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Supplementary Figure Legends

Supplementary Figure 1. The magnitude of TNF-α-induced cell death is positively correlated with MAPK signaling. (A) Phosphorylated Mek1 time course measured as a surrogate for MAPK pathway activation by TNF-α. p-Mek1 is elevated in a sustained manner in conditions that display a high magnitude of TNF-α-induced cell death, for example, in the case of mice treated with neutralizing antibody to MCP-1. Controls are mice pretreated with nonspecific IgG. Error bars represent SEM for 3 animals. (B) p-Mek1 is up-regulated at 0.5 hours after TNF-α stimulation in mice that are co-treated with IFN-γ, another condition that displays high magnitude of cell death. Controls are mice co-treated with PBS vehicle. Error bars represent SEM for 3 animals.

Supplementary Figure 2. TNF-α induced proliferation is not affected by different Ras perturbations. (A) Phospho-histone H3 immunohistochemistry of duodenal tissues from WT control mice treated with vehicle or treated with TNF-α for 0.5 or 2 hours. TNF-α induces a proliferative arrest early, followed by hyperproliferation late. (B) Phospho-histone H3 immunohistochemistry of duodenal tissues from K-Ras^{G12D} mice treated with vehicle or treated with TNF-α for 0.5 or 2 hours. K-Ras mutant mice inherently possess larger crypt-villus structures. (C-F) Quantification of phospho-histone H3 immunohistochemistry of duodenal (solid line) and ileal (broken line) tissues from mice with different Ras perturbations. Images are quantified by taking the fractional area of phospho-histone H3 positive cells over the area of cells in the crypt. Crypts from K-Ras^{G12D} mice have more positive cells, but also have a greater numbers of cells in general. Duodenal tissues display proliferative arrest early, followed by hyperproliferation. Ileal tissues display hyperproliferation late. These TNF-α induced phenotypes are not affected by Ras perturbations. Error bars represent SEM for 3 animals.

Supplementary Figure 3. Time courses of protein phosphorylation signals activated following exposure to TNF-α *in vivo*. Data points are the means of the median fluorescent intensities resulting from the phospho-protein assays, normalized to a loading control dataset on each plate. The color scheme denotes different Ras perturbations. Error bars represent SEM for 3 animals.

Supplementary Figure 4. Hierarchical clustering of phosphorylated proteins measured in Ras-mutant mice by Bio-Plex. (A) Each signal, measured in triplicate, for every genotype and time point was clustered both by genotype and by protein identity. (B) Clustering of all measurements of each signal. (C) Clustering of genotypes and proteins with replicates averaged. The intensity of the color represents the median fluorescence intensity normalized to the highest value of each signal.

Supplementary Figure 5. Classification of Ras perturbation signaling datasets using PLSDA. Numerical classification of Ras perturbation signaling datasets (specified by color) into the “low magnitude cell death” (A), “high magnitude cell death” (B), and “no cell death” (C) classes. The y-axis shows the numerical result calculated with the PLSDA function of classification into each of the different classes. The broken red line is the threshold defining classification. The signaling datasets of WT control mice (cyan) and N-Ras^{G12D} mice (green) surpass the classification threshold of the low magnitude class, while that of N-Ras null mice (orange) classifies into the high magnitude class. Data from K-Ras^{G12D} mice (dark blue) does not meet the classification threshold of any class, but is the closest to being classified into the no cell death class.

Supplementary Figure 6. Normalized data for cFL modeling. Data normalization of 30 and 60 minute time-points as used in cFL modeling and described in Materials and Methods. Background colors show increases (yellow), decreases (gray), or no change/no data (white) of signals above baseline.

Supplementary Figure 7. Training models to data using cFL while expanding "and-not" gates. (A) Ensemble topology of model fit to data at 60 minutes. Nodes represent ligand stimulation or genetic activation (green), inhibitors or knockouts (red), measured phosphorylation sites (blue), or proteins that are not measured or perturbed, but cannot be compressed while maintaining logical consistency (white). Edges are either activating (black) or inhibitory (red). Only edges appearing in greater than 90% of models are shown for clarity. (B) Plotted fit of model in (A) to data.

Supplementary Figure 8. cFL model of 30 minute signals without autocrine edges. (A) Topology of cFL model to trained to data using no autocrine signaling at 30 minutes, without expanding "and-not" gates. Nodes represent ligand stimulation or genetic activation (green), inhibitors or knockouts (red), measured phosphorylation sites (blue), or proteins that are not measured or perturbed, but cannot be compressed while maintaining logical consistency (white). Edges are either activating (black) or inhibitory (red). (B) Fit of Model in (A) to data. Plots include normalized data at 30 minutes (solid black lines), predicted values from individual models (pink dashed lines), and averages of simulations from family of models (blue dashed lines. The background color represents goodness of fit, with green being the least discrepant between simulation and data, red being the most, and gray signifying that no data was available.

Supplementary Figure 9. Systematic comparison of 30 and 60 minute cFL models. Comparison of edges in models at 30 minutes (x-axis) to those at 60 minutes (y-axis). Each data point represents the fraction of models that an edge appears in for models trained to the 30 minute data versus the 60 minute data. Only edges with more than a 25% difference in fraction between time-points are labeled - all other edges are assumed to exist in the network with little time specificity. Cyan highlights edges from TNF-α, dark blue highlights edges from K-Ras, and green highlights edges from N-Ras.

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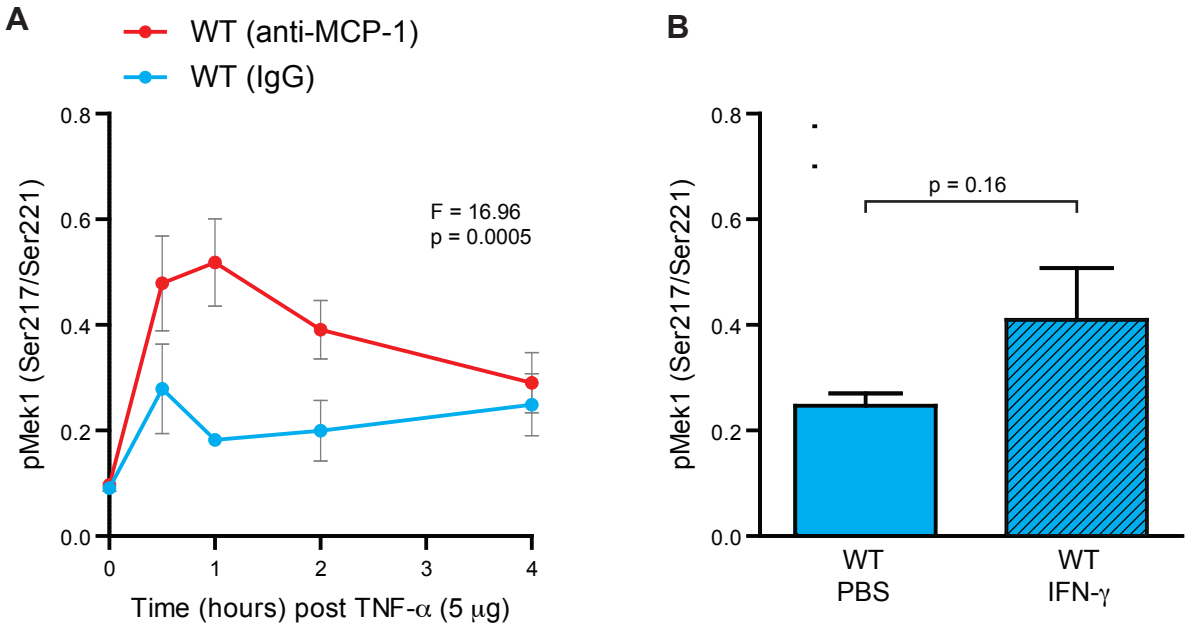
Supplementary Figure 1



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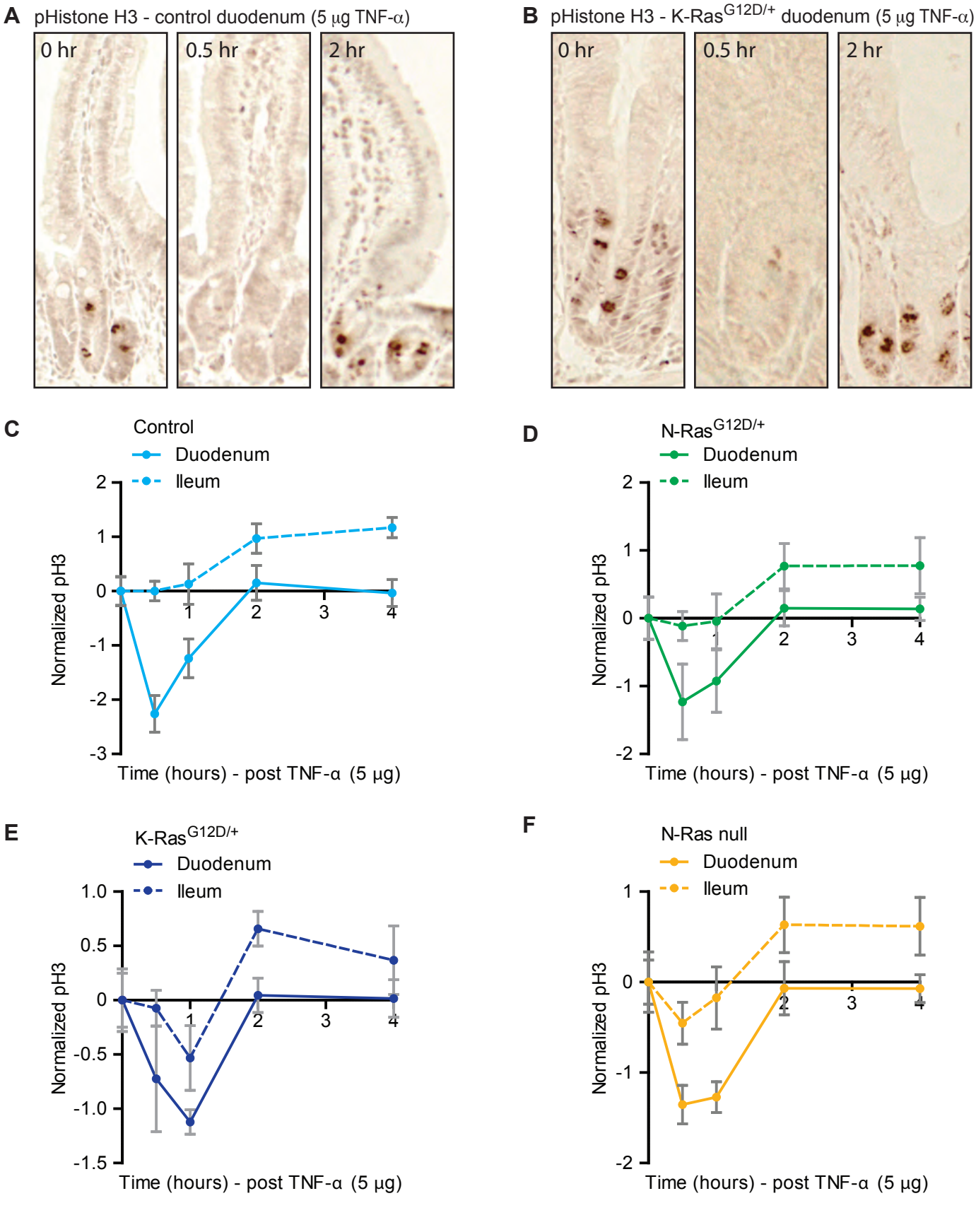
Supplementary Figure 2



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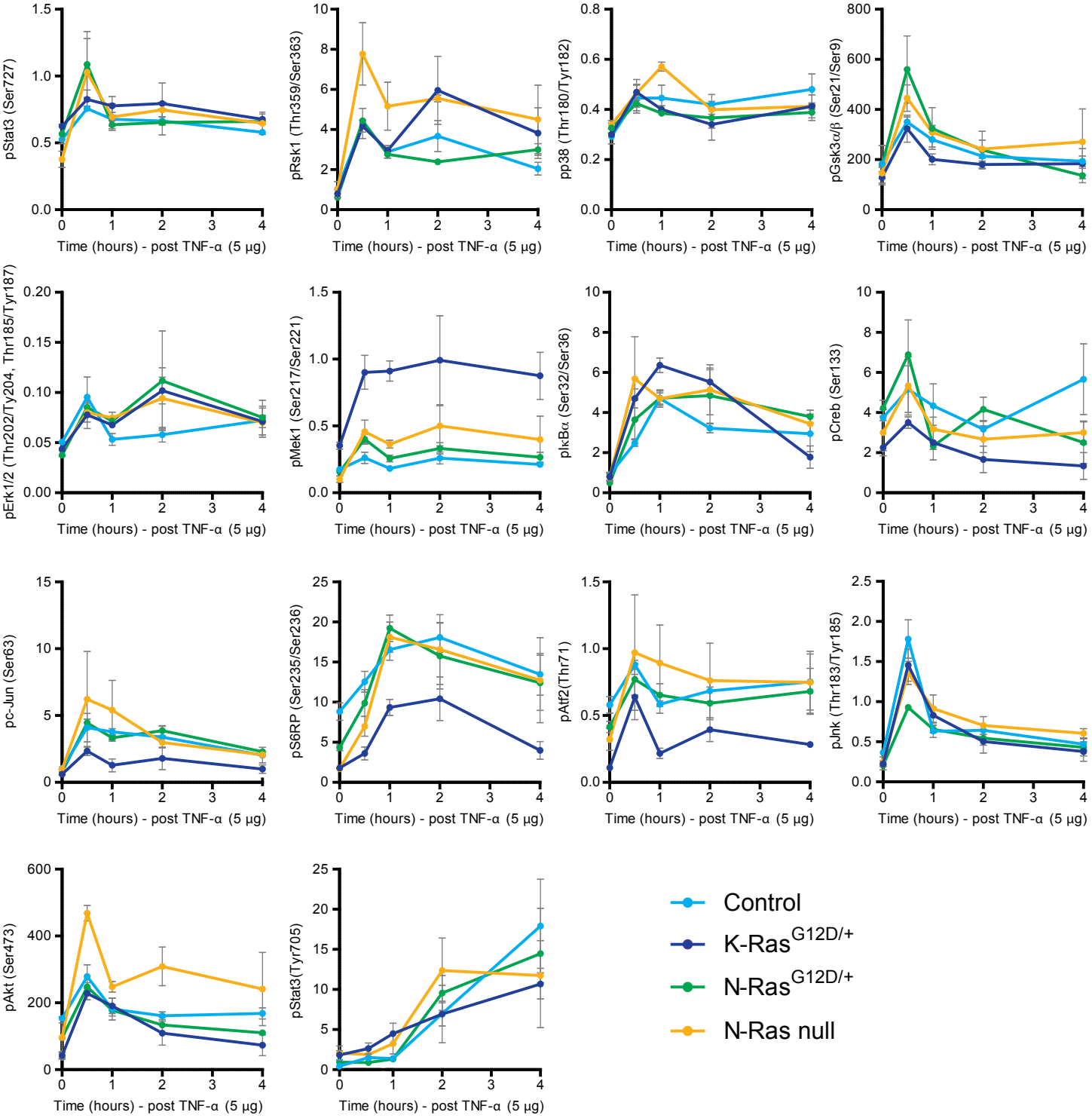
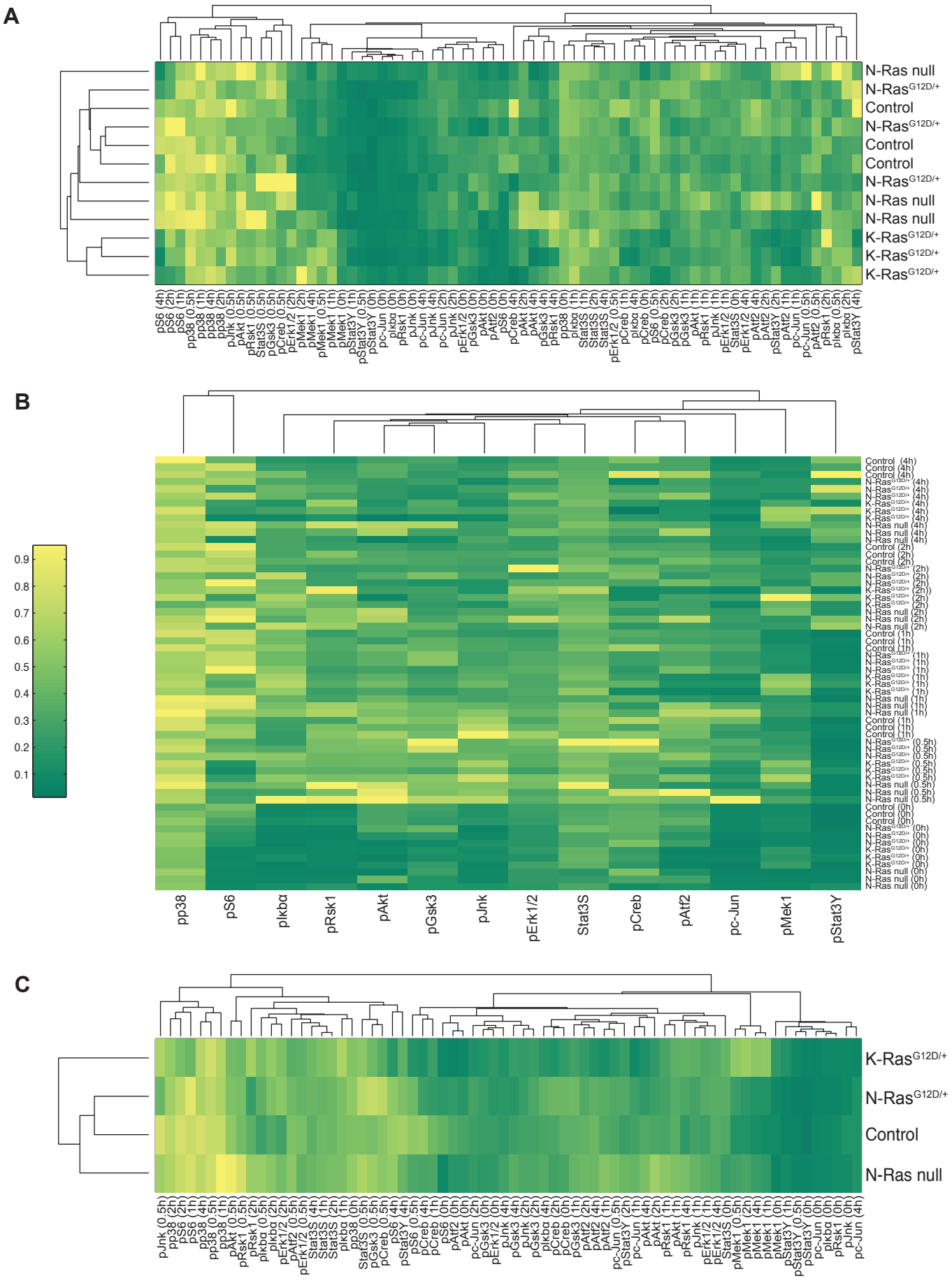
Supplementary Figure 3



Supplementary Figure 4



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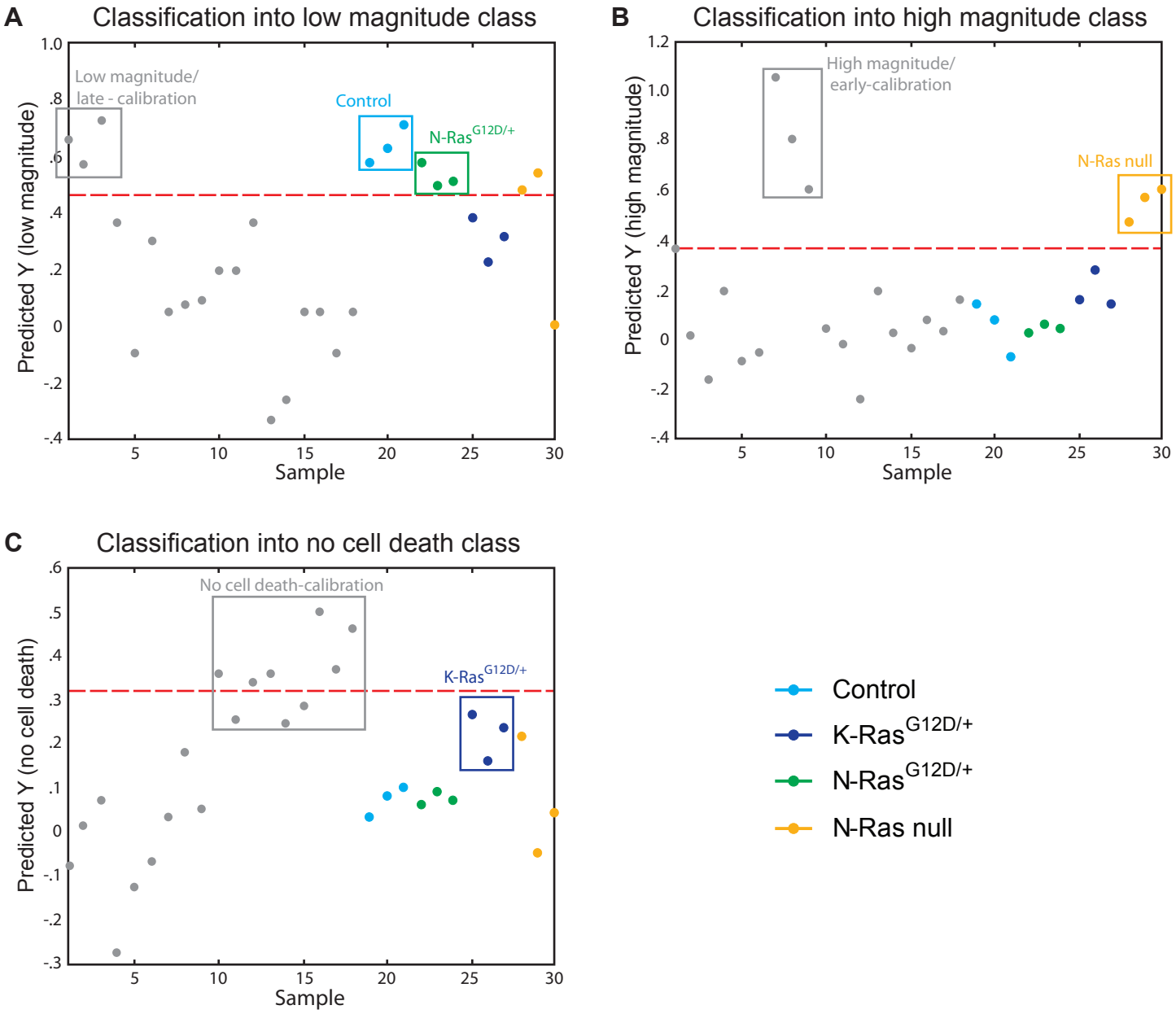
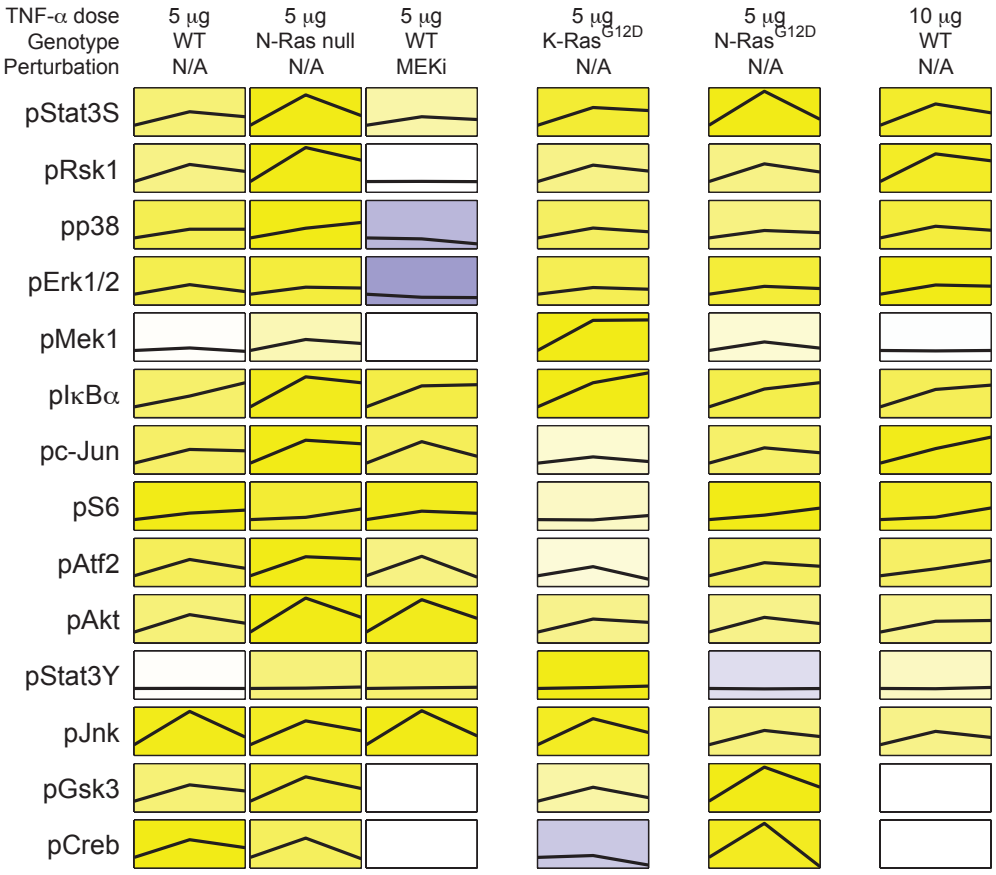
Supplementary Figure 5



Supplementary Figure 6



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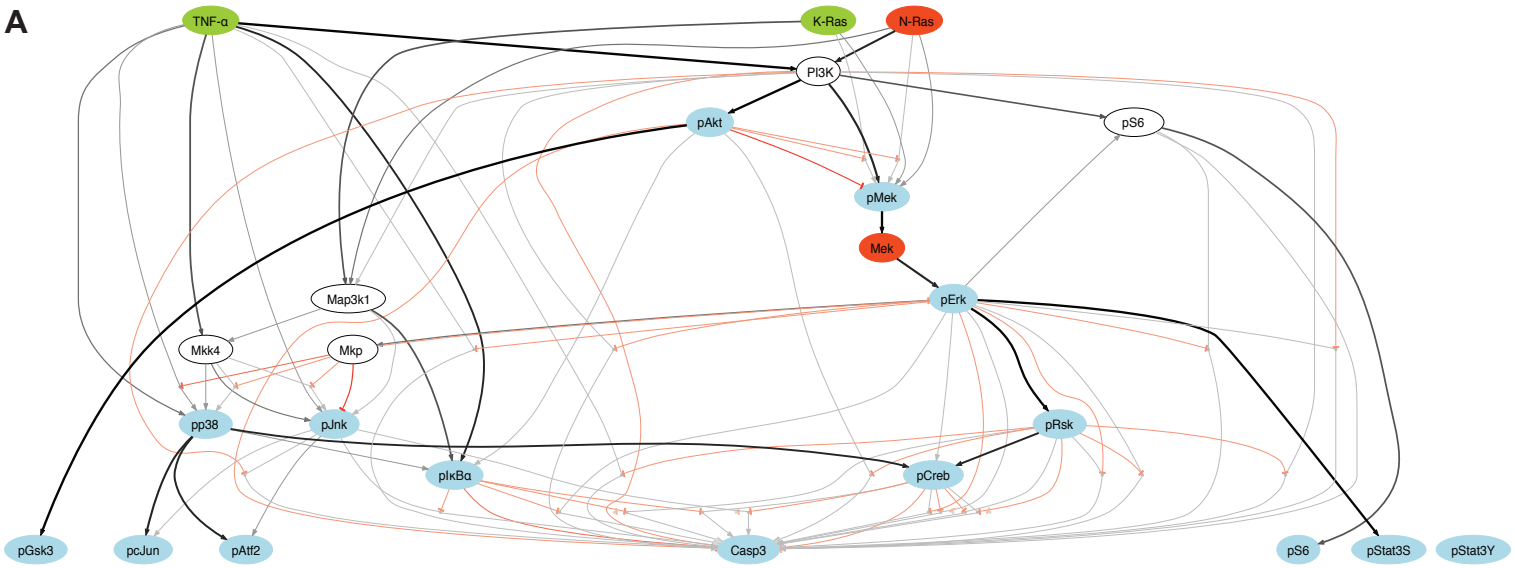
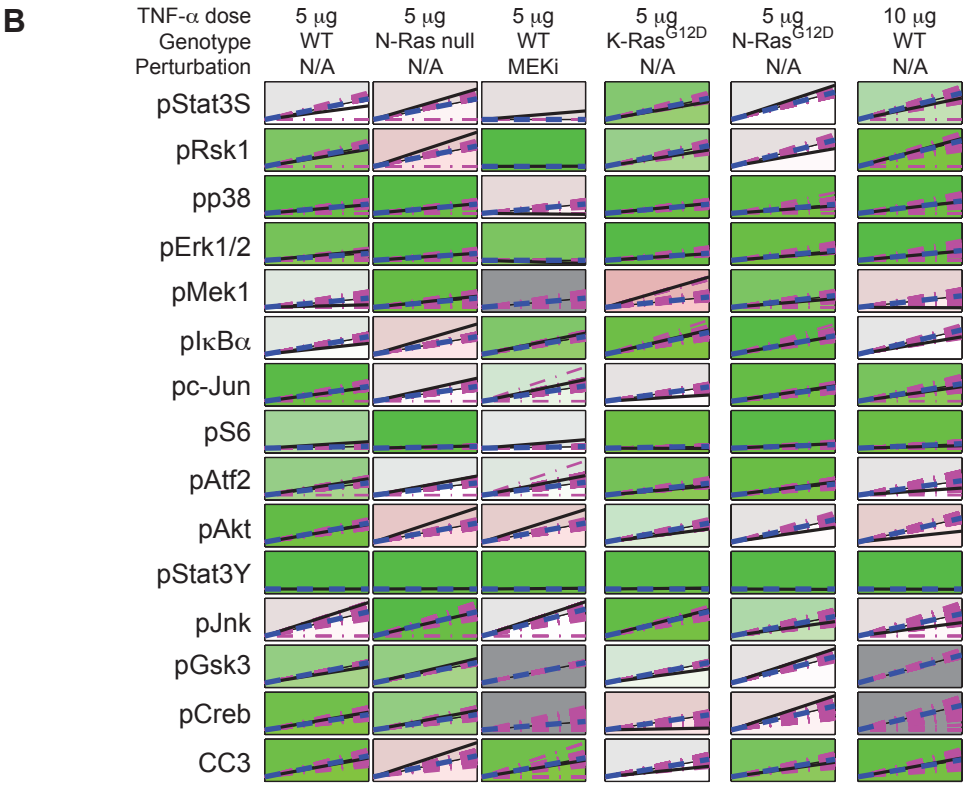
Supplementary Figure 7





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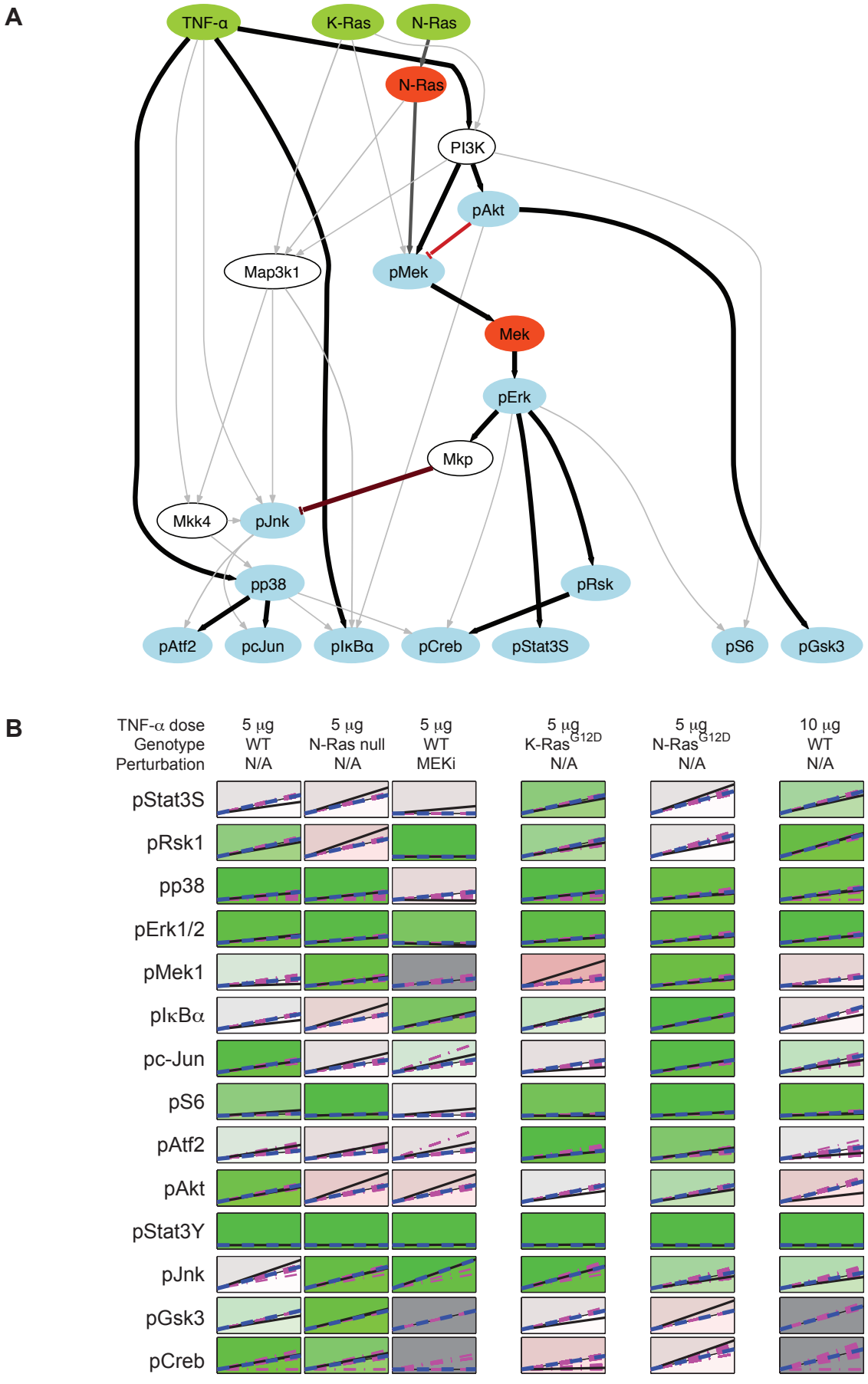
Supplementary Figure 8



Supplementary Figure 9