

1 File Name: Supplementary Data 1
2 Description: Proteins identified in mESCs and MEFs. S1 Proteomes sheet: Results from MaxQuant
3 containing all the proteins identified in mESCs and MEFs using trypsin. Protein intensities were
4 normalized with the LOESS function in the software Prostar.

5

6 File Name: Supplementary Data 2
7 Description: Protein isoforms identified in mESCs and MEFs. S2 All IDs trypsin-chymo sheet: Results
8 from MaxQuant containing all the protein isoforms identified in mESCs and MEFs resulting from the
9 combined analysis of trypsin and chymotrypsin data sets using the Ensembl database. S2 RMTs-
10 KMTs-KDMs: Detailed information for all the protein isoforms identified in arginine methyl-
11 transferases, lysine methyl-transferases and lysine de-methylases genes. All the remaining sheets
12 show comparisons between the experimental spectra and the predicted spectra (using Prosit) for
13 those unique peptides identified in the protein isoforms.

14

15 File Name: Supplementary Data 3
16 Description: Quantification by Parallel Reaction Monitoring of methyl-transferases and de-
17 methylases in mESCs and differentiated cell types. S3 PRM sheet: Monitored peptides were
18 quantified with Skyline and their abundances were summarized to calculate total protein intensity
19 values (log scale) in each sample. Differential analysis was performed with Prostar using a
20 moderated t-test (limma) (two-sided). Data was normalized using the LOESS function and missing
21 values (displayed in blue in the table) were imputed with the K-Nearest Neighbors (KNN) function.

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23 File Name: Supplementary Data 4
24 Description: Methylated residues and proteins identified in mESCs and MEFs. S4 Modifications
25 sheet: Results from MaxQuant containing all the Arg and Lys methylation modifications identified in
26 mESCs and MEFs. Arg methylation modifications are classified in different types of motifs. The
27 probability of a residue to be localized within a disordered region is estimated with the IUPRED and
28 ANCHOR scores. The intensities of all modifications were normalized with the LOESS function in
29 Prostar. Additional functional information is shown in yellow for all the reported modifications which
30 was annotated with Perseus software. S4 Residues sheet: information collapsed at the level of
31 residues (i.e. modified amino acids). S4 Proteins sheet: information collapsed at the level of
32 methylated proteins.

33

34 File Name: Supplementary Data 5
35 Description: GO enrichment analysis of identified methylated proteins. S5 Arg methylation sheet:
36 Over-representation of GO terms (complete biological processes) was done with PantherDB using as
37 input all the identified Arg methylated proteins. P-values were calculated with the Fisher's Exact test.
38 FDR was estimated for multiple testing correction. Only terms found over-represented are shown. S5
39 Lysine methylation sheet: Over-representation of GO terms (complete biological processes) was
40 done with PantherDB using as input all the identified Lys methylated proteins. P-values were
41 calculated with the Fisher's Exact test. FDR was estimated for multiple testing correction. Only terms
42 found over-represented are shown.

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44 File Name: Supplementary Data 6
45 Description: Motif analysis of Arg methylated residues. S6 Non canonical RG sheet: Motif analysis for
46 Arg methylation sites classified as non-canonical RG was done using MoMo. S6 Non canonical RG
47 sheet: Motif analysis for Arg methylation sites classified as non-RG was done using MoMo. In both
48 cases, the minimum number of occurrences was set to 8 and the p-value threshold was 0.000001. P-
49 values were calculated with the Fisher's Exact test (two-sided).

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51 File Name: Supplementary Data 7
52 Description: Stability and Abundance changes in mESCs and MEFs in response to Prmt5 and Ezh2
53 inhibitors. S7 Stability and Abundance sheet: Protein identification and quantification was done with
54 MaxQuant. For the analysis of the effect of individual inhibitors, proteins were considered regulated
55 when the $p.val < 0.01$ and $\log_2FC < -0.1$ or > 0.1 . To call a protein regulated with "both" inhibitors, a
56 protein must be regulated with the above criteria in at least one inhibitor and in the other inhibitor
57 the change must be $\log_2FC < -0.1$ or > 0.1 and the $p.val < 0.05$. P-values were calculated using limma
58 (two-sided) and adjusted for multiple testing with Benjamini-Hochberg.

59

60 File Name: Supplementary Data 8
61 Description: GO enrichment analysis of proteins with altered thermal stability upon Prmt5 inhibition.
62 S8 GO analysis sheet: Over-representation of GO terms (complete biological processes) was done
63 with PantherDB using as input proteins with increased or decreased thermal stability in response to
64 GSK595 or GSK591 in mESC. P-values were calculated with the Fisher's Exact test. FDR was estimated
65 for multiple testing correction.

66

67 File Name: Supplementary Data 9
68 Description: GO enrichment analysis of proteins with altered thermal stability upon Ezh2 inhibition.
69 S9 GO analysis sheet: Over-representation of GO terms (complete biological processes) was done
70 with PantherDB using as input proteins with increased or decreased thermal stability or abundance
71 in response to Ezh2 inhibitors in mESC and MEFs. P-values were calculated with the Fisher's Exact
72 test. FDR was estimated for multiple testing correction.

73

74 File Name: Supplementary Data 10
75 Description: Analysis of Ezh2 interacting proteins in mESCs. S10 Interactors Analysis: Results from
76 the statistical analysis (limma) using Prostar showing the enrichment ratios, and p-values compared
77 to negative controls (IgG) for all the identified proteins in mESCs treated with DMSO or GSK126. S10
78 GSK126 vs DMSO Analysis: Results from the statistical analysis (limma) comparing the levels of Ezh2
79 interactors between mESCs treated with GSK126 and DMSO. Proteins with partially observed values
80 (POV) were imputed with the SLSA function in Prostar and are shown in blue. Proteins with missing
81 on entire condition (MEC) were imputed with the DET quantile function in Prostar and are shown in
82 orange. P-values were calculated using limma (two-sided) and adjusted for multiple testing with
83 Benjamini-Hochberg.

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