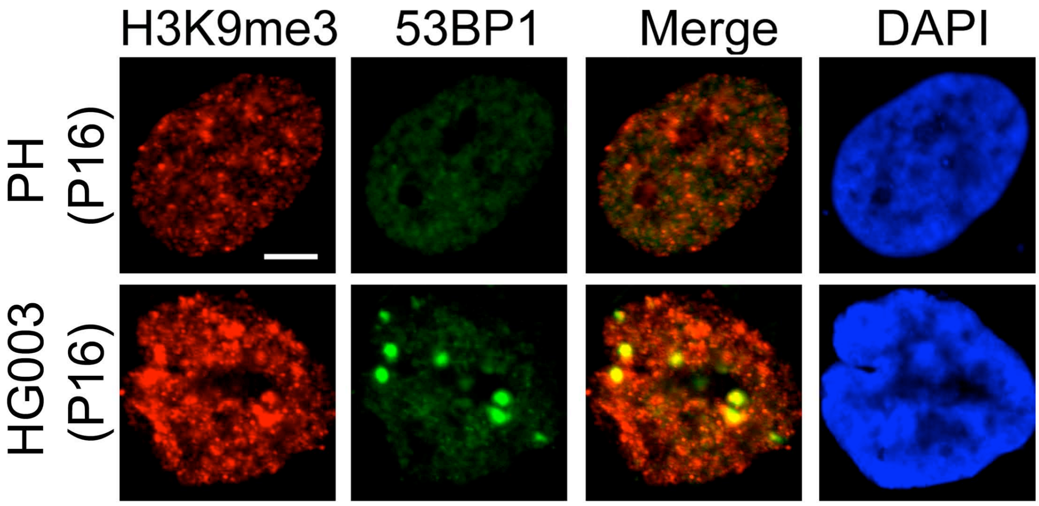
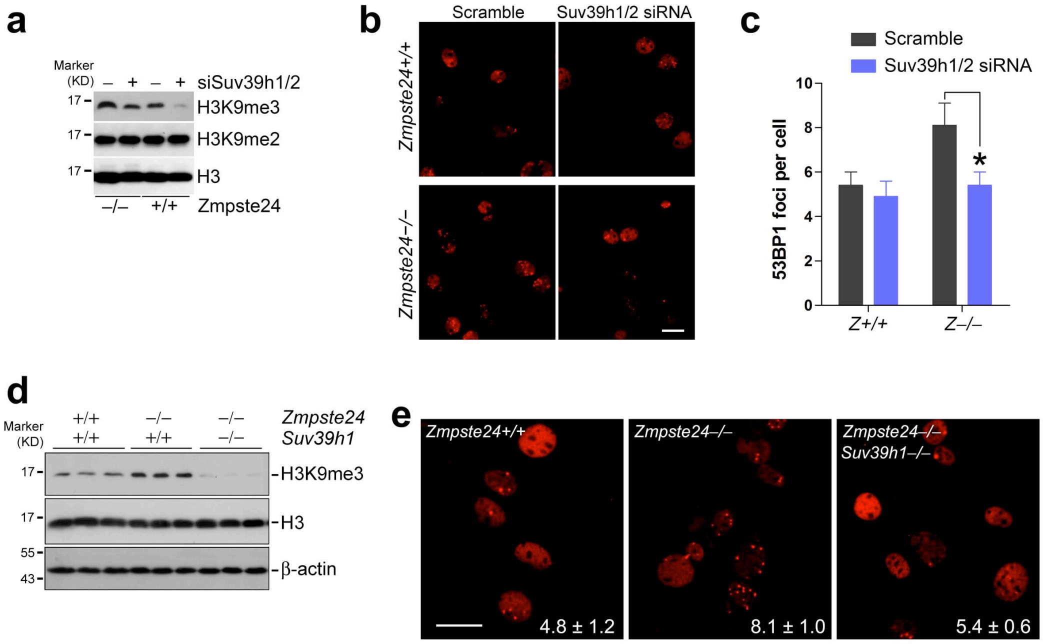
Supplementary Figure S1



Supplementary Figure S1: Defective heterochromatin repair in HGPS progeroid cells

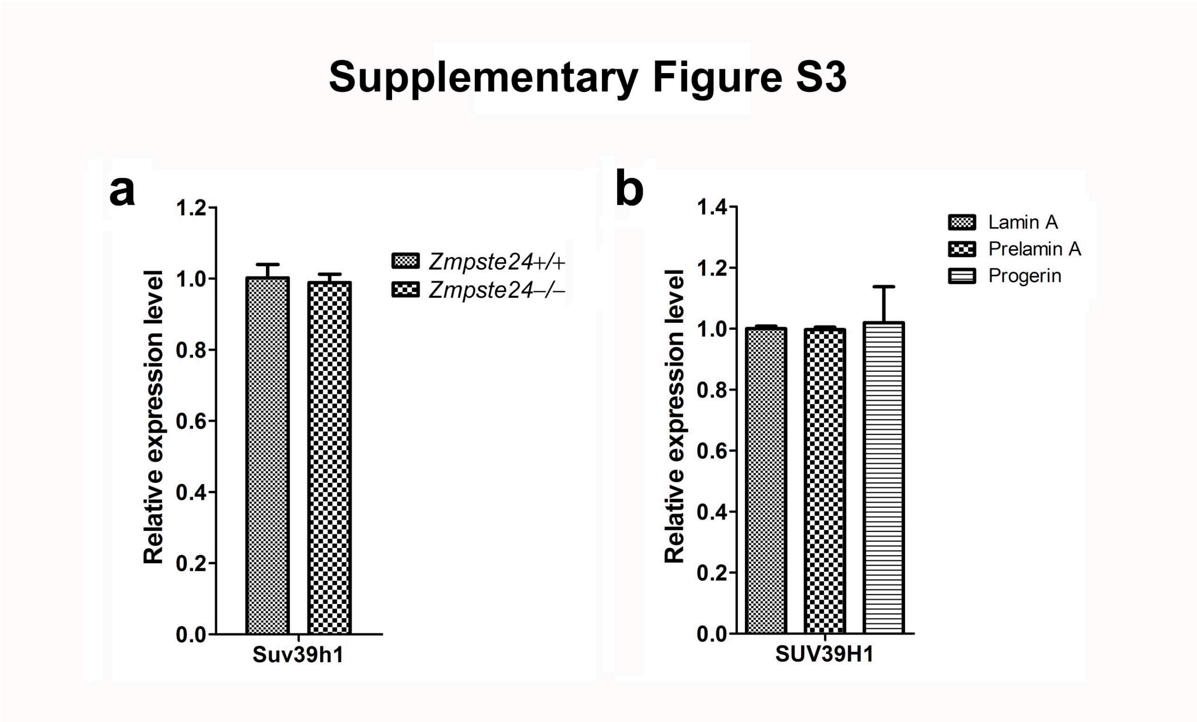
Immunofluorescence staining of H3K9me3 and 53BP1 in PH and HGADFN003 (HG003) cells at 24 h after γ-irradiation. Scale bar, 10μm.

Supplementary Figure S2



Supplementary Figure S2: Knocking down or deleting Suv39h1 rescues defective DNA repair in *Zmpste24*$^{-/-}$ cells.

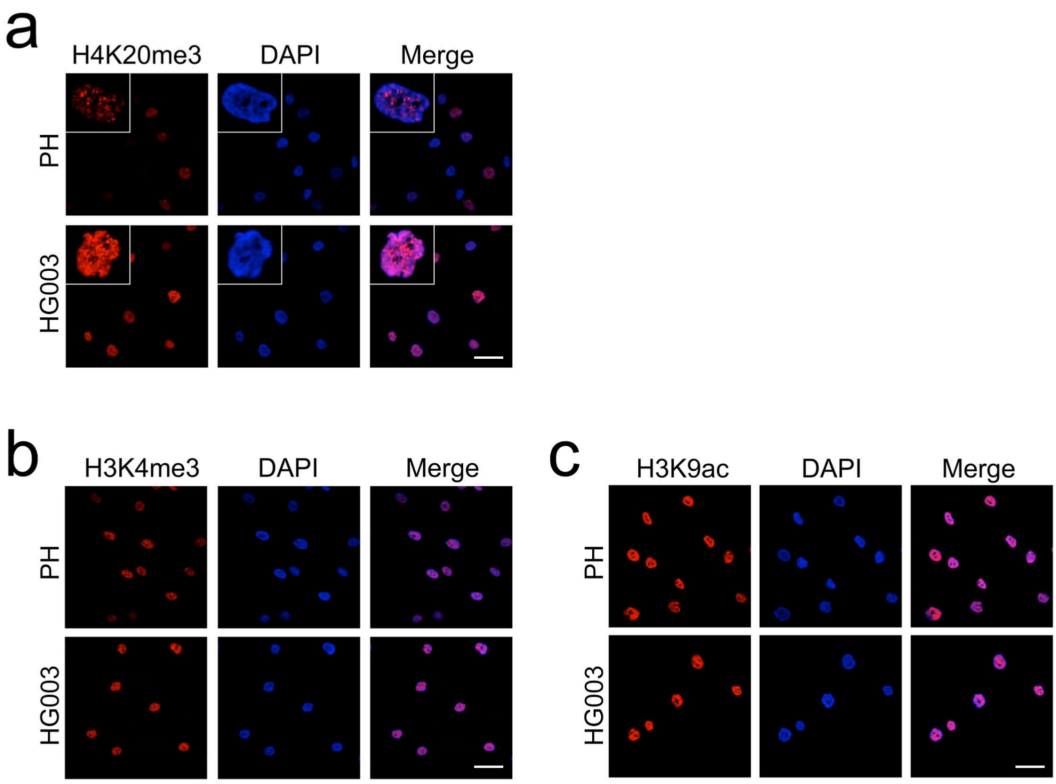
(**a**) H3K9me3 level in wild-type and *Zmpste24*$^{-/-}$ MEFs treated with Suv39h1/2 or scramble siRNA determined by Western blotting. (**b**) 53BP1 foci staining in wild-type and *Zmpste24* null MEFs treated with Suv39h1/2 or scramble siRNA 24 h after 5 Gy of γ-irradiation. Scale bar, 50 μm. (**c**) Quantification of 53BP1 foci 24 h after 5 Gy of γ-irradiation in at least 200 cells in wild-type and *Zmpste24*$^{-/-}$ MEFs, with/without Suv39h1/2 siRNA. Data represent mean ± s.e.m., n > 200. **P* < 0.05, 2-tailed *t*-test. (**d**) Representative immunoblot showing downregulated H3K9me3 in *Zmpste24*$^{-/-}$/*Suv39h1*$^{-/-}$ MEFs. (**e**) Representative immunofluorescence staining showing 53BP1 foci 24 h after γ-irradiation in *Zmpste24*$^{-/-}$/*Suv39h1*$^{-/-}$, *Zmpste24*$^{-/-}$ and wild-type cells. 53BP1 foci per cell were quantified in at least 200 cells. Data represent mean ± s.e.m., n > 200. *P* < 0.05, 2-tailed *t*-test, *Zmpste24*$^{-/-}$/*Suv39h1*$^{-/-}$ Vs *Zmpste24*$^{-/-}$ MEFs. Scale bar, 50 μm.



Supplementary Figure S3: SUV39H1 mRNA level in progeroid cells

(**a**) Real-time PCR analyses of Suv39h1 mRNA level in three lines of *Zmpste24*$^{-/-}$ MEFs compared with wild-type controls. Data represent mean ± s.e.m., n = 3. $P > 0.05$, 2-tailed *t*-test. (**b**) Real-time PCR analyses of SUV39H1 mRNA level in HEK293 cells transfected with lamin A, prelamin A or progerin. Data represent mean ± s.e.m., n = 3. $P > 0.05$, 2-tailed *t*-test.

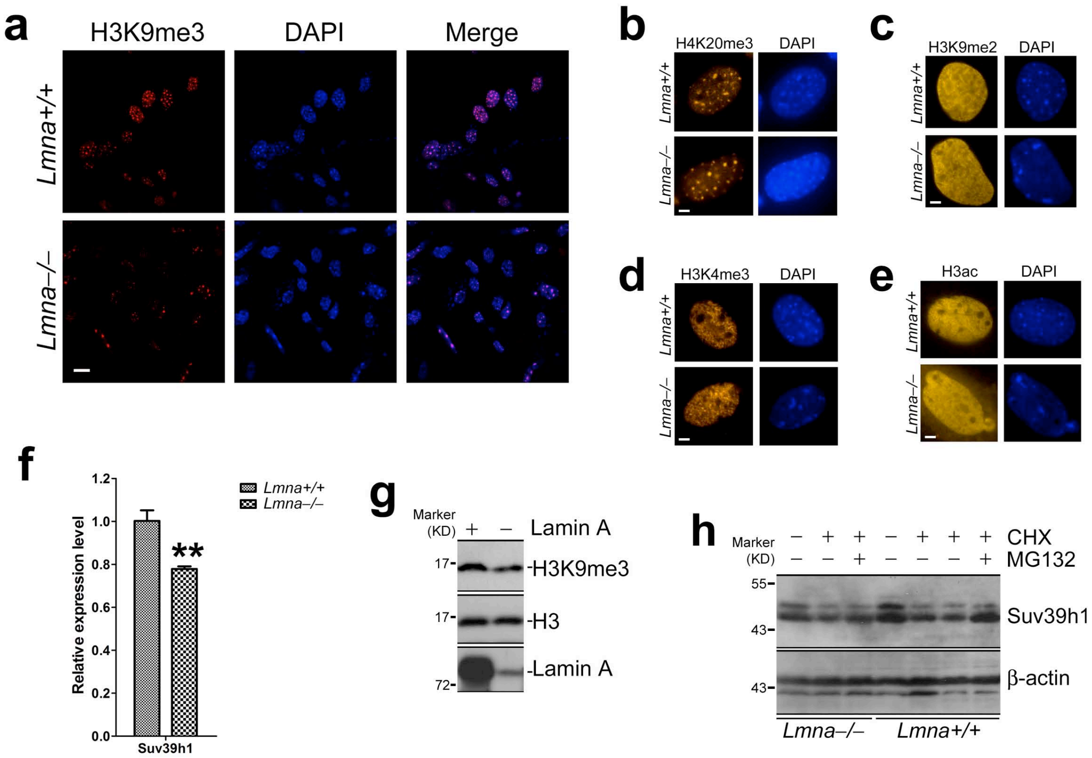
Supplementary Figure S4



Supplementary Figure S4: Histone modifications in progeroid cells

Representative photos of immunofluorescence staining of H4K20me3 (**a**), H3K4me3 (**b**) and H3K9ac (**c**) in PH and HGADFN003 (HG003) cells at passage 16. Scale bar, 40 µm.

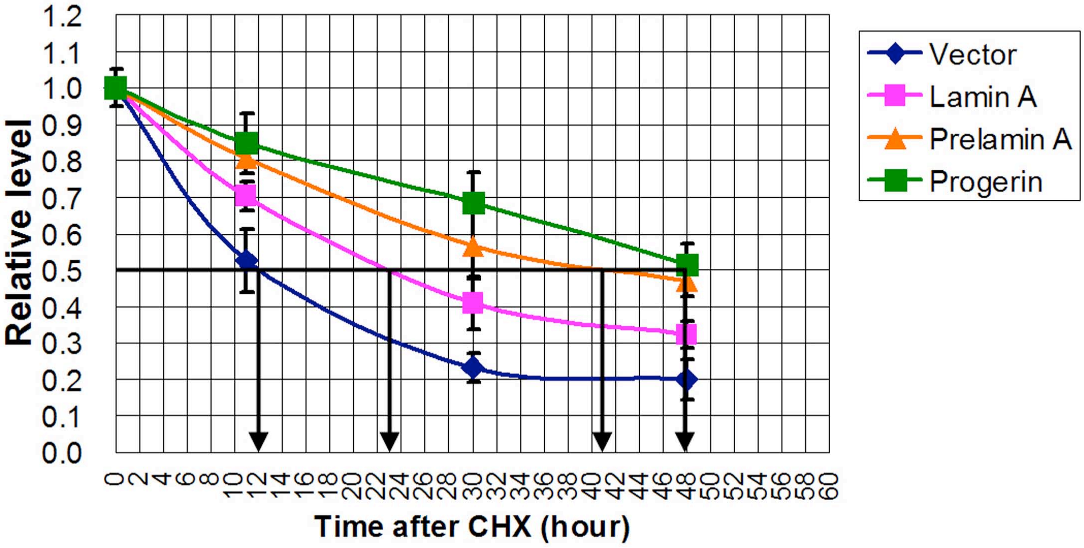
Supplementary Figure S5



Supplementary Figure S5: Levels of histone modifications and Suv39h1 in *Lmna* null cells

(**a**) Representative photos of immunofluorescence staining of H3K9me3 in *Lmna*$^{-/-}$ cells and wild-type controls from littermate. Scale bar, 20 µm. (**b-e**) Representative photos of immunofluorescence staining of H4K20me3 (**b**), K3K9me2 (**c**), H3K4me3 (**d**) and acetyl H3 (**e**) in *Lmna* null and wild-type cells. Scale bar, 5 µm. (**f**) Real-time PCR analyses of Suv39h1 mRNA level in three lines of *Lmna* null MEFs and wild-type controls. Data represent mean ± s.e.m., n = 3. **$P < 0.01$, 2-tailed *t*-test. (**g**) Representative immunoblots showing upregulated H3K9me3 in HEK293 cells with ectopic lamin A. (**h**) Representative Western blotting of Suv39h1 in *Lmna* null and wild-type MEFs with CHX and MG132 treatment (30 µM, 6 h).

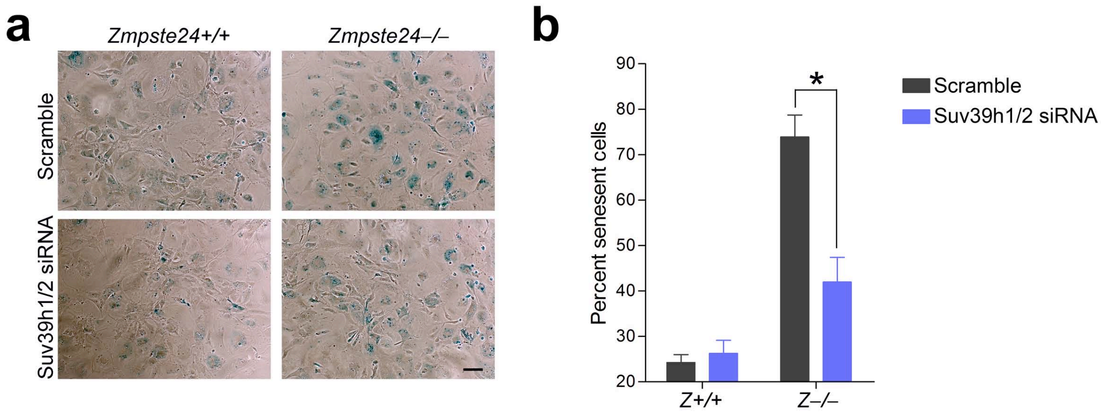
Supplementary Figure S6



Supplementary Figure S6: Degradation rate and half-life of GFP-SUV39H1 in HEK293 cells with ectopic A-type lamins.

The protein level of GFP-SUV39H1 in HEK293 cells with indicated ectopic A-type lamins was determined at various time points after CHX treatment. Half-life of GFP-SUV39H1 in different HEK293 cell lines is indicated by arrow. Data represent mean ± s.e.m., n = 3.

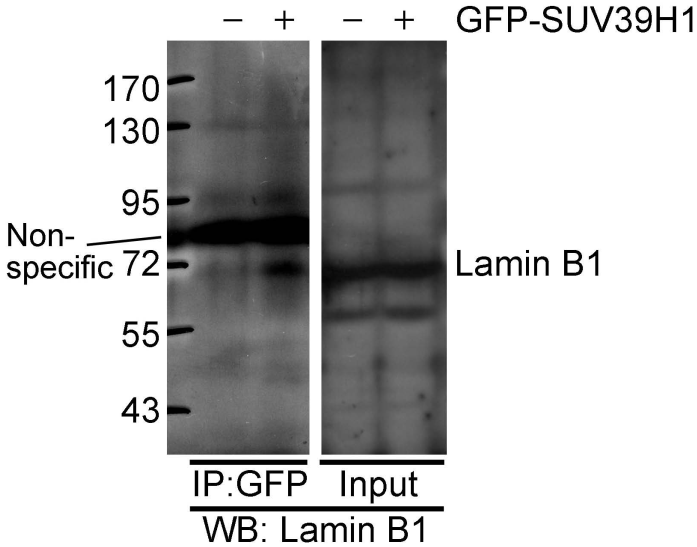
Supplementary Figure S7



Supplementary Figure S7: Knocking down Suv39h1/2 rescues early senescence in *Zmpste24*$^{-/-}$ MEFs.

(**a**) Senescence-associated β-galactosidase assay in wild-type and *Zmpste24*$^{-/-}$ MEFs treated with Suv39h1/2 or scramble siRNA. Scale bar, 200 µm. Levels of H3K9me3 were shown in Fig. S3a. (**b**) Quantification of senescent cells of at least 200 cells in wild-type or *Zmpste24*$^{-/-}$ MEFs, with Scramble or Suv39h1/2 siRNA. Data represent mean ± s.e.m., n > 200. . *$P < 0.05$, 2-tailed *t*-test.

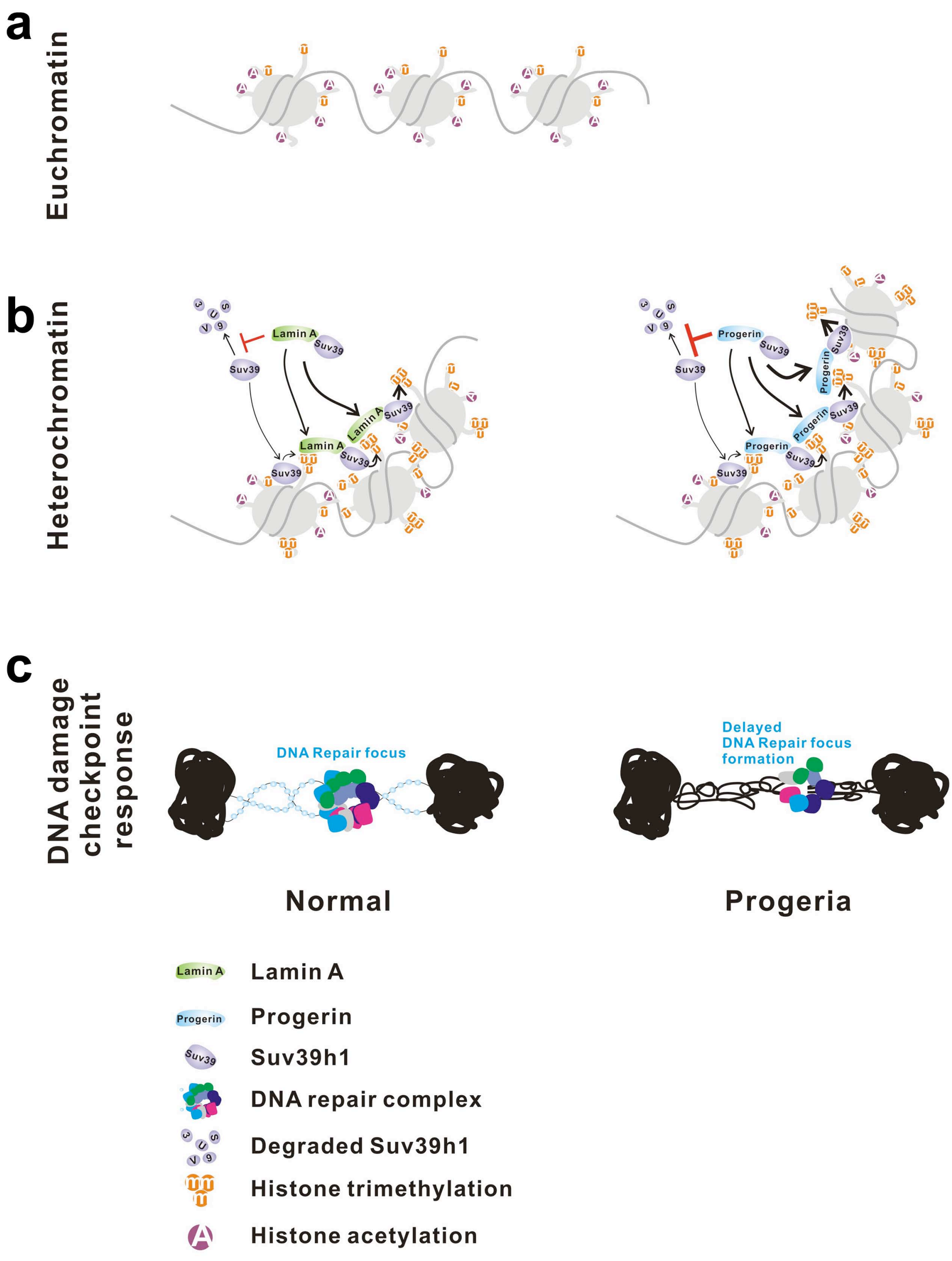
Supplementary Figure S8



Supplementary Figure S8: SUV39H1 interacts with lamin B1.

GFP-SUV39H1 was ectopically expressed in HEK293 cells. Representative immunoblots showing lamin B1 in the anti GFP immunoprecipitates. Data are representative of three independent experiments.

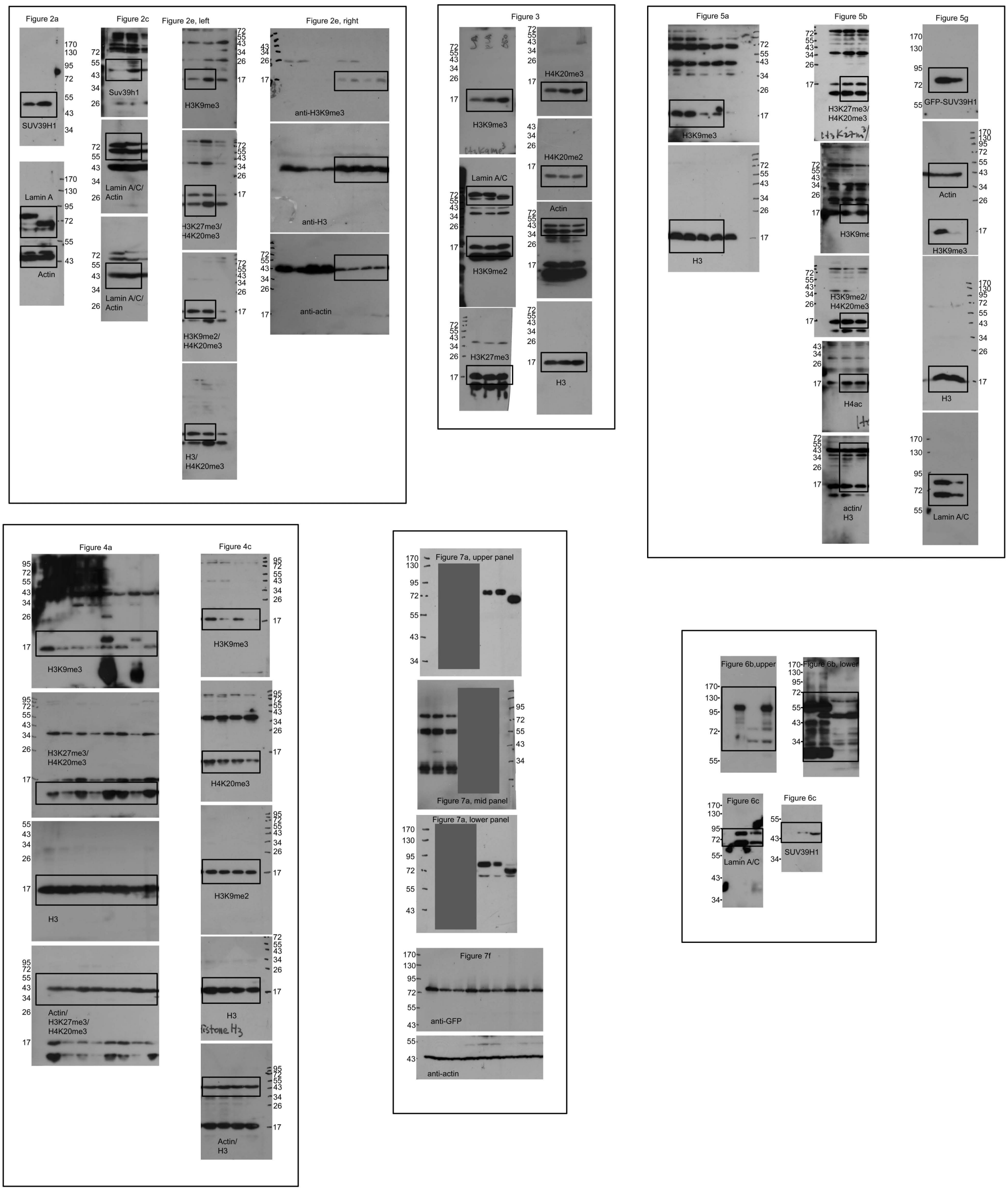
Supplementary Figure S9



Supplementary Figure S9: Schematic model of lamin A in the regulation of H3K9me3 marked heterochromatin.

(**a**) Euchromatin. (**b**) Lamin A interacts with Suv39h1 thus protecting it from proteasomal degradation. Suv39h1 alone or in cooperation with other co-factors initiates H3K9me3 mark on individual nucleosome. The direct interaction between trimethylated H3K9 and lamin A (ref 34) facilitates recruiting chromatin to the nuclear compartment wherein the lamin A-Suv39h1 complex resides and Suv39h1 trimethylates H3K9 on adjacent nucleosomes thus expanding heterochromatic marks. Increased binding of progerin/prelamin A to Suv39h1 and H3K9me3 enhances the level of Suv39h1 and the recruitment of adjacent nucleosomes, thus increasing H3K9me3-marked heterochromatin in progeria. (**c**) Elevated heterochromatin marked with H3K9me3 imposes a barrier in DNA damage-induced nucleosomal remodeling, which delays the recruitment of necessary repair proteins and compromises DNA repair, leading to accumulation of unrepaired/irreparable DNA damages in progeria cells.

Supplementary Figure S10



Supplementary Figure S10. Full length images of immunoblots.