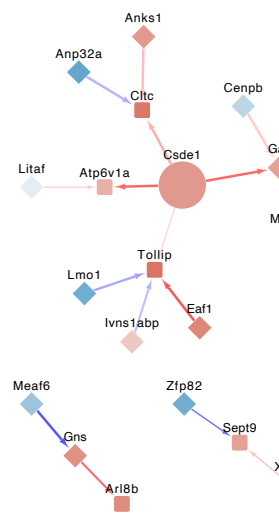
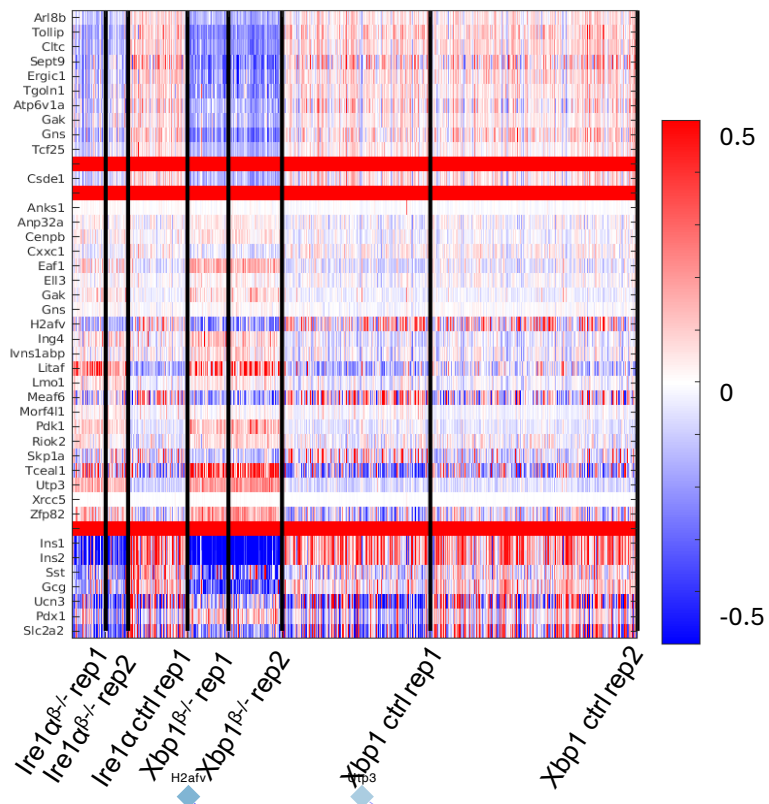
Ire1a $\beta^{-/-}$

Shared Down: Module 3793

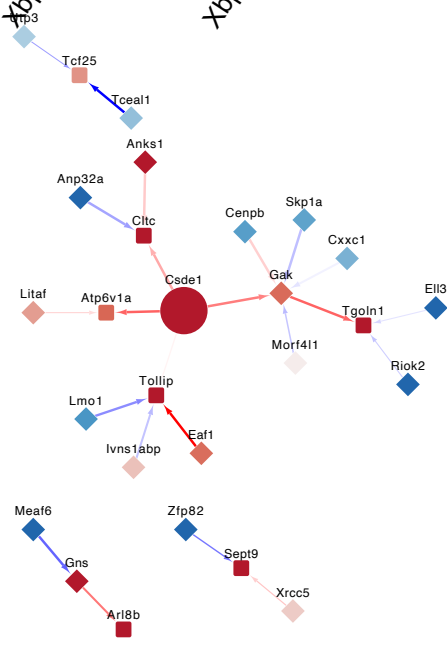


Edge color
Node color

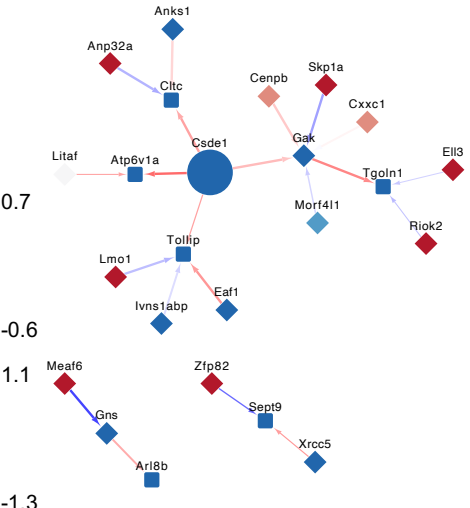
Shared Down: Module 3353



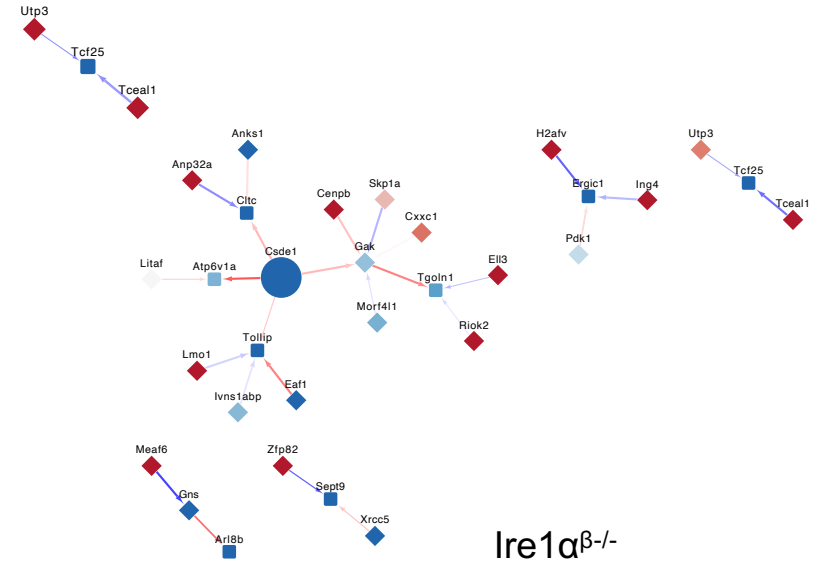
Xbp1ctrl



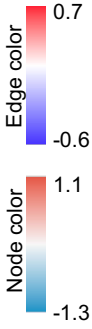
Ire1α ctrl



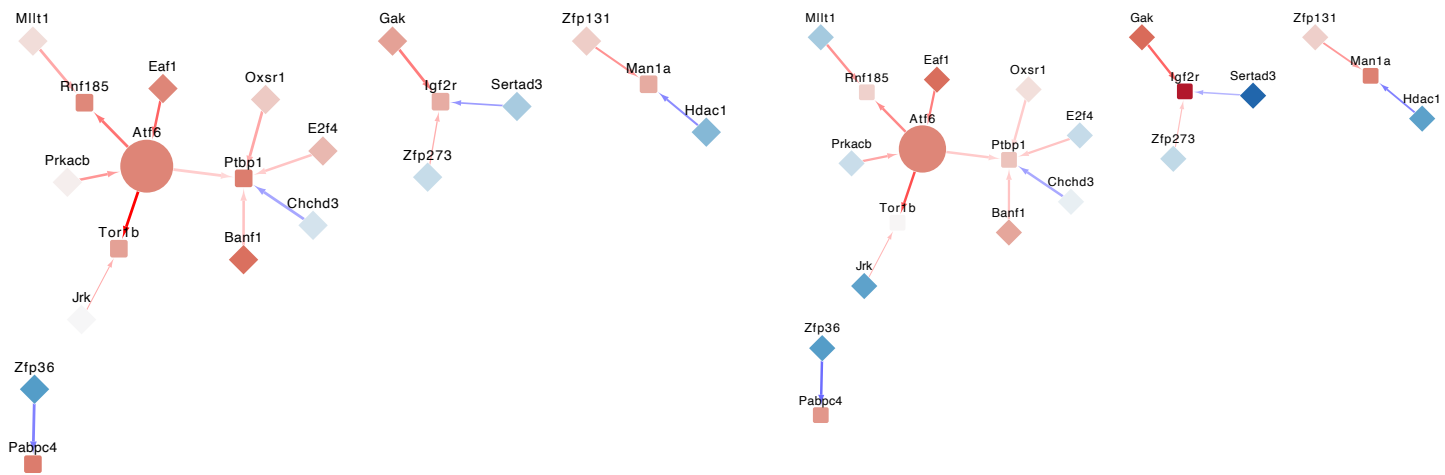
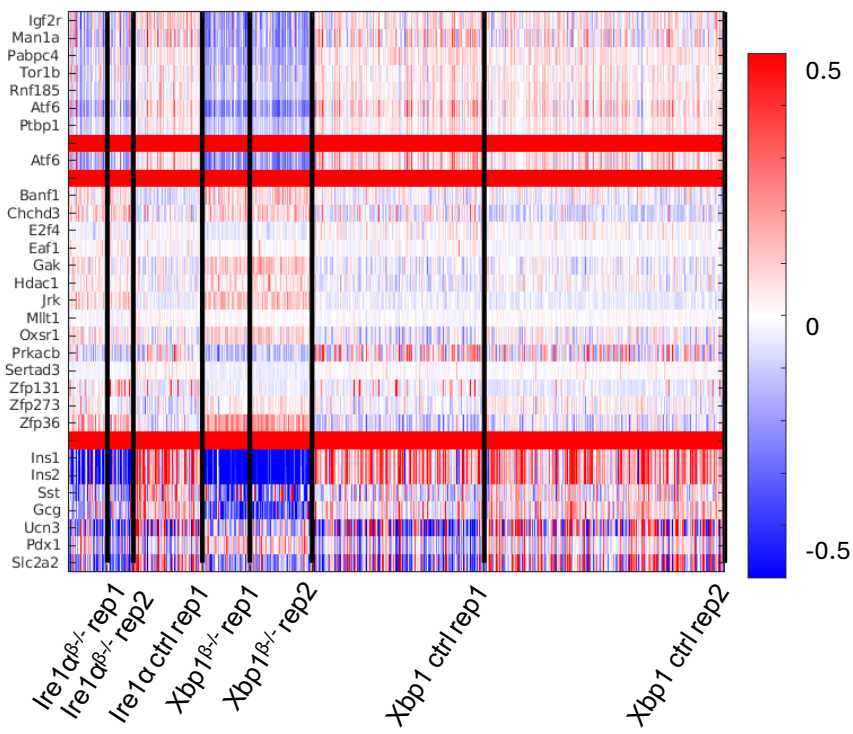
Xbp1β-/-



Ire1αβ-/-

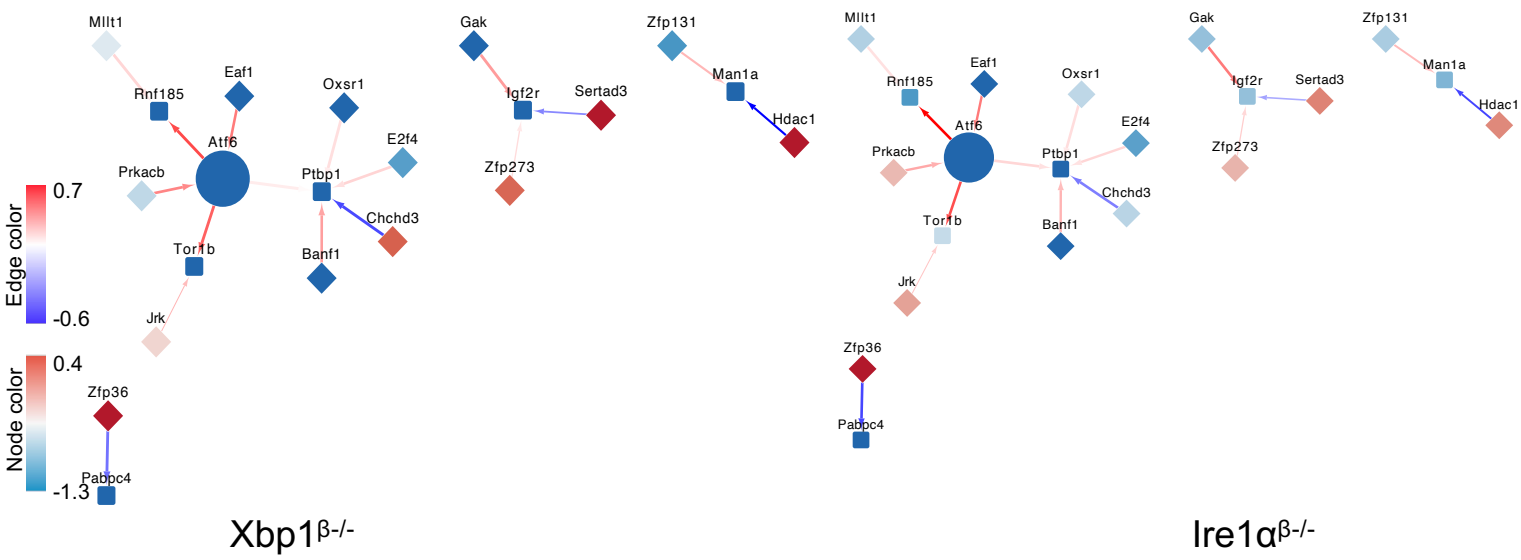


Shared Down Module 3663



Xbp1ctrl

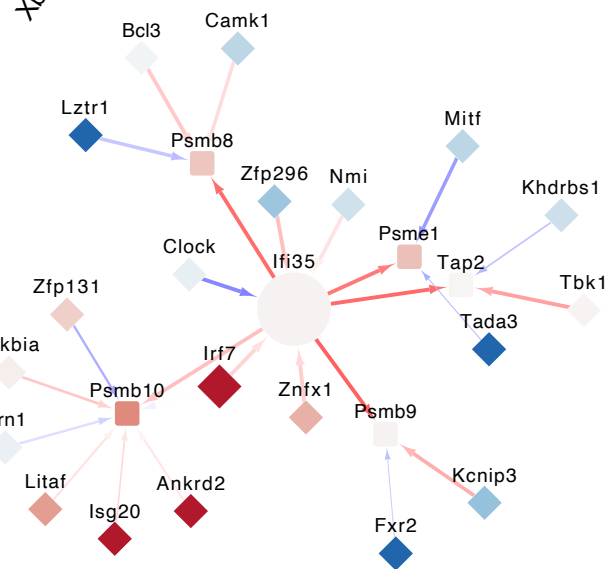
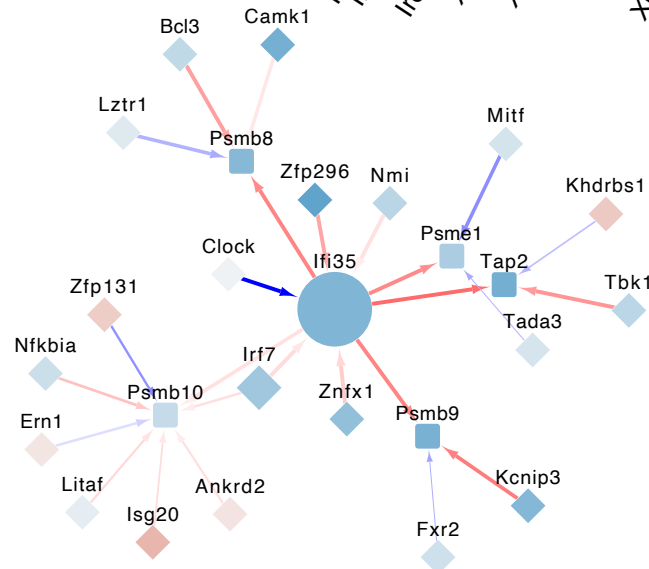
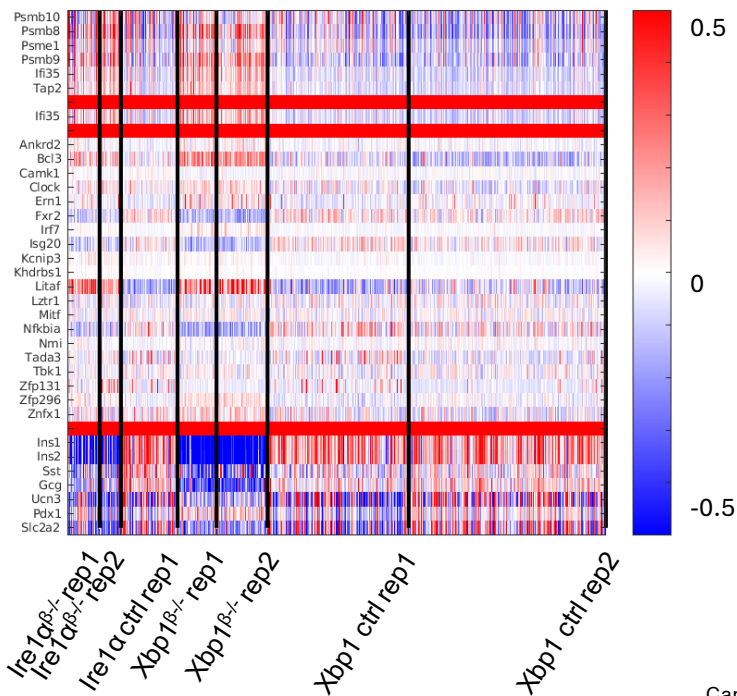
Ire1α ctrl



Xbp1β^{-/-}

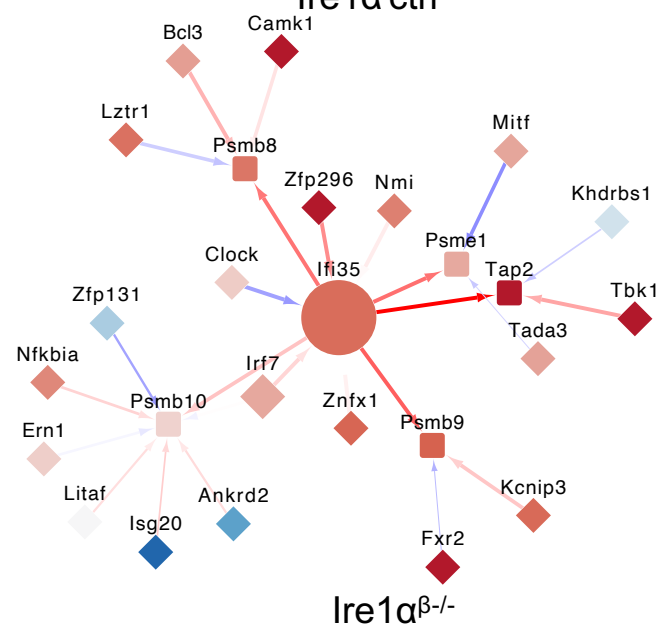
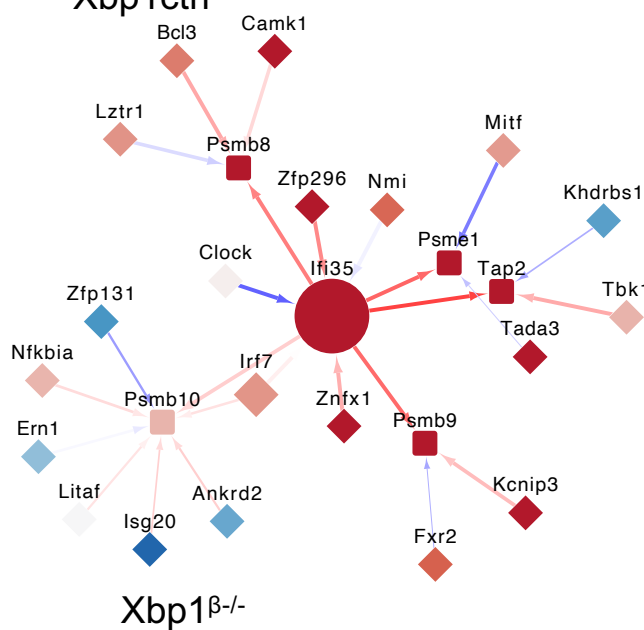
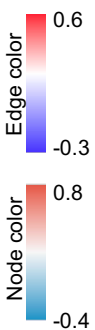
Ire1αβ^{-/-}

Shared Up: Module 2398

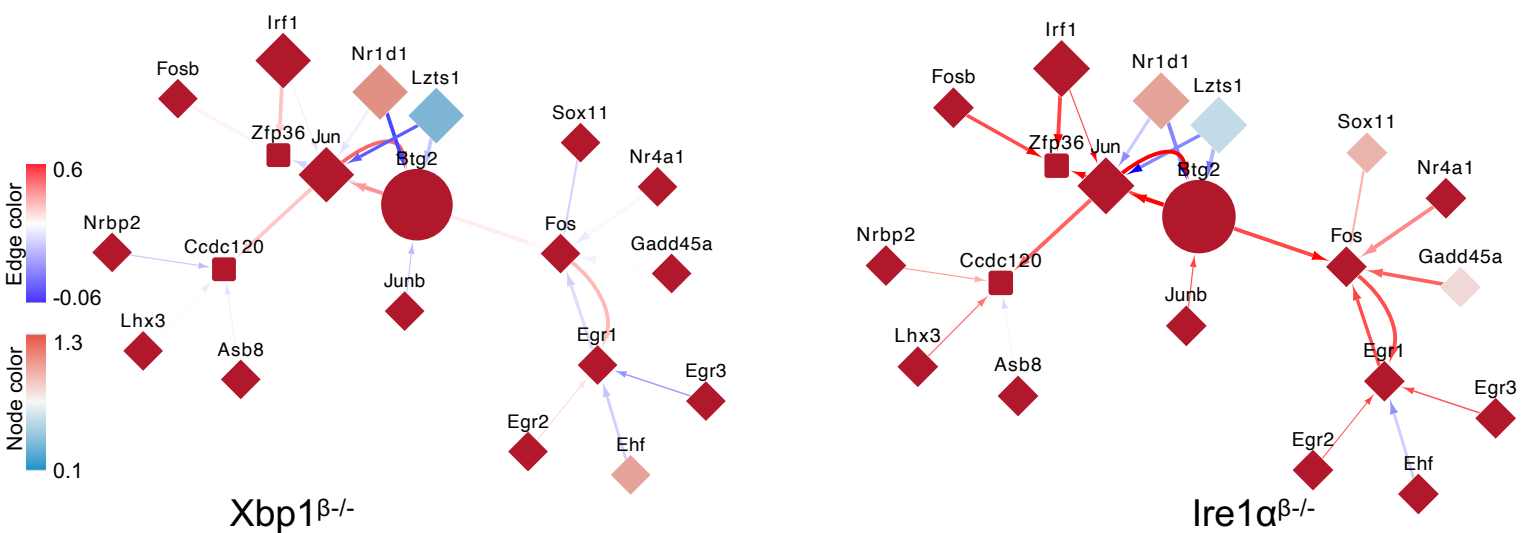
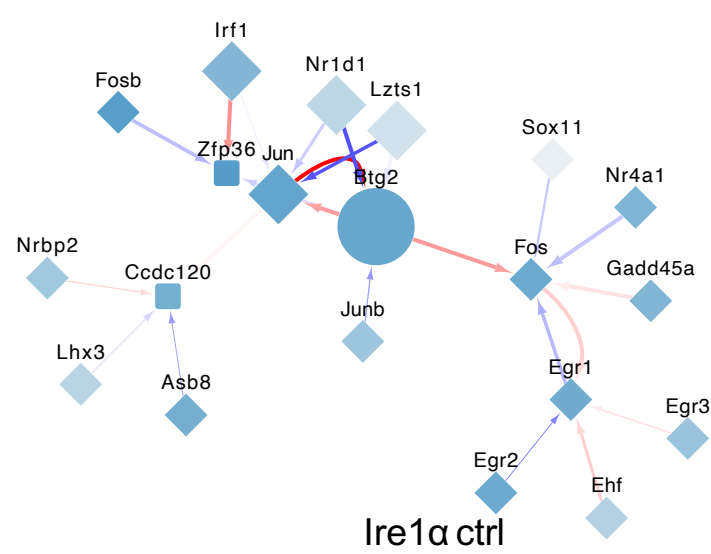
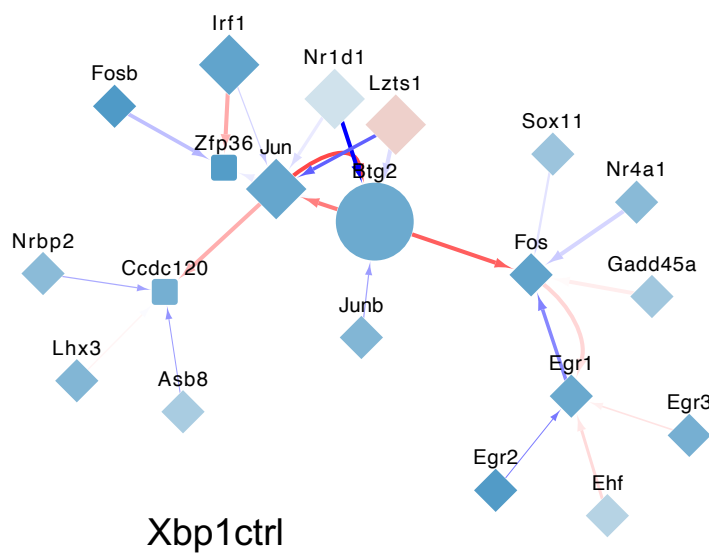
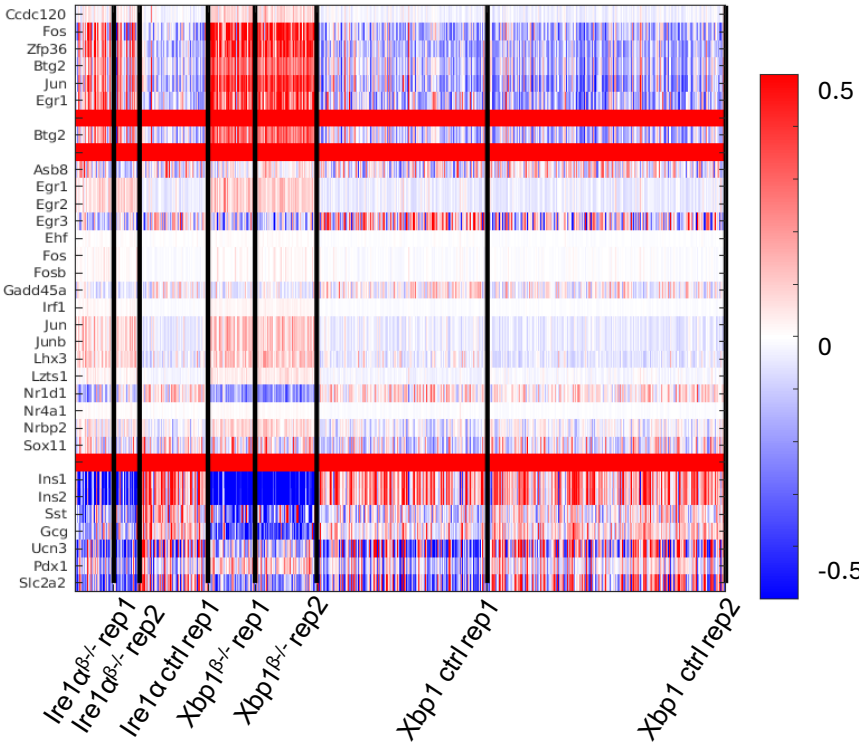


Xbp1ctrl

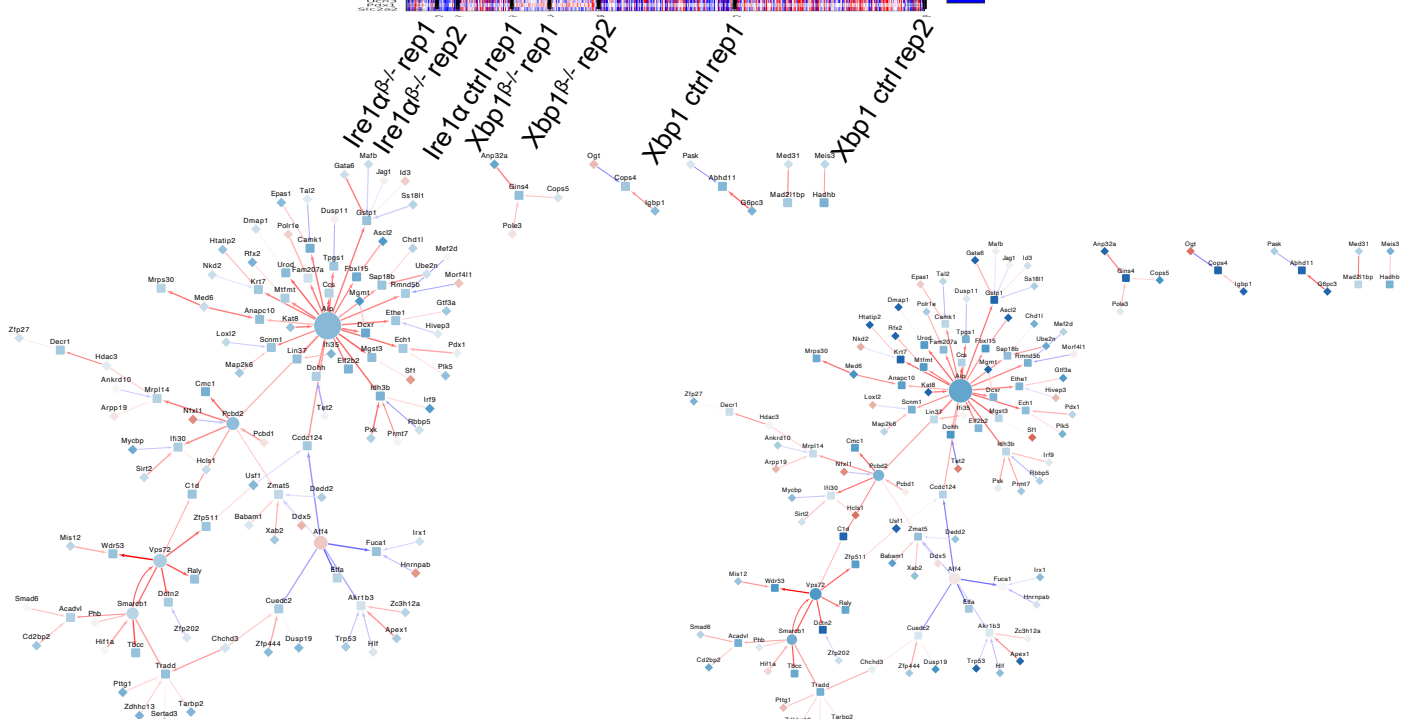
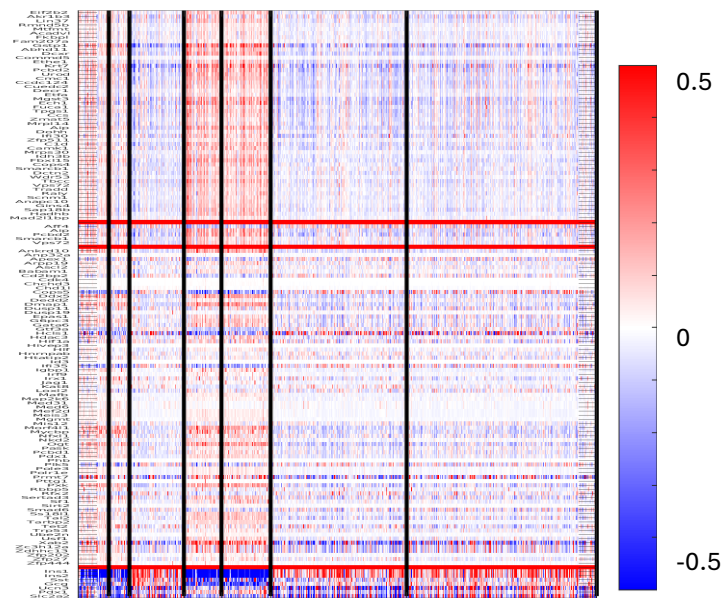
Ire1α ctrl



Shared Up: Module 3061

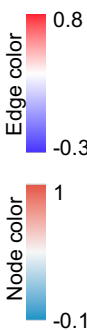


Shared Up: Module 3146



Xbp1ctrl

Ire1α ctrl



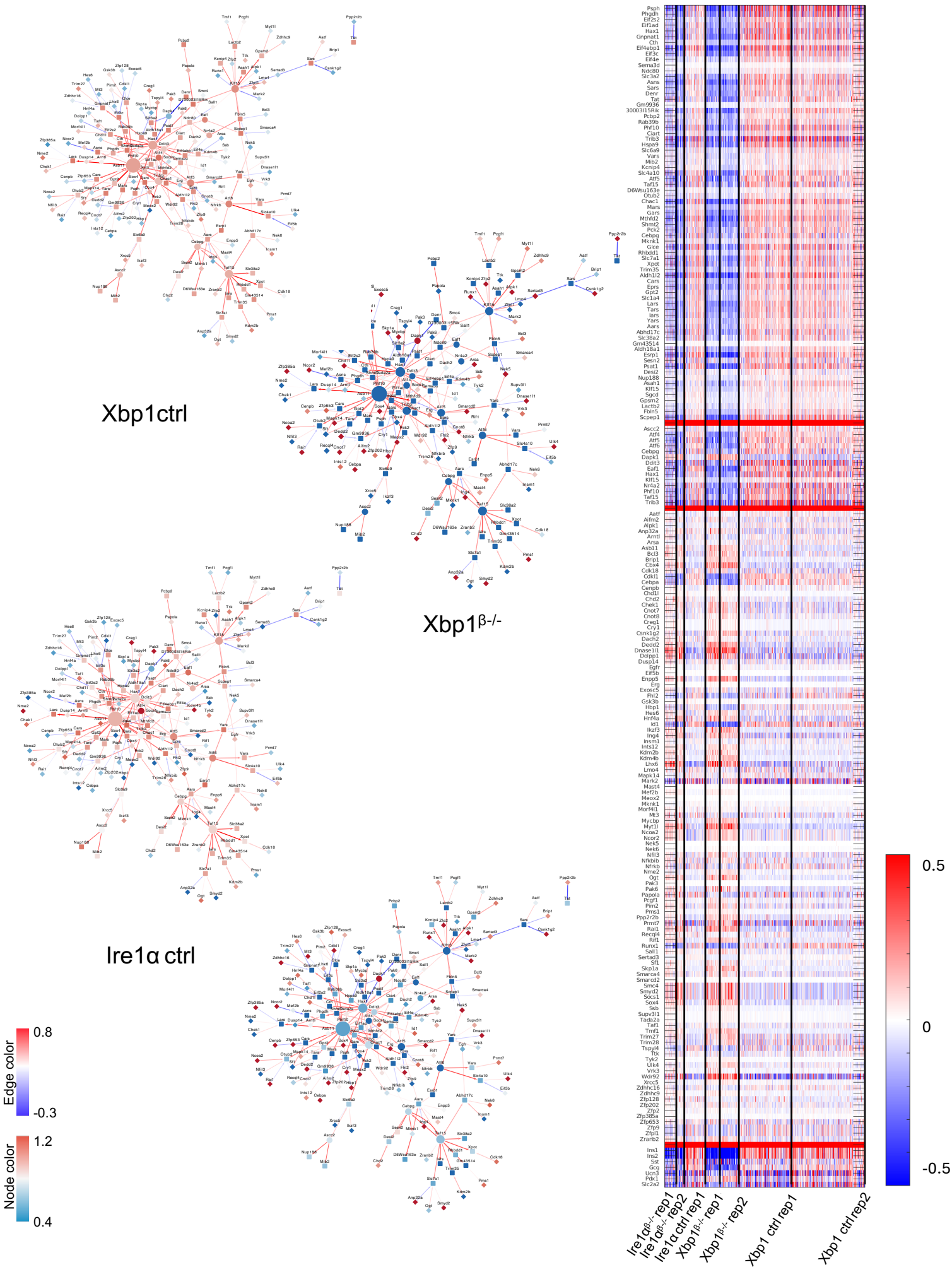
Xbp1β-/-

Ire1αβ-/-

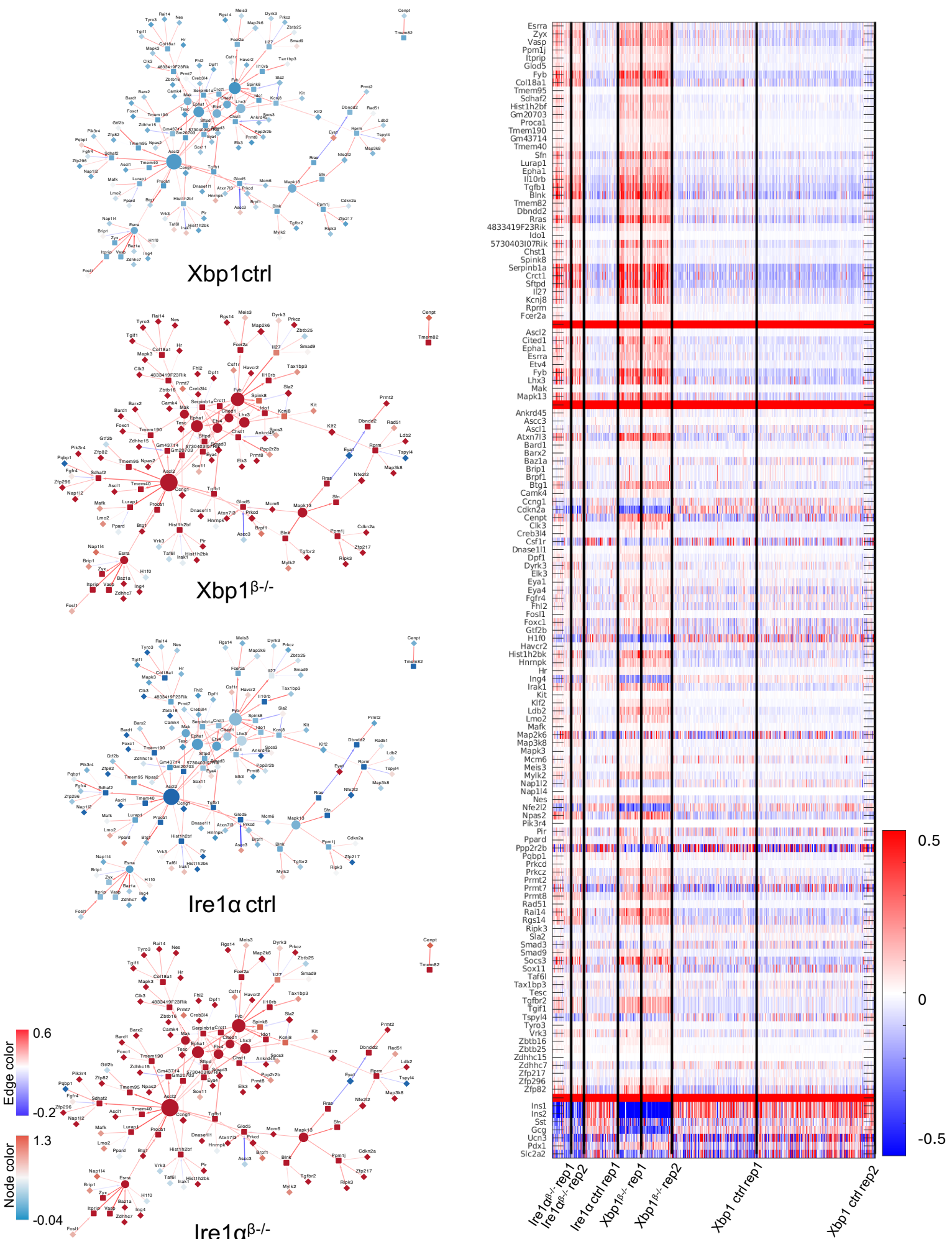
Cdk4

Conn5

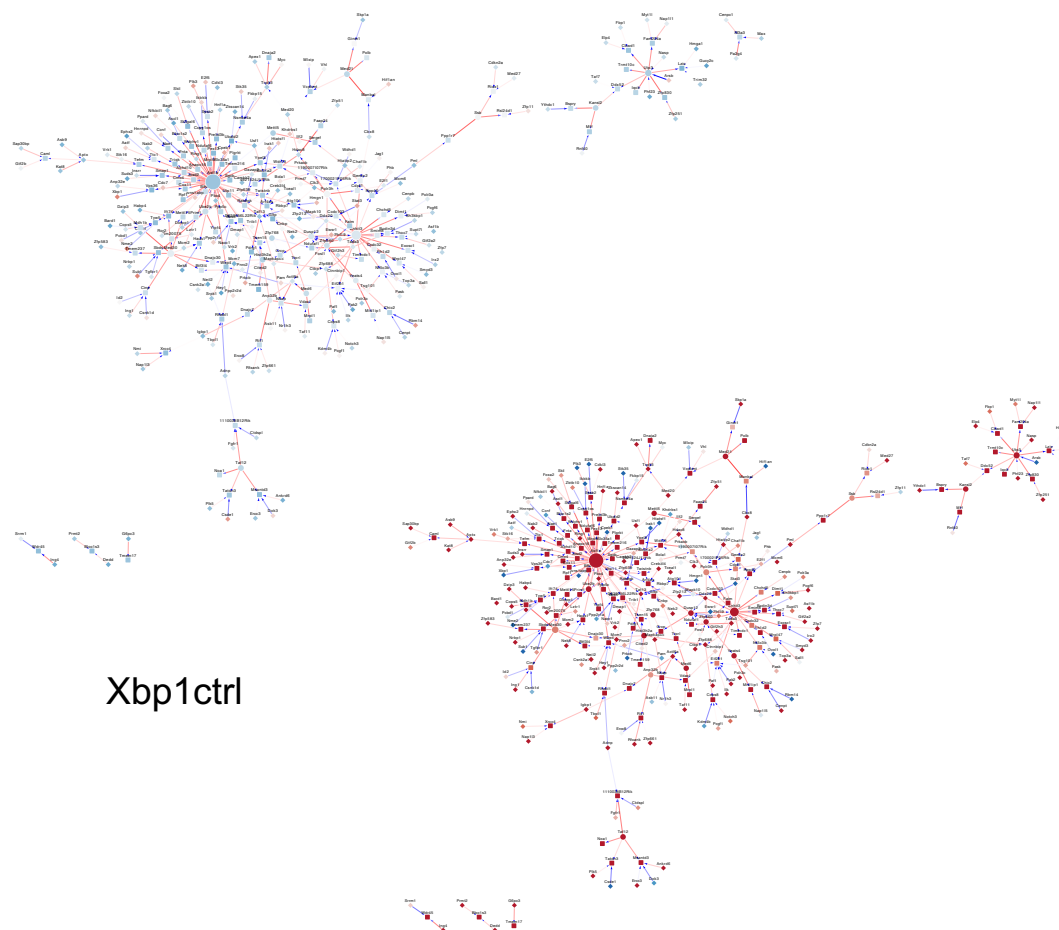
Shared Up: Module 3339



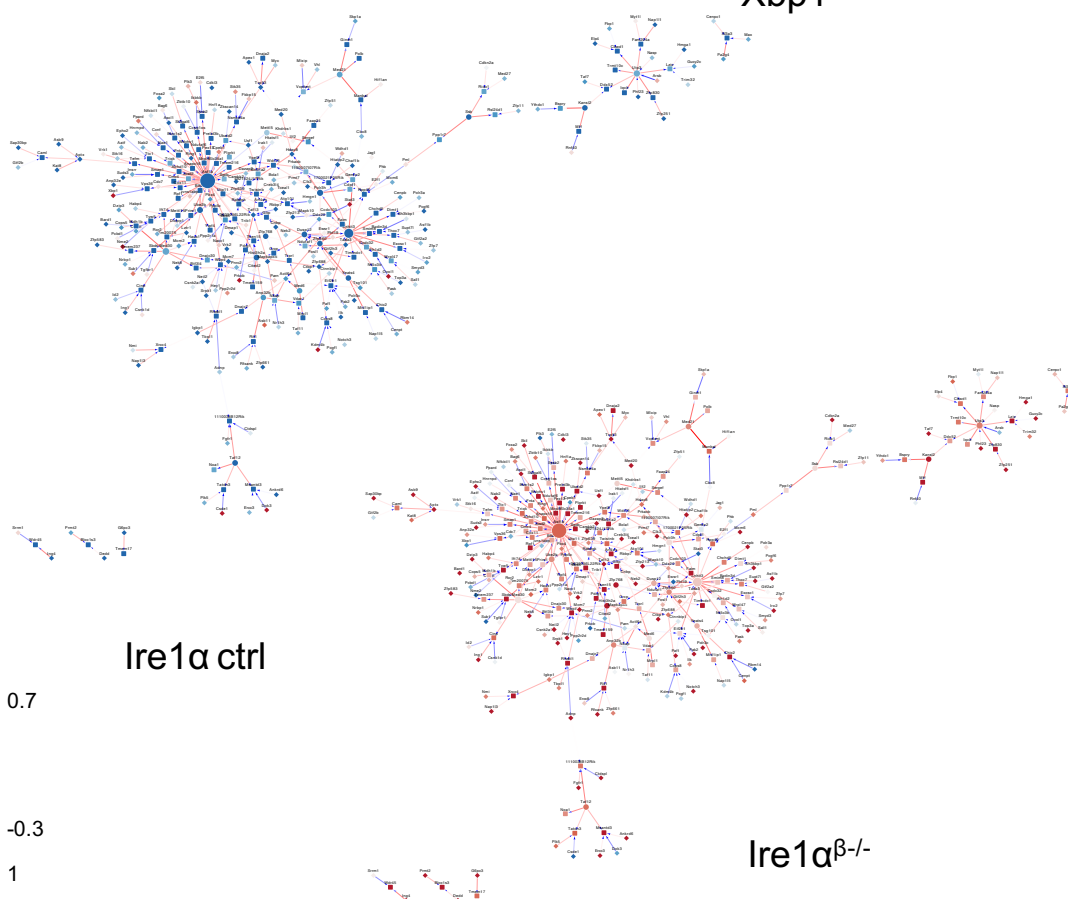
Shared Up: Module 3476



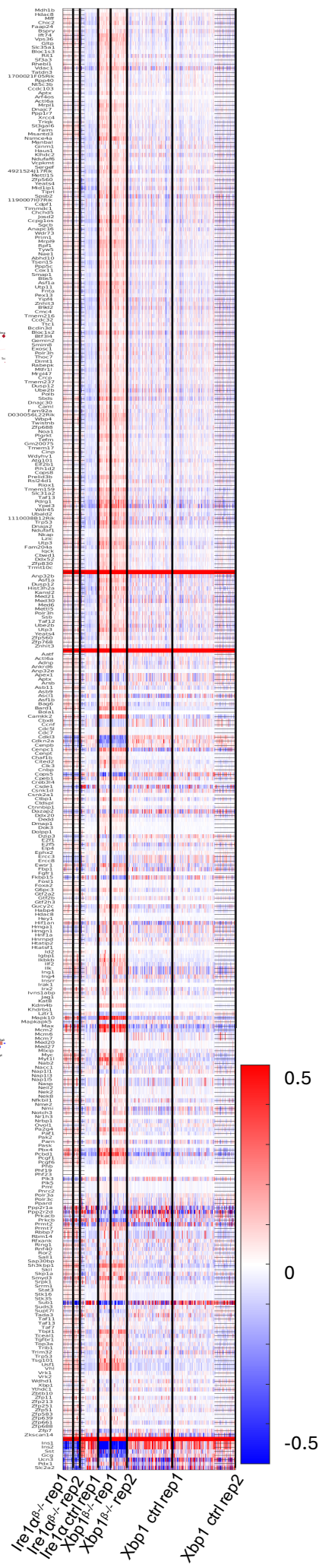
Shared Up: Module 3897



Xbp1 ctrl

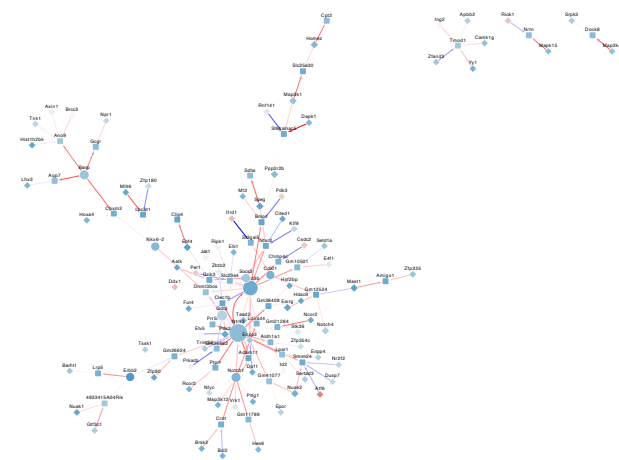
Xbp1^{β-/-}

Ire1α ctrl

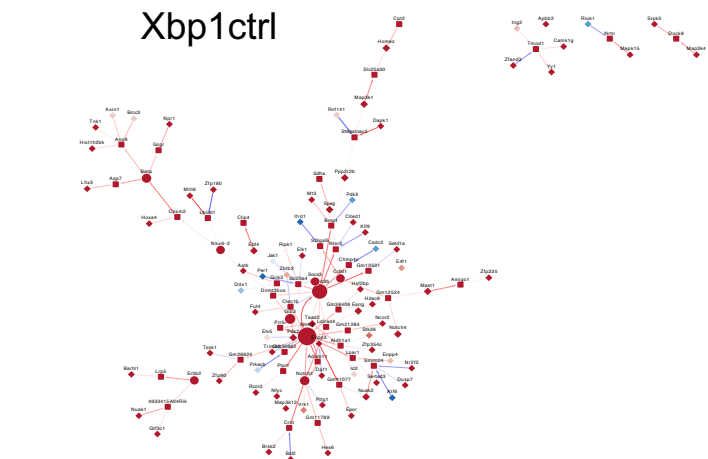
Ire1 $\alpha^{\beta-/-}$ 

Heatmap showing ChIP-seq signal for Irf1, Xbp1, and Xbp2 across various conditions. The signal is highest for Irf1 and Xbp1 in the Irf1aβ-/- conditions and for Xbp2 in the Xbp1β-/- conditions.

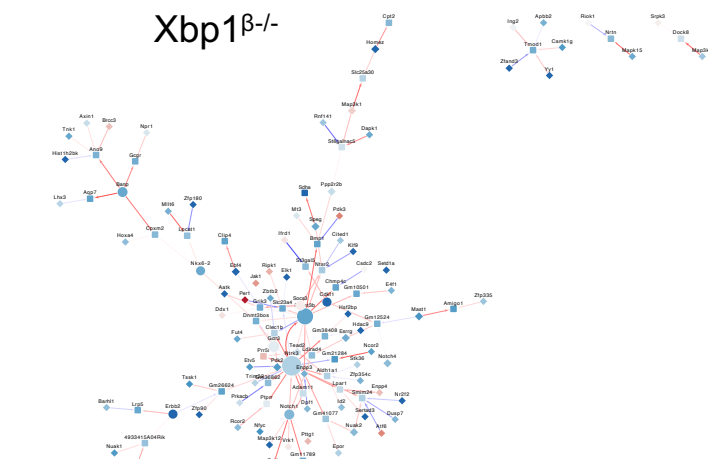
Shared Up: Module 3916



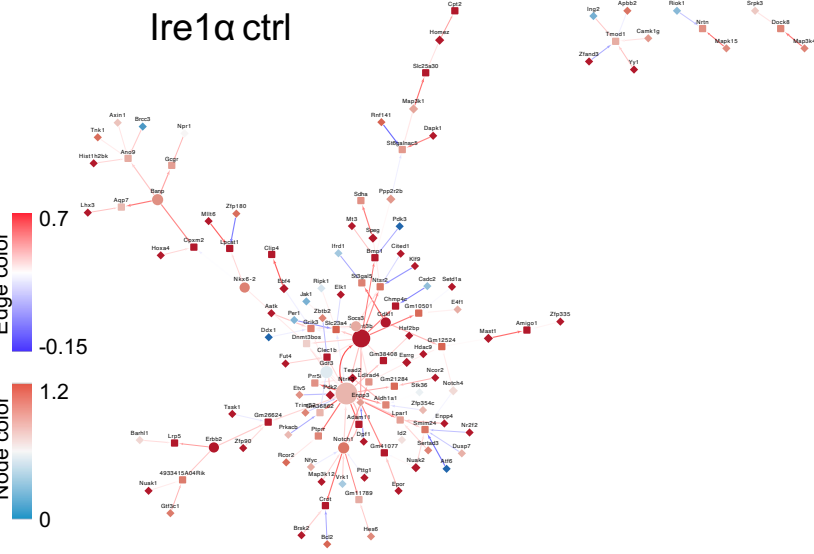
Xbp1ctrl



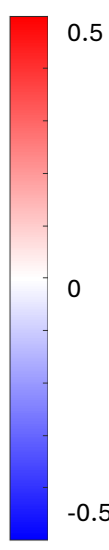
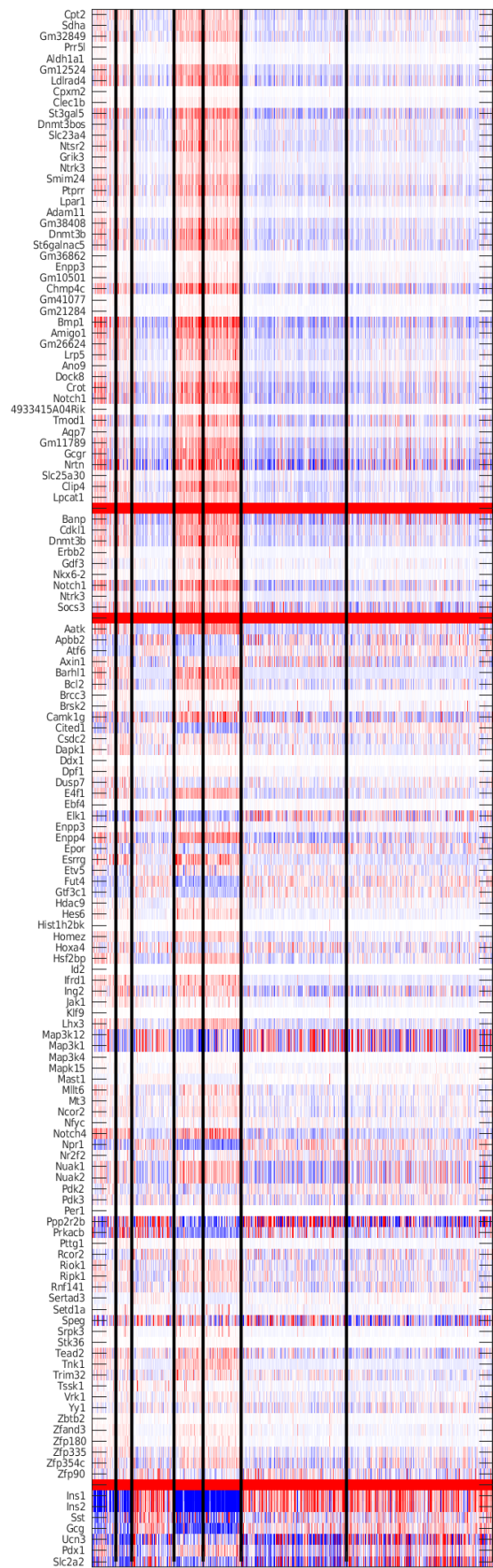
Xbp1β^{-/-}



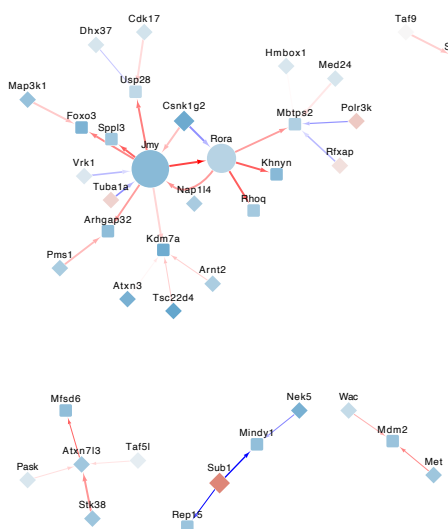
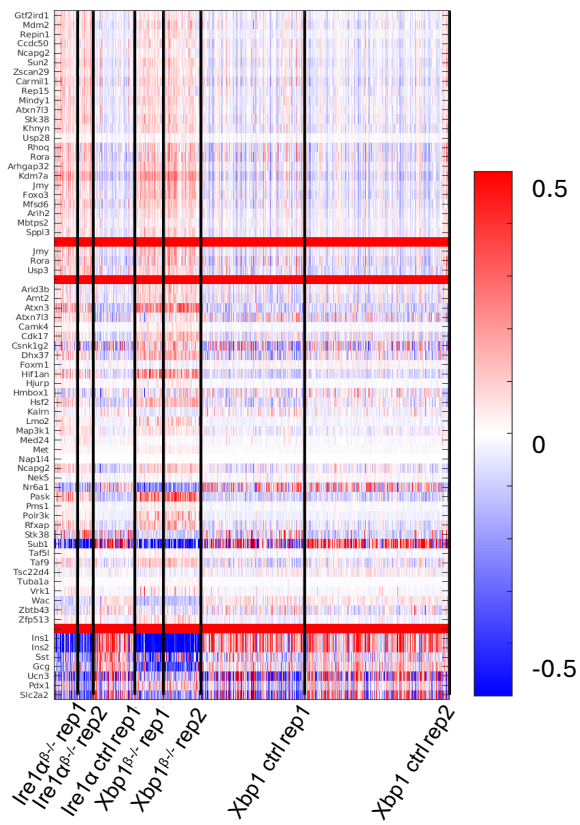
Ire1α ctrl



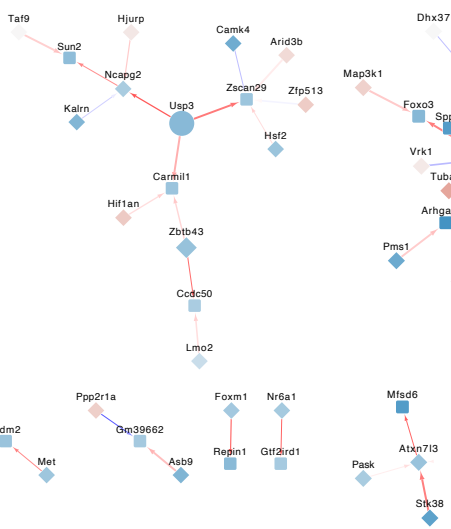
Ire1αβ^{-/-}



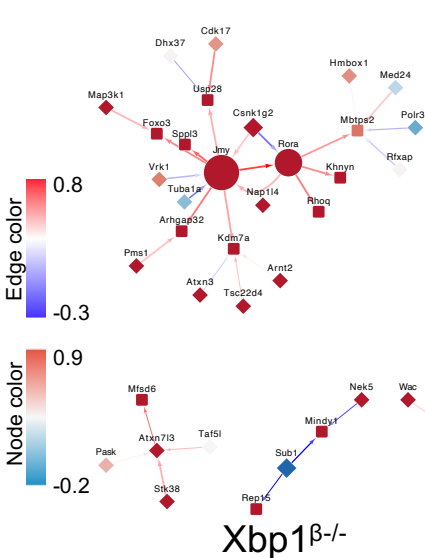
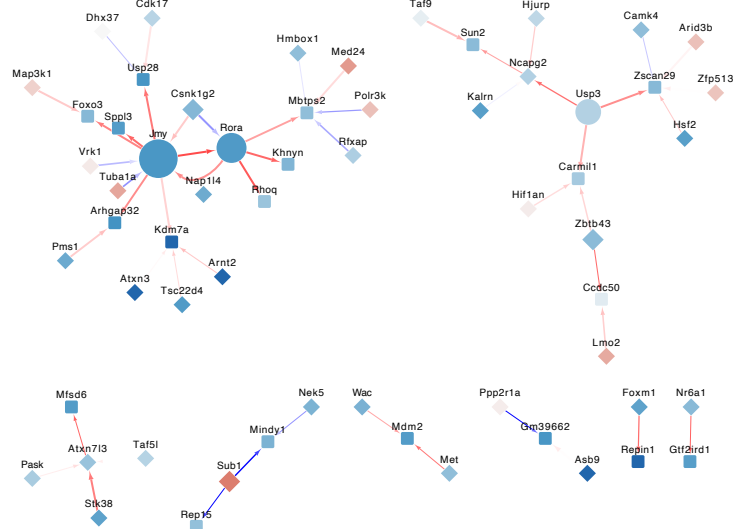
Shared Up: Module 3966



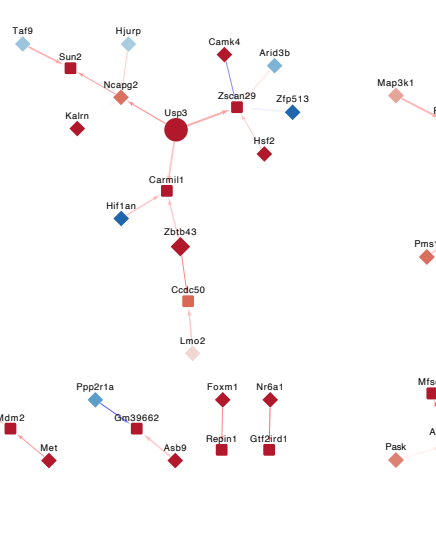
Xbp1 ctrl



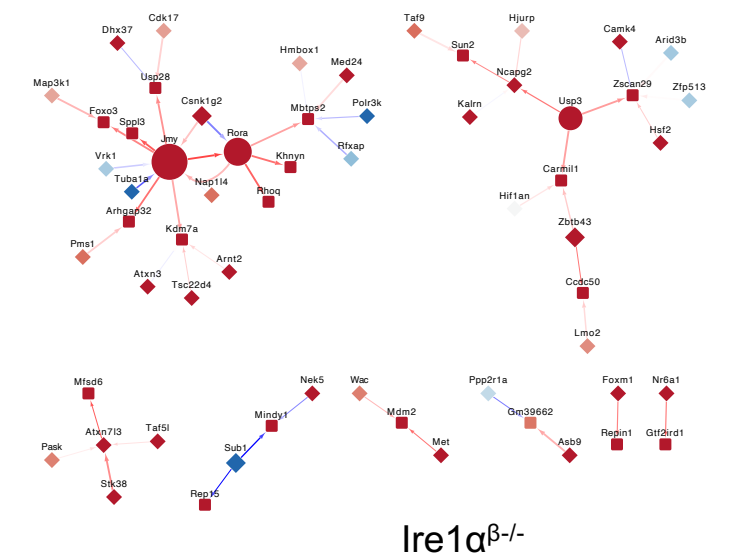
Ire1α ctrl



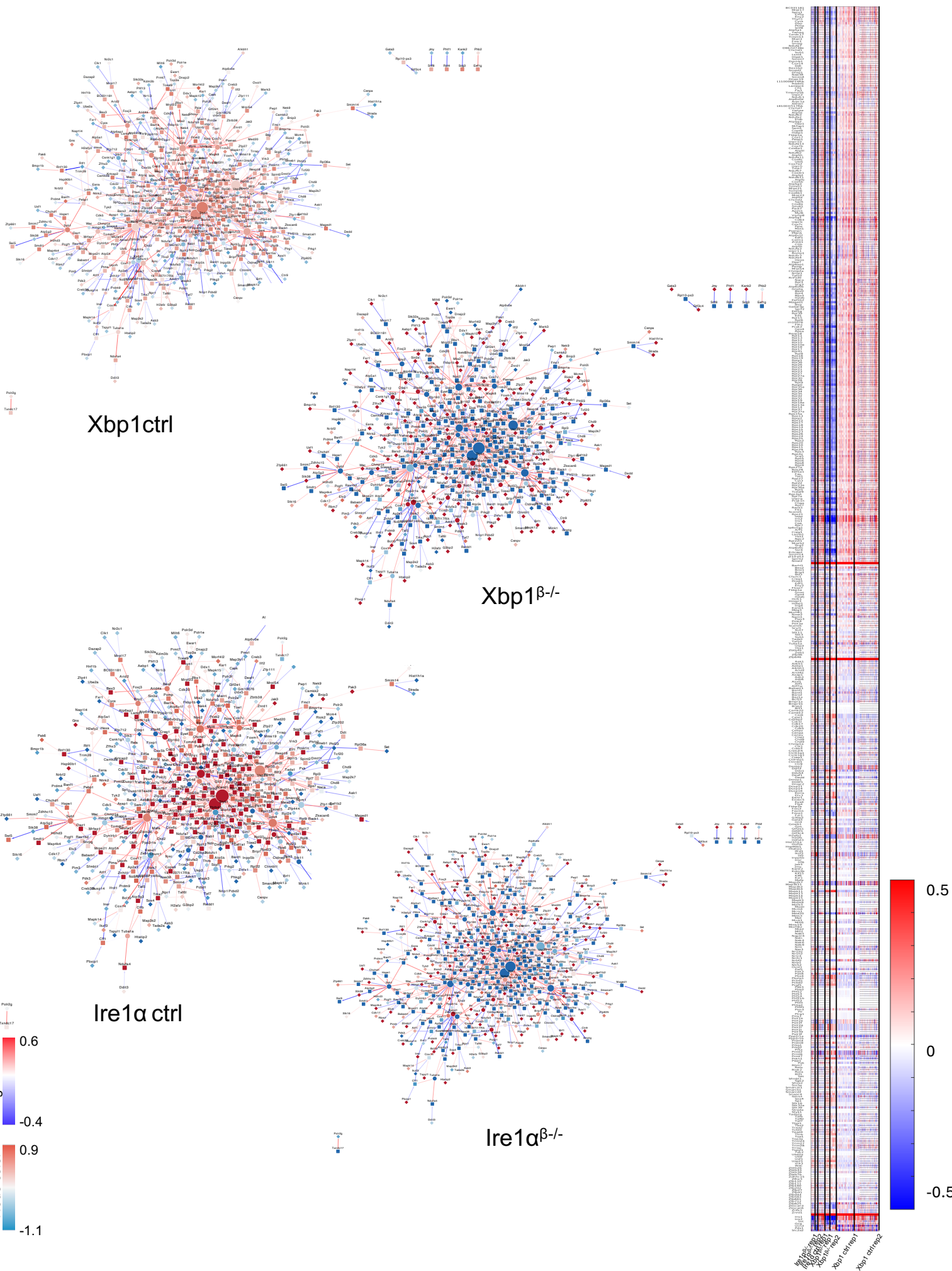
Xbp1^{β-/-}



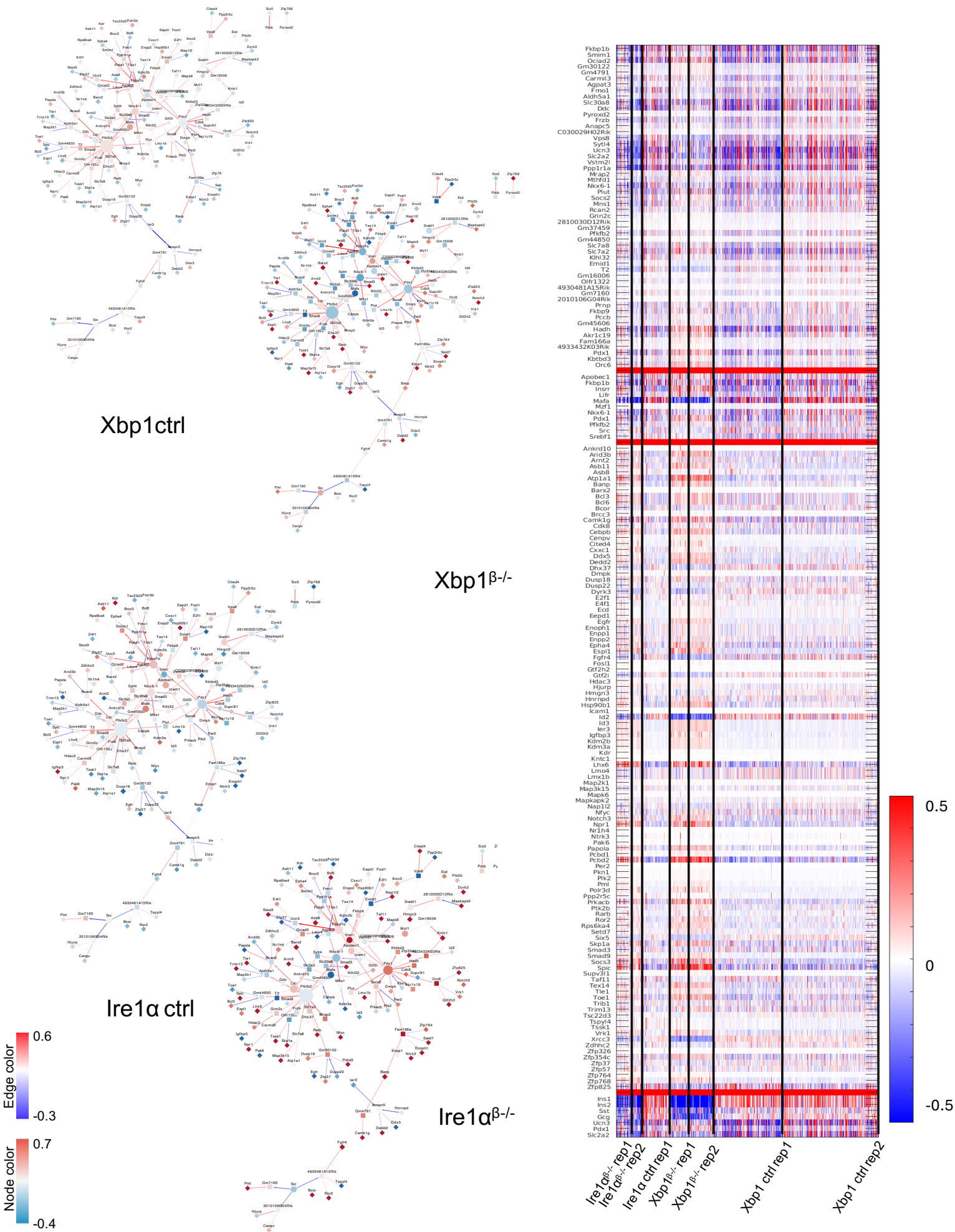
Ire1α^{β-/-}



Xbp1 $\beta^{-/-}$ Down: Module 3542



Xbp1^{β-/-} Up: Module 3483



Supplementary Method

Example of gating strategy for immunophenotyping

