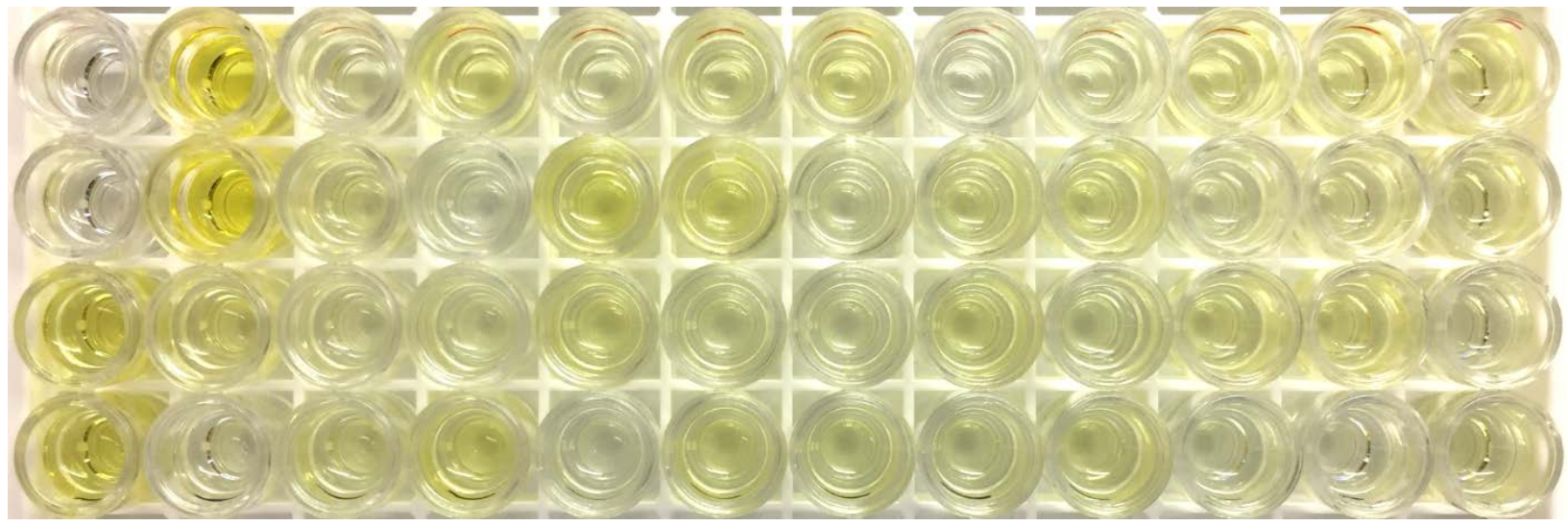
A

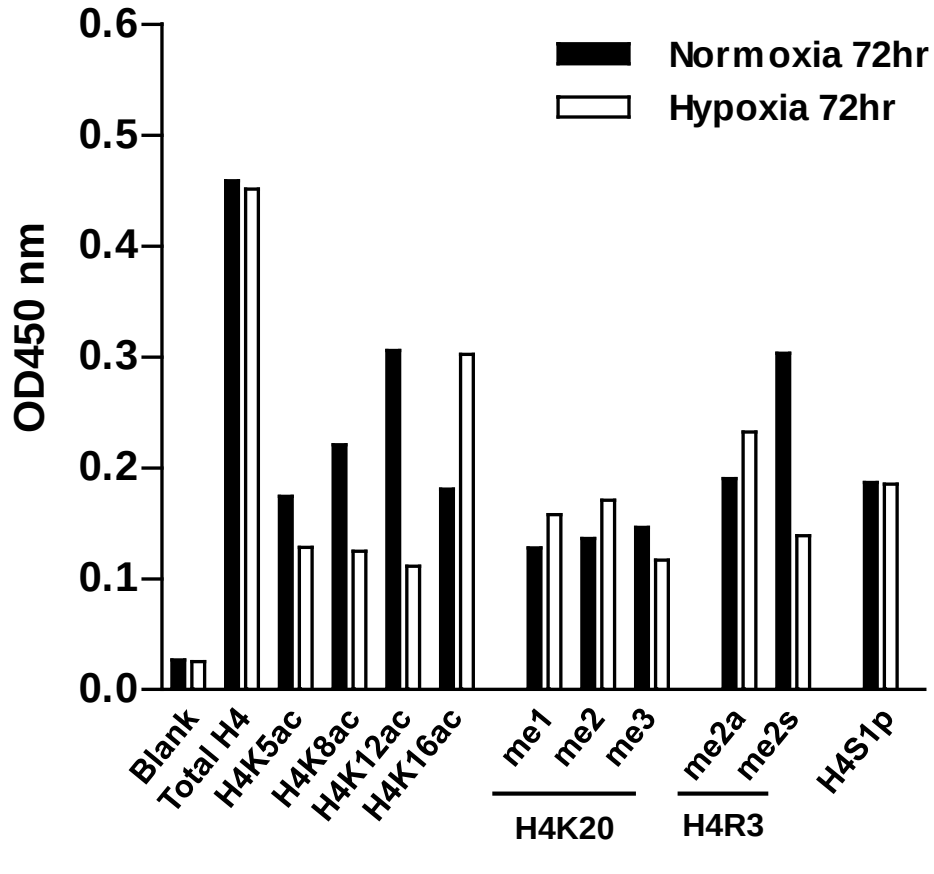
Histone H3 modification



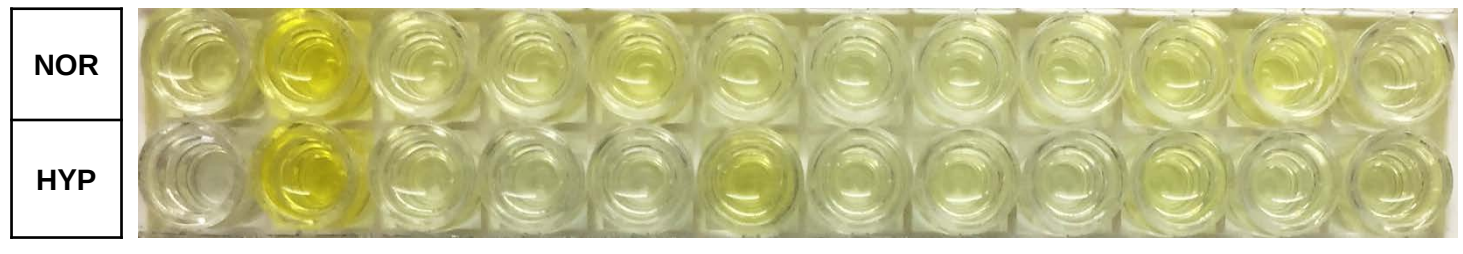
NOR	Blank	Control 25ng	K4me2	K9me1	K9me3	K27 me2	K36 me1	K36 me3	K79 me2	K9ac	K18ac	Ser10p
HYP	Blank	Control 25ng	K4me2	K9me1	K9me3	K27 me2	K36 me1	K36 me3	K79 me2	K9ac	K18ac	Ser10p
NOR	Total H3	K4me1	K4me3	K9me2	K27 me1	K27 me3	K36 me2	K79 me1	K79 me3	K14ac	K56ac	Ser28p
HYP	Total H3	K4me1	K4me3	K9me2	K27 me1	K27 me3	K36 me2	K79 me1	K79 me3	K14ac	K56ac	ser28p

B

H4 modification



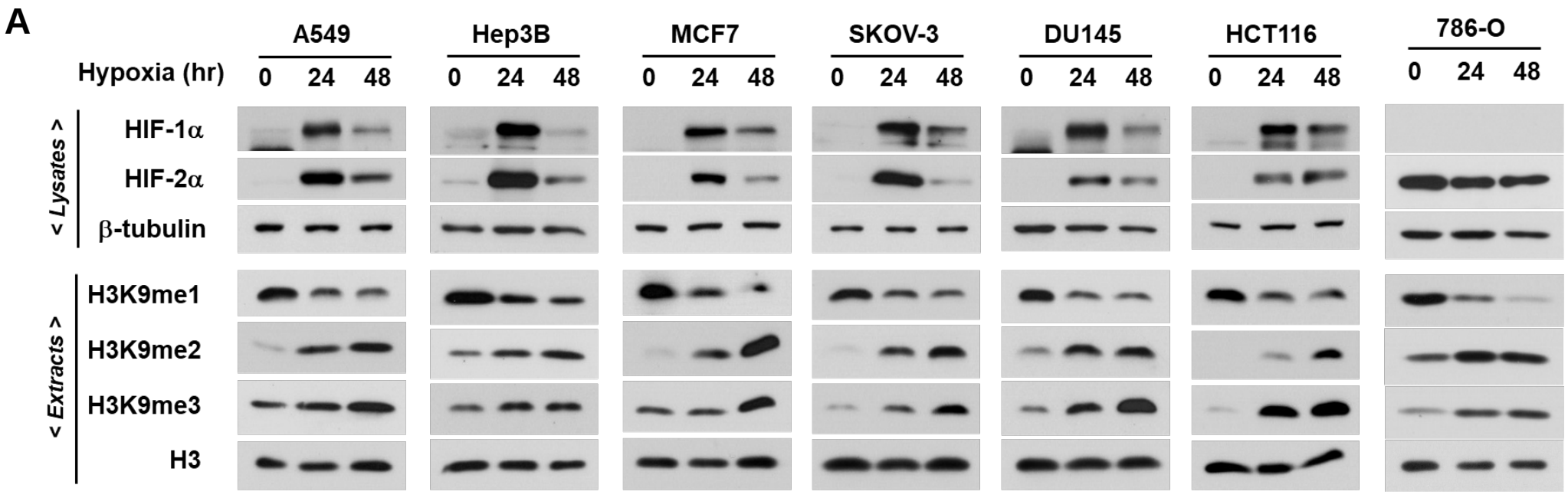
H4 modification

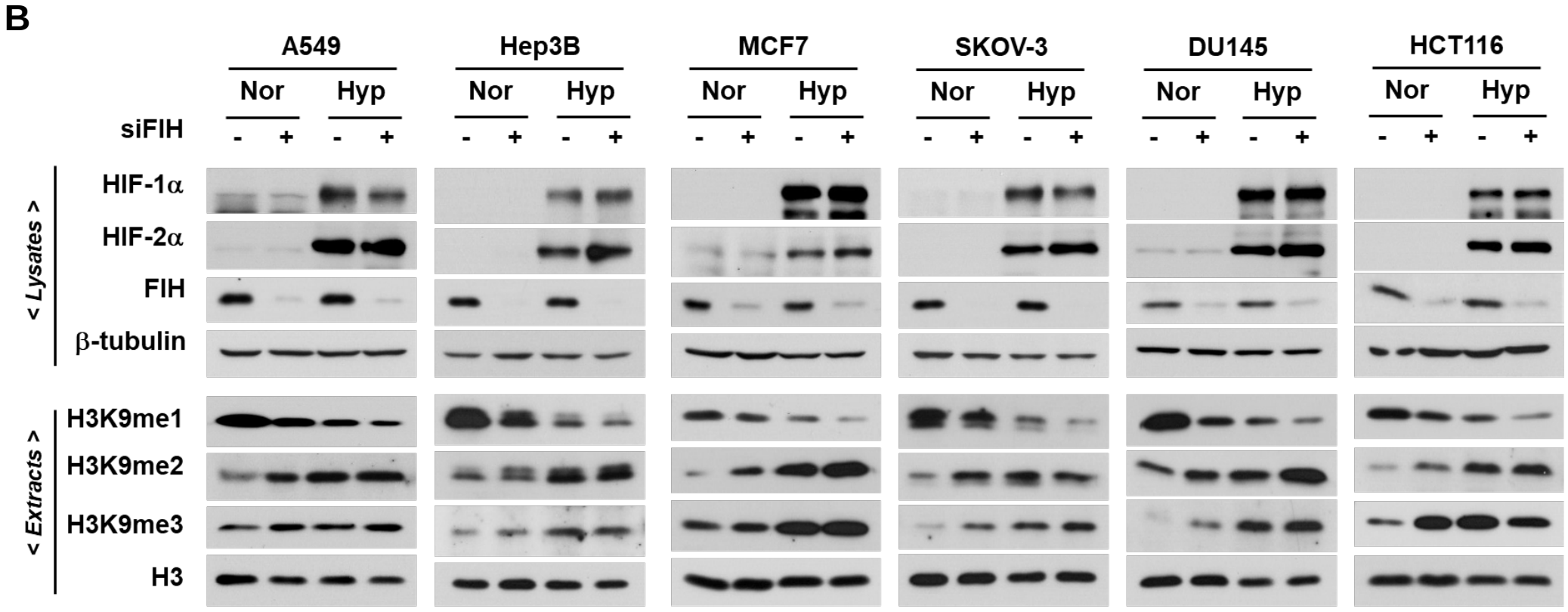


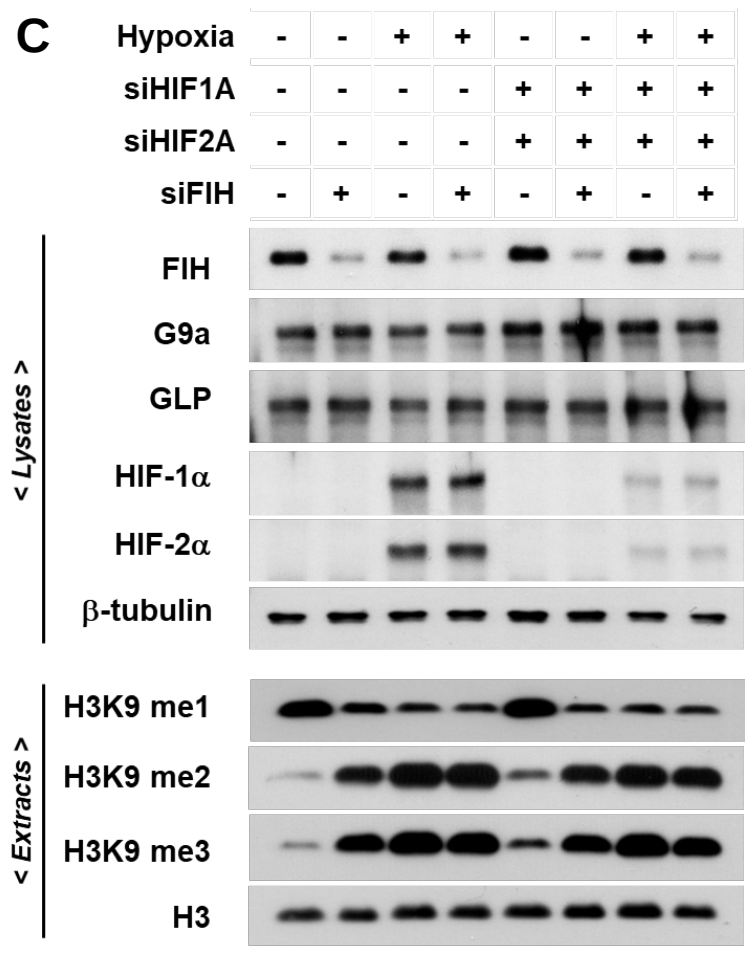
NOR	Control 25ng	Total H4	K5ac	K8ac	K12 ac	K16 ac	K20 me1	K20 me2	K20 me3	R3m e2a	R3m e2s	Ser 1p
HYP	Blank	Total H4	K5ac	K8ac	K12 ac	K16 ac	K20 me1	K20 me2	K20 me3	R3m e2a	R3m e2s	Ser 1p

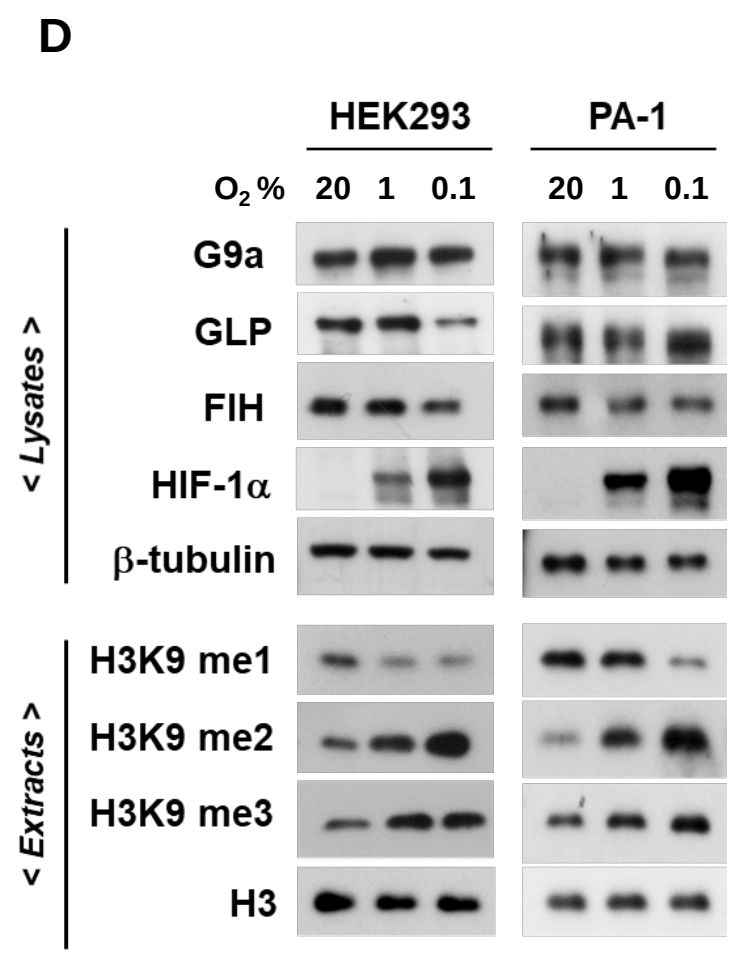
Fig. S1. Screening for histone H3 and H4 modifications

A, Representative photograph of microplate for H3 modification assay. H3 modifications were measured using the EpiQuik H3 Modification Muliplex Assay Kit. Histone extract (25 ng of protein) was used per well and experiments were performed according to manufacturers' protocol. **B,** H4 modifications were measured using EpiQuik H4 Modification Muliplex Assay Kit. Histone extracts were prepared from HEK293 cells which were incubated under normoxia (NOR) or hypoxia (HYP) for 72 hr. Histone extract (200 ng of protein) was used per well and experiments were performed according to manufacturers' protocol. Representative photograph of microplate for H4 modification assay (Left). Bar graph represents mean value of OD450 for indicated modification (Right). Two independent assays were performed.









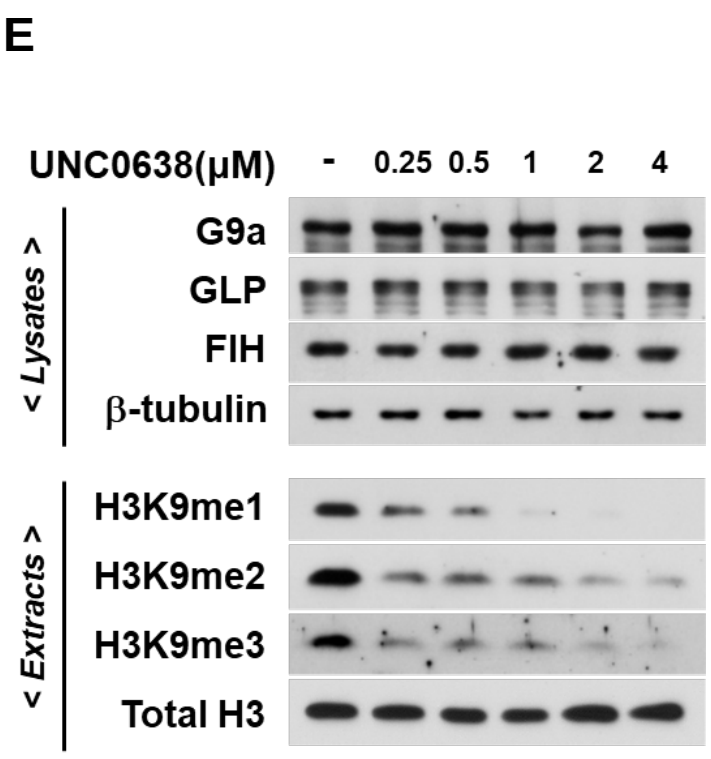


Fig. S2. FIH inactivates G9a and GLP O_2-dependently

A, Various cell lines (A549, Hep3B, MCF7, SKOV-3, DU145, HCT116, and 786-O) were incubated under normoxia or hypoxia for 24 or 48 hr, and the status of histone H3K9 methylation was analyzed by immunoblotting. **B,** Various cell lines were transfected with a FIH-silencing siRNA and incubated under normoxia or hypoxia for 24 hr. Cell lysates and histone extracts were subjected to immunoblotting. **C,** HIF-1α and HIF-2α both were knocked down in HEK293 cells with or without FIH knockdown, and incubated under normoxia or hypoxia for 24 hr. H3K9 methylation status was measured by immunoblotting. **D,** HEK293 and PA-1 cells were incubated under 20%, 1%, or ~0.1% O_2 for 24 hr. Cell lysates and histone extracts were subjected to immunoblotting. **E,** HEK293 cells were treated with UNC0638 at the indicated concentrations for 48 hr. Histones were extracted and methylation levels of H3K9 were measured by immunoblotting.