SUPPLEMENTARY METHODS:

PLSR – Partial least-squares regression (PLSR) was conducted in MATLAB R2008a using the function 'npls_cross_validation' from the *DataRail* toolbox (based on the 'npls' function from the *N-way* toolbox) (83). The PLSR models were constructed using the data collected in the presence of inhibitors (Figure 3). The input or X-block consisted of a matrix of the PCA scores of the *centered* signaling data, with each row corresponding to a different treatment and each column corresponding to a different intracellular phosphoprotein. The output or Y-block consisted of a row vector of the PCA scores for a single cytokine, with each row corresponding to a different treatment. Although PLSR is capable of utilizing the entire timecourse data, the PCA scores were used in the model to facilitate the interpretation of the model in terms of dominant pathways, independent of their dynamics. The X and Y data were auto-scaled, so that the mean and standard deviation of each column were 0 and 1, respectively.

The function 'npls_cross_validation' determines the number of components in the model using 7-fold cross-validation (84, 85). However, the maximum number of components was limited to 3 in order to facilitate interpretation. To construct a more interpretable model, a reduced model was also determined using only those input variables with regression coefficients determined to be significant, as defined using a shuffling/permutation algorithm (86, 87). The shuffling algorithm constructs 100 random permutations of the Y data and determines the corresponding PLSR models and their regression coefficients. A regression coefficient is considered to be significant if it is more than one standard deviation away from the mean of the corresponding coefficient from the random models.

Additional cutoffs were applied to facilitate visualization of the models (Supplementary Figure 6). For each LV, the loading for a phosphoprotein was not plotted if its magnitude was less than 0.33 times the maximum loading magnitude. Similarly, a regression coefficient for a particular phosphoprotein was not plotted if its magnitude was less than 0.33 times the maximum coefficient magnitude. In Supplementary Figure 6B, only PLSR models with $R^2 > 0.66$ are shown.