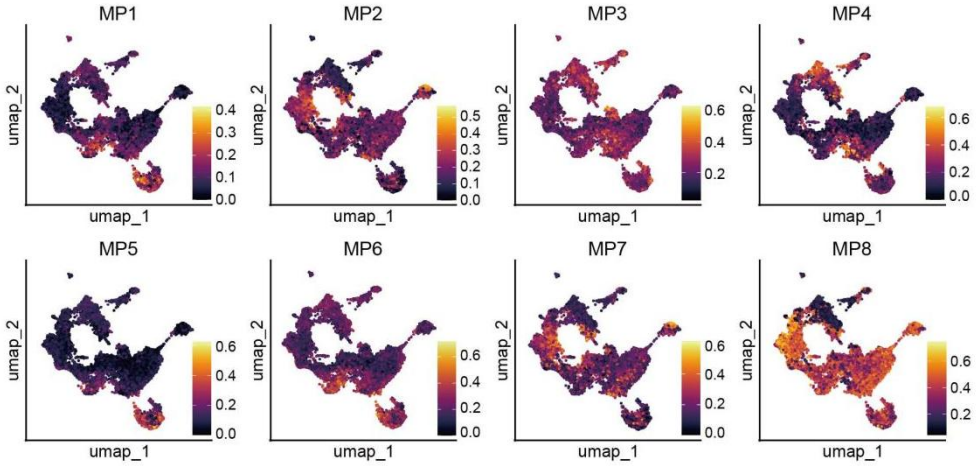
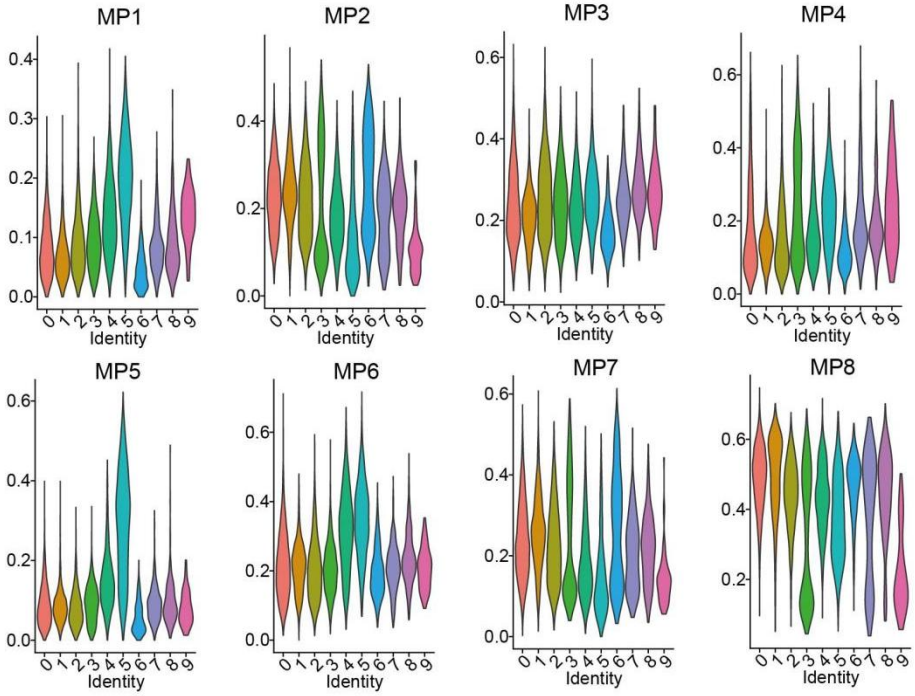
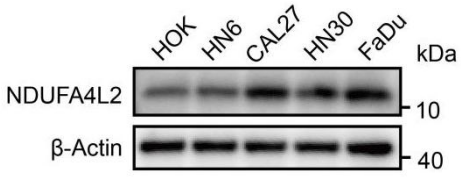


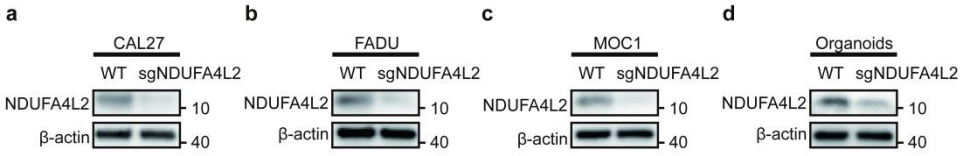
Supplementary Fig. 1 FeaturePlots. FeaturePlots displaying the expression of each module.



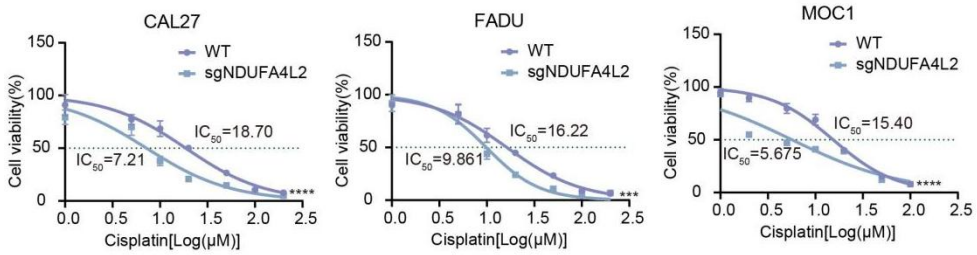
Supplementary Fig. 2 Violin plots. Violin plots illustrating the expression of each module across clusters.



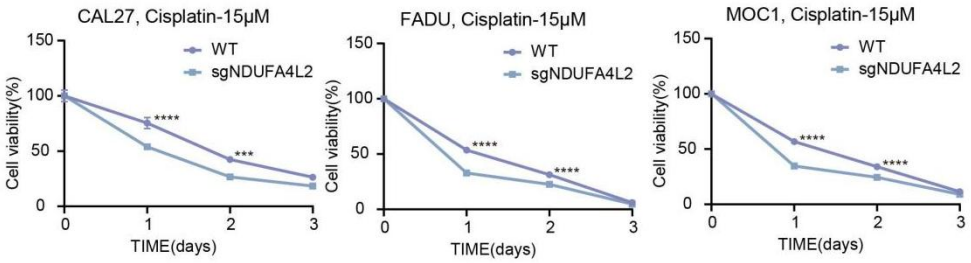
Supplementary Fig. 3 NDUFA4L2 Expression in HNSCC Cell Lines. Western blot analysis of NDUFA4L2 in HOK keratinocytes and HNSCC cell lines (HN30, HN6, FaDu, CAL27)



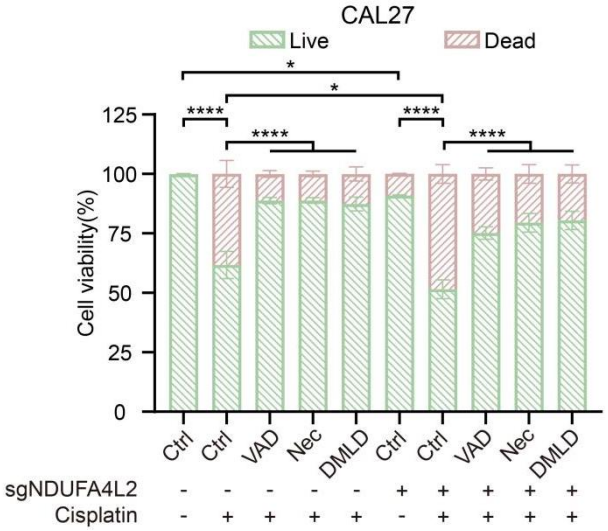
Supplementary Fig. 4 Knockout verification of NDUFA4L2. The situation of CAL27**(a)**, FaDu**(b)**, MOC1**(c)** cells and Organoids**()** transfected with sgRNA (NDUFA4L2) was detected by Western blotting.



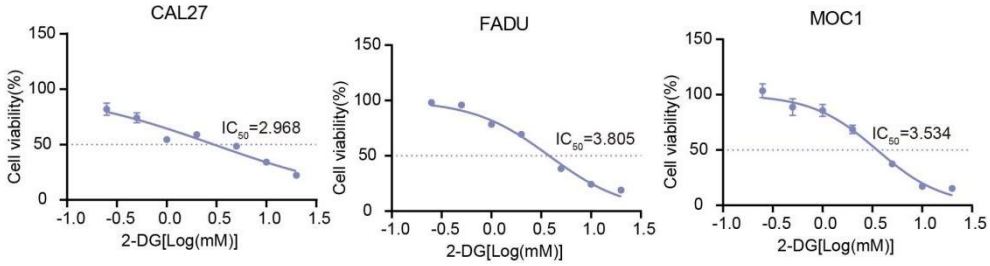
Supplementary Fig. 5 Measurement of the Half Inhibitory Concentration (IC_{50}) for cisplatin in wild-type vs. NDUFA4L2-KO cells. Wild-type and NDUFA4L2-KO CAL27, FaDu and Moc1 cells were treated with 0, 1, 5, 10, 20, 50, 100 μM cisplatin. Cell proliferation was assessed using CCK8 assay after 24 hours (n = 3, biological replicates); IC_{50} values were calculated using GraphPad Prism 10. The data are expressed as the mean ± *S.D.* Statistical significance is denoted by *P < 0.05, **P < 0.01, ***P < 0.001 and ****P < 0.0001, as determined by a t-test.



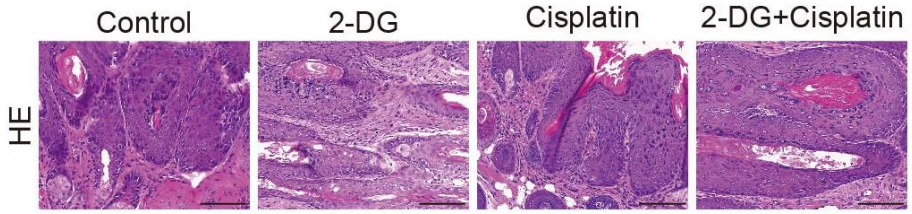
Supplementary Fig. 6 Three-day cell viability of wild-type vs. NDUFA4L2-KO cells with cisplatin. The cell viability of wild-type and NDUFA4L2-KO CAL27, FaDu, and Moc1 cells treated with cisplatin (15μM) was evaluated using the CCK8 assay on days 0, 1, 2, and 3 (n = 3, biological replicates). The data are expressed as the mean ± *S.D.* Statistical significance is denoted by *P < 0.05, **P < 0.01, ***P < 0.001 and ****P < 0.0001, as determined by a t-test.



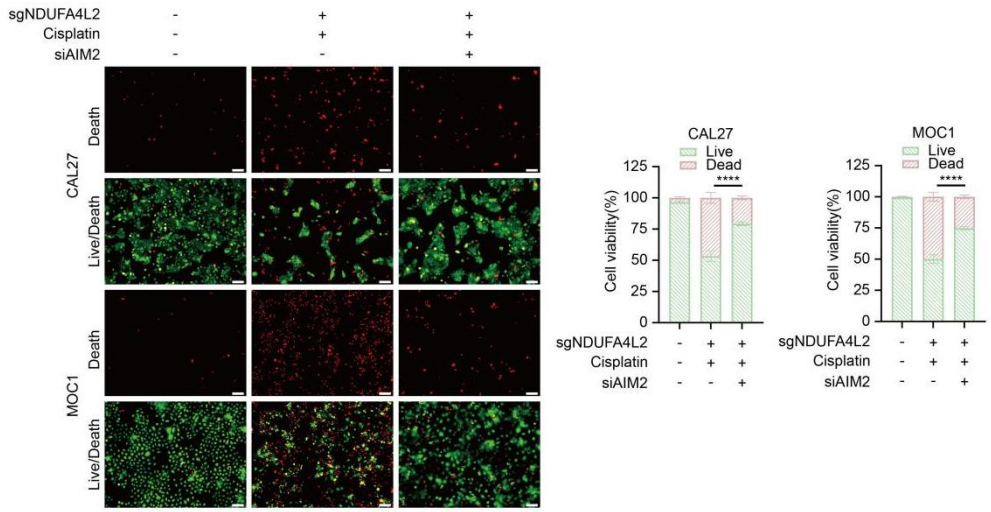
Supplementary Fig. 7 Viability analysis of CAL27 cells after 24-hour treatment with cisplatin and inhibitors. Live/dead assay (red = dead, green = live) in control and NDUFA4L2-KO CAL27 cells treated for 24 h with: cisplatin alone (15 μM), or combined with Z-VAD-FMK (25 μM), necrostatin-1 (20 μM), or Ac-DMLD-cmk (20 μM)(n = 3, biological replicates). The data are expressed as the mean ± *S.D.* Significance was determined by two-way ANOVA (*P < 0.05, **P < 0.01, ***P < 0.001 and ****P < 0.0001).



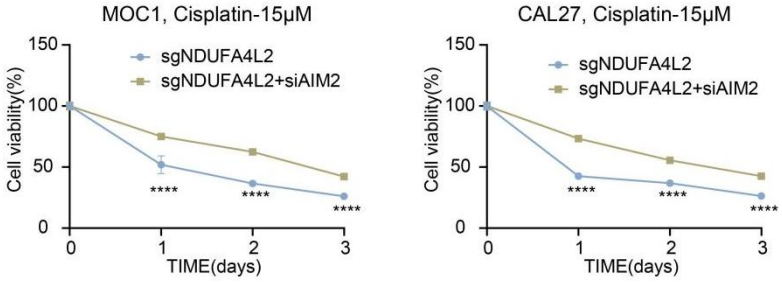
Supplementary Fig. 8 Measurement of the Half Inhibitory Concentration (IC_{50}) for 2-DG in cells. CAL27, FaDu and Moc1 cells were treated with 0, 0.25, 0.5, 1, 2, 5, 10, 20 mM 2-DG. Cell proliferation was assessed using CCK8 assay after 24 hours (n = 3, biological replicates); IC_{50} values were calculated using GraphPad Prism 10. All experiments were conducted in triplicate.



Supplementary Fig. 9 Hematoxylin and Eosin staining (H&E staining) results of *Tgfbr1/Pten* 2cKO tumors. H&E staining results of *Tgfbr1/Pten* 2cKO tumors across treatment groups (scale bar: 100 μm; n = 3, biological replicates).



Supplementary Fig. 10 Viability analysis. Live/dead assay (red = dead, green = live) in control, NDUFA4L2-KO and NDUFA4L2-KO with AIM2 knockdown CAL27 cells and MOC1 cells treated for 48 h with: cisplatin (15 μM))(n = 3, biological replicates). The data are expressed as the mean ± *S.D.* Significance was determined by two-way ANOVA (*P < 0.05, **P < 0.01, ***P < 0.001 and ****P < 0.0001).



Supplementary Fig. 11 Three-day cell viability of NDUFA4L2-KO vs. NDUFA4L2-KO and AIM2 knockdown cells with cisplatin. The cell viability of wild-type and NDUFA4L2-KO CAL27, FaDu, and MOC1 cells treated with cisplatin (15μM) was evaluated using the CCK8 assay on days 0, 1, 2, and 3 (n = 3, biological replicates). The data are expressed as the mean ± *S.D.* Statistical significance is denoted by *P < 0.05, **P < 0.01, ***P < 0.001 and ****P < 0.0001, as determined by a *t*-test.

Western blotting raw data

Fig. 1

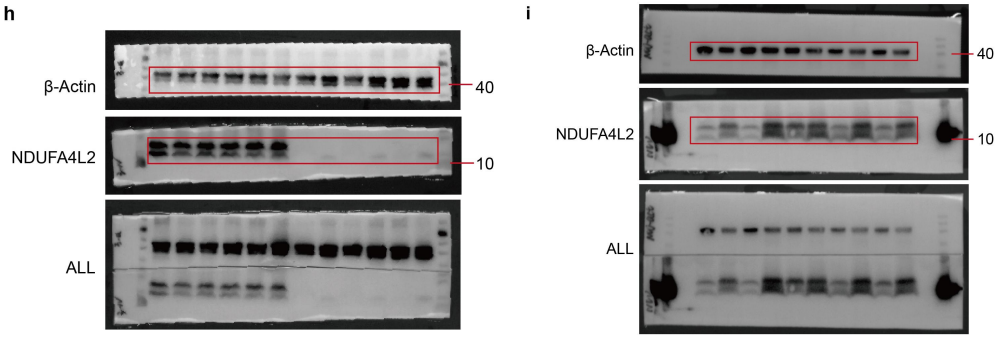
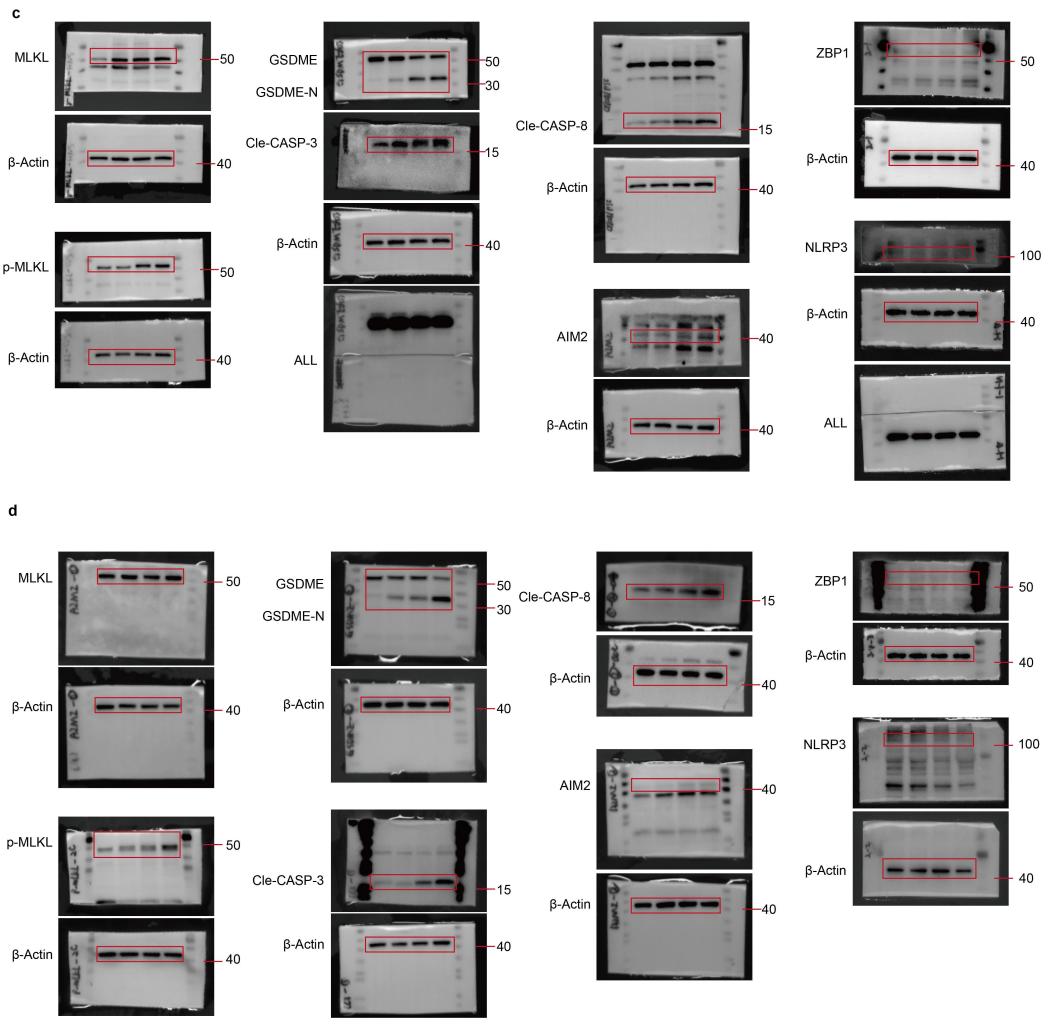
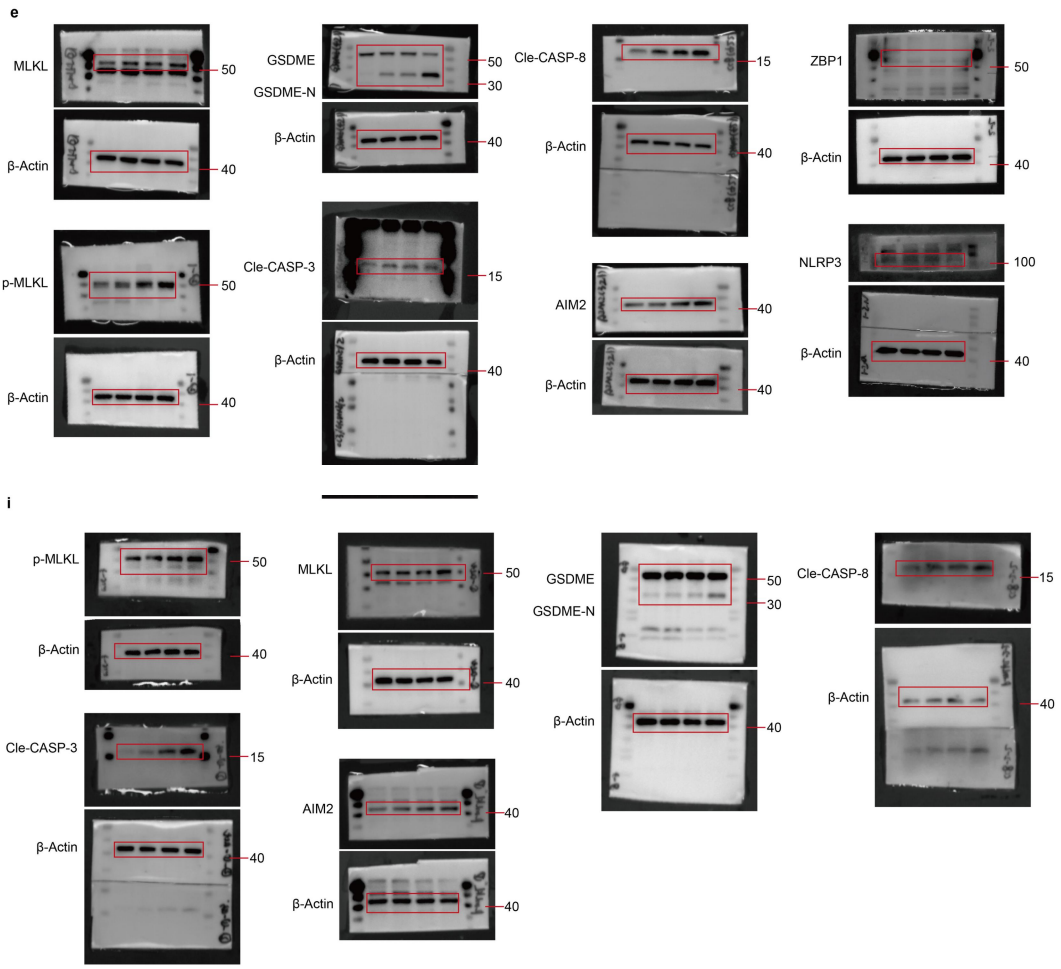


Fig. 2

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β-Actin
40
AIM2
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β-Actin
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NLRP3
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β-Actin
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i
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β-Actin
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Fig. 3

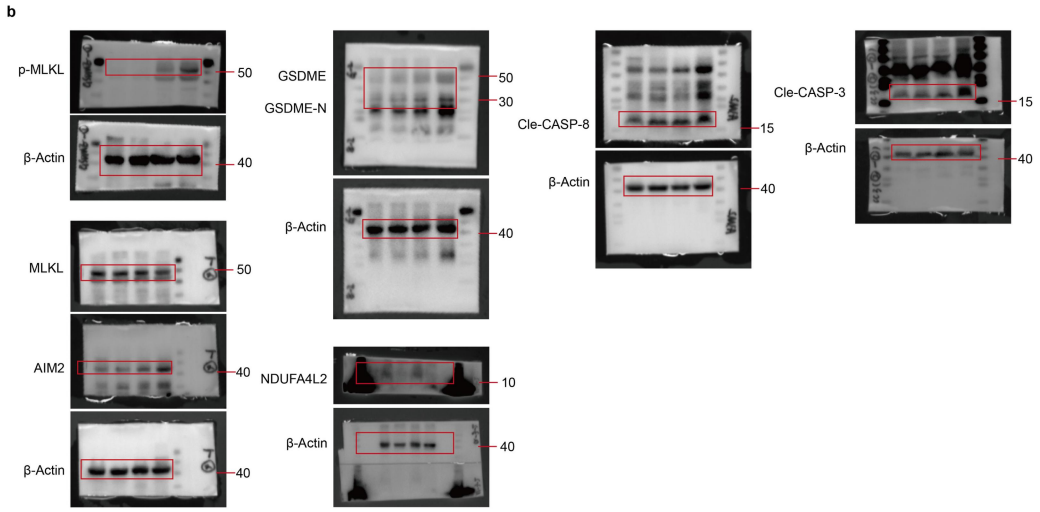
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Fig. 4

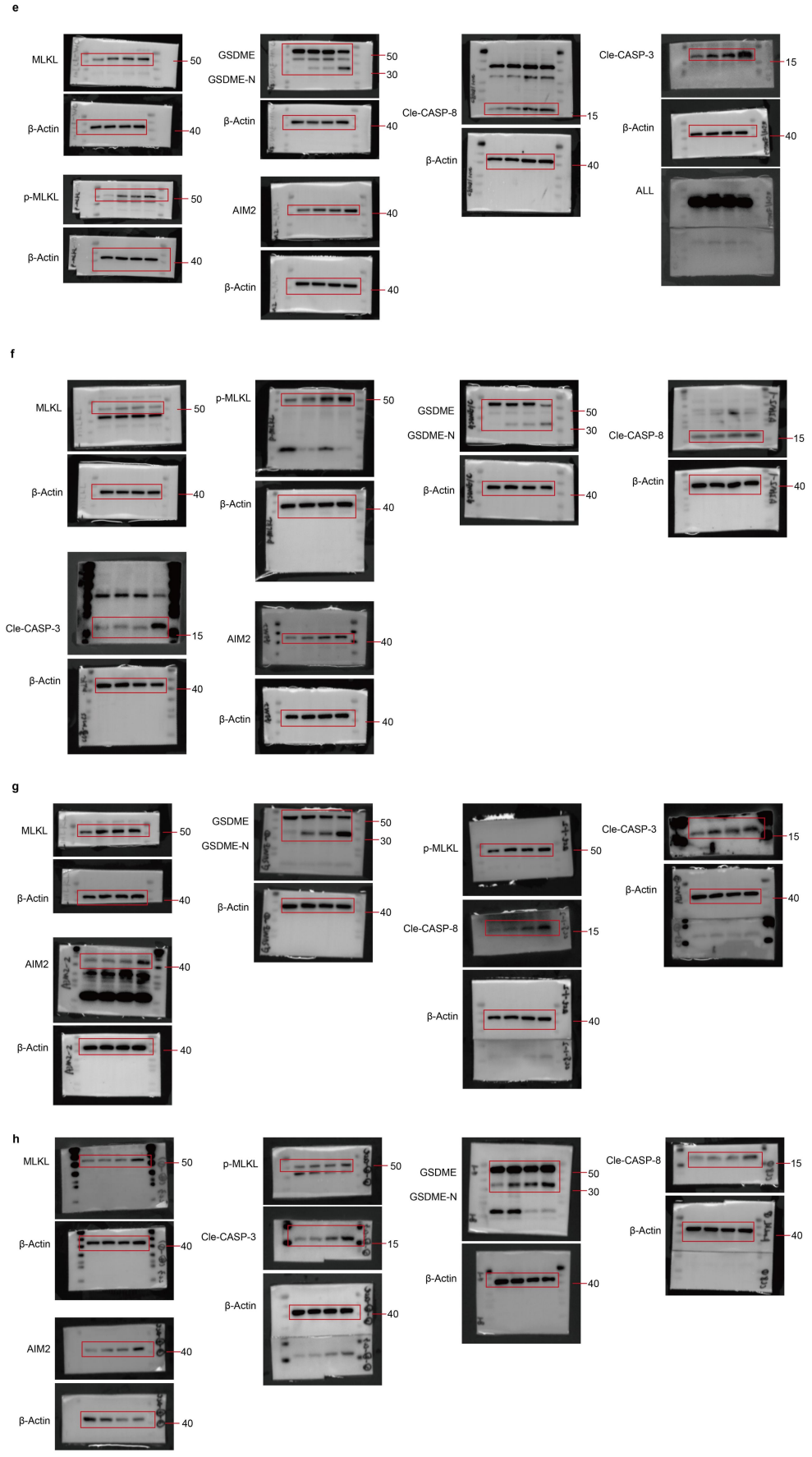
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Fig. 5

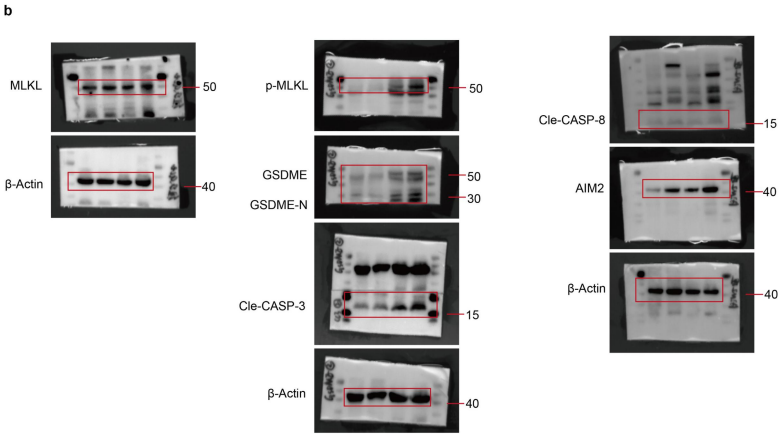
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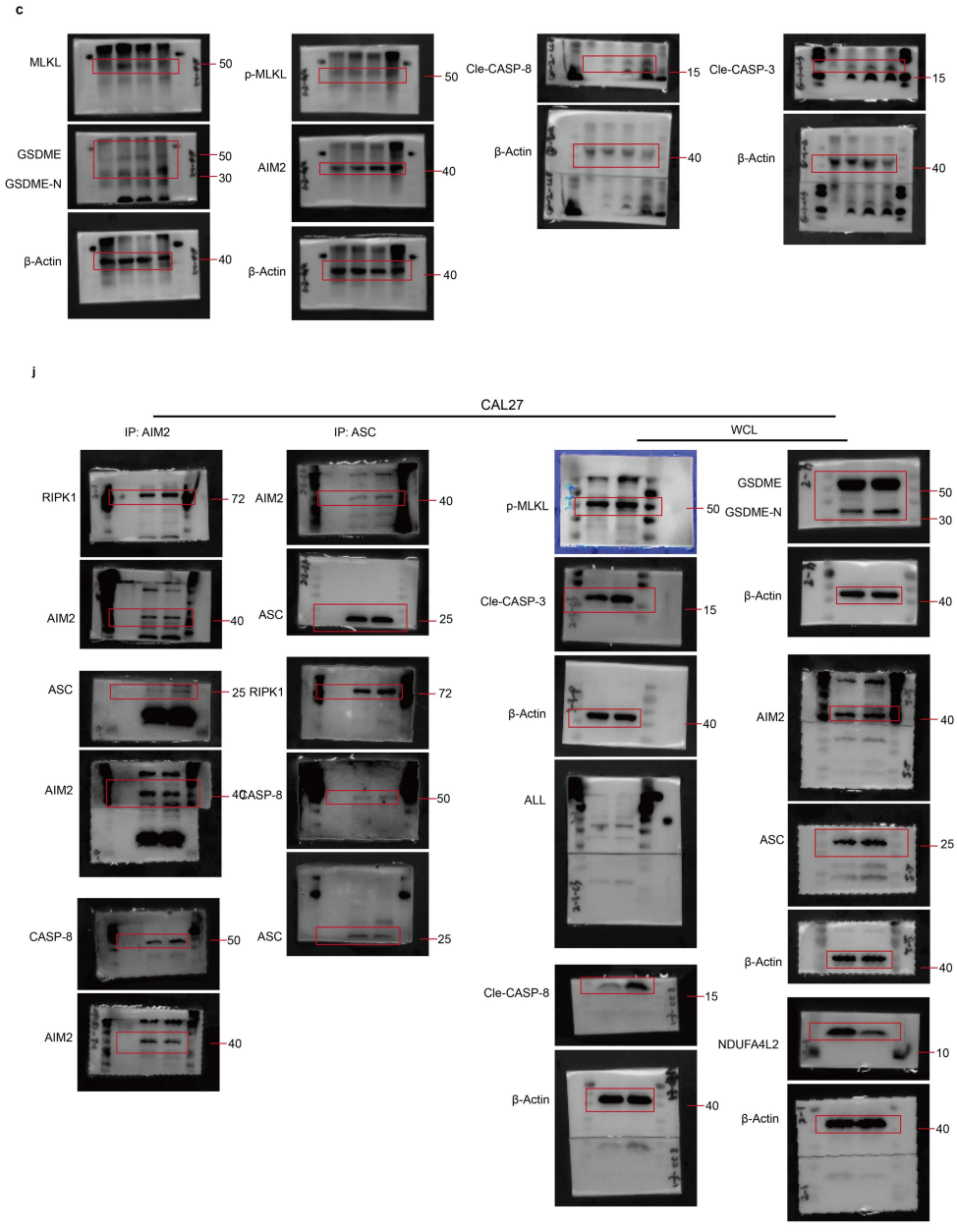
Fig. 6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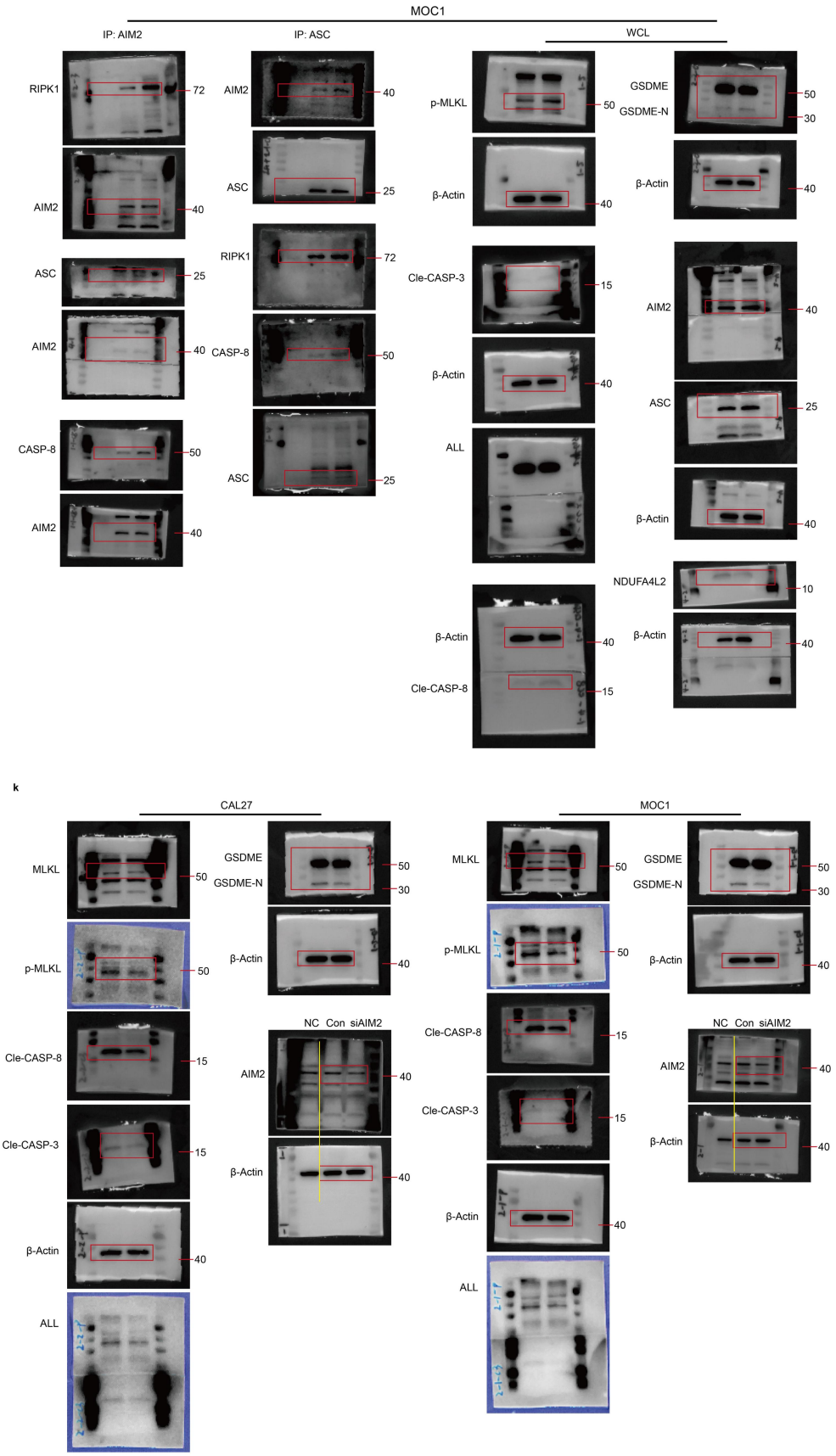
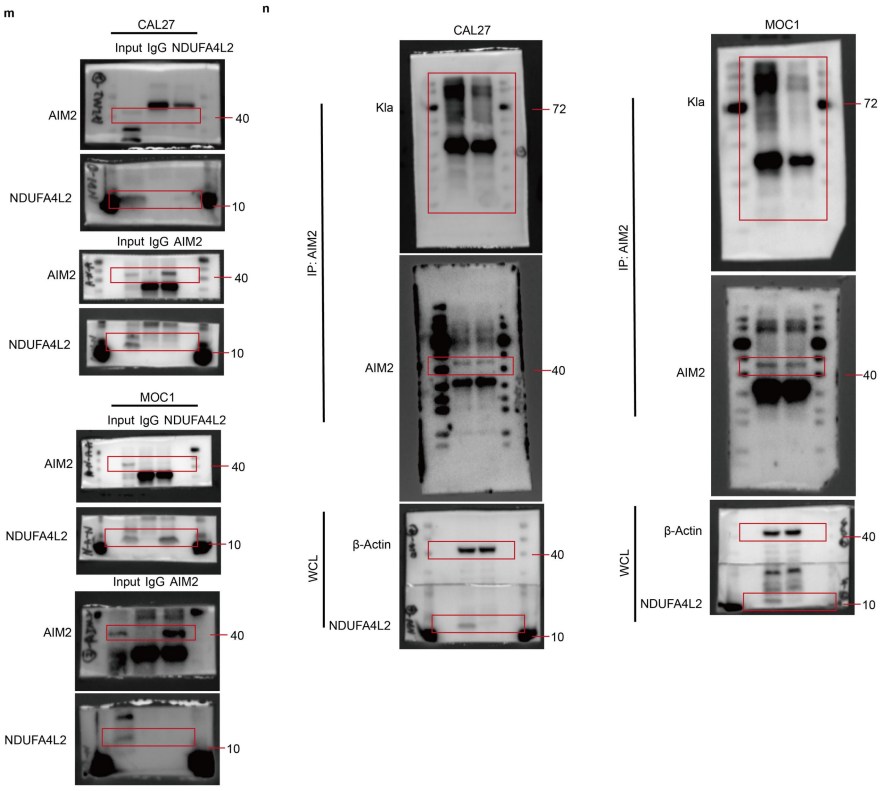
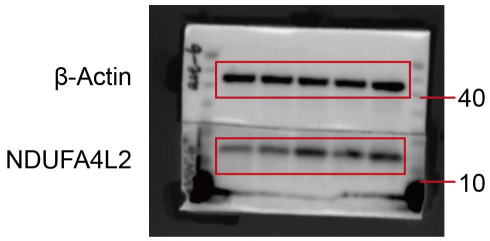


In Fig. 6k, the first lane of the AIM2 Western blot analysis image corresponded to an empty vector plasmid. Therefore, this lane was not included in the main text. Only the second and third lanes, representing the control group and the AIM2 knockdown group, respectively, were presented.



Supplementary Fig. 3



Supplementary Fig. 4