**Supplementary Figure 1:** Panels A and B: clustering and Multidimensional Scaling of sample profiles. Panel C and D, comparisons of difference between time points in both strains and differences between strains at each time point.
Supplementary Figure 2:
Average expression of transcription factors with over-represented targets amongst MGC precursor specific genes in WKY strain at day 5. Expression is expressed in Fragments per Kilobase per Million (FPKM) reads. Error bars show standard error of the mean.
Supplementary Figure 3:
Glycolysis gene expression after culture with 2-DG. Measured by qPCR (panel A) and western blot (panel B).
ns, not significant; * P<0.05; ** P<0.01.
Supplementary Figure 4 illustration of the criteria used for identification of MGC specific phosphopeptide signatures.

Panel A MGC specific increase in phosphopeptide abundance

Panel B MGC specific decrease in phosphopeptide abundance
Supplementary Figure 5:
Panel A: abundances of phosphopeptides showing MGC specific absence of presence. Grey indicates no quantification, strong red corresponds to high abundance. White to light blue indicates extremely low abundance (assimilated to background). Panel B: Fold Changes of transcriptomic expression of differentially expressed phosphopeptides relative to the median across all samples. The color scale the same as the one used in for figure 3A. Red shows high RNA expression and blue shows low RNA expression compared to the median across all samples. Panel C: Compared Fold change between WKY and LEW of proteins and phosphopeptide abundance, during the peak of multinucleation. Fold changes are shown for differentially expressed phosphopeptides, where the underlying protein could be observed by quantitative proteomics.
Supplementary Figure 6: Panel A, C and E show extracted ion chromatograms of poly-phosphate Inositol Phosphatases across time points in both strain. On each graph the blue, green and red curve show the intensity of the three main isotopic peaks. Panel B,D and F show the quantification of the normalized phosphopeptides abundances across strains and time points. Panel G recapitulates the role of PIP3 in multi-nucleation. Briefly RANKL of IL4 stimulation activates phosphatidyl inositol 3 kinase (PI3K) that phosphorylates PIP2 into PIP3 which further activates Akt leading to multi-nucleation. Poly-phosphate Inositol Phosphatases reverse the effect of PI3K thus reducing multi-nucleation.
Supplementary Figure 7

Panel A: FDR associated with various P-value thresholds in the prediction of interacting phosphoprotein/TF pair.
Panel B shows the set of significant pairs when computing a null distribution conditional to each TF (scoring of proximity random phosphoproteins to the TF under consideration)
Panel C shows the set of significant pairs when computing a null distribution conditional to each phosphoprotein (scoring of proximity random TFs to the phosphoprotein under consideration).
Supplementary Figure 8
Set of significant pairs when overlapping test conditional to each TF (Supplementary Figure 7B) and conditional to each phosphoprotein (Supplementary Figure 7C).

double permutation scheme,
Both P-values under 5% or 1%
Protein analysis of USF2 (an LRRFIP1 target), and LDHA (DNMT1 and SMARCA4 target) in siRNA experiments presented in Figures 5G and Figures 6B and E by Western Blot. Note that siRNA of LRRFIP1 which results in increased USF2 mRNA (Figure 5G) is also accompanied by a relative increase in USF2 protein levels. In keeping with this Smarca4 siRNA which has resulted in a significant decrease in Ldha mRNA levels (Figure 6E) is also characterised by relatively low Ldha protein levels. However DNMT1 siRNA which caused a relatively modest decrease in Ldha mRNA (Figure 6B) did not result in a change in protein levels. These results are representative of 3 independent experiments.

**Supplementary Figure 9**