Nuclear rupture as a potential shared mechanism of nuclear envelope-associated progeria

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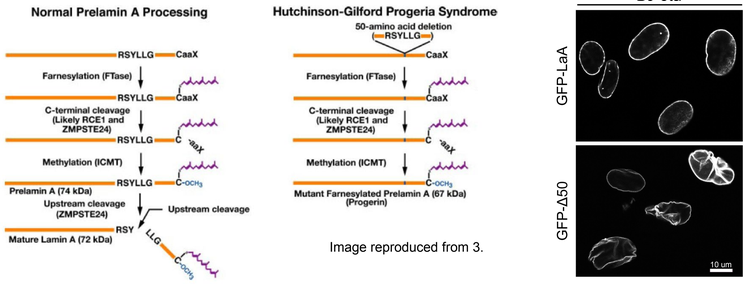
Abstract

Specific mutations in any one of the genes encoding A-type lamins, barrier-to-autointegration factor (BAF), and LEMD2 have been reported to cause progeria, a premature aging disease with variable phenotypes. These three nuclear envelope proteins are all capable of physically interacting with each other. It is therefore reasonable to hypothesize that there is a shared mechanism of disease underlying these nuclear envelope-associated progerias. We have recently demonstrated that BAF localizes to sites where the nuclear envelope is ruptured and is required to recruit A-type lamins and transmembrane LEM-domain proteins, including LEMD2, to repair the nuclear envelope. Nuclear ruptures result from exposure to mechanical forces on the nucleus and/or a weakened nucleoskeleton that compromises the integrity of the nuclear envelope and leads to the loss of nucleocytoplasmic compartmentalization. Under normal conditions, nuclear ruptures are rapidly repaired to stop the unrestricted exchange of cellular constituents between the cytosol and nucleus that is reported to, among other likely consequences, lead to DNA damage and a block in the cell cycle. Here we show that, compared to wild-type BAF, progeric BAF exhibits a reduced residency at sites of nuclear rupture suggestive of an impaired ability to bind to DNA. Compared to wild-type lamin-A, progeric lamin A exhibits a substantially reduced accumulation at sites of nuclear rupture. Progeric LEMD2 localizes similarly to wild-type LEMD2, but is severely aggregated at discrete sites on the envelope that may reflect improperly repaired prior rupture sites. Collectively, these results begin to support the hypothesis that progeria-associated mutations in A-type lamins, BAF, and LEMD2 lead to an enhanced propensity for nuclear rupture and/or compromised nuclear rupture repair, contributing to progeria phenotypes including increased DNA damage and cellular senescence.

Hutchinson-Gilford Progeria Syndrome (HGPS)

- Symptoms appear ~18 months of age
  - Skeletal defects, reduced growth, hair loss, atherosclerosis, subcutaneous fat loss.
  - Abnormal shaped nuclei, DNA damage, senescence
- Average age at death ~15 yr
  - Some common aging phenotypes
  - No cognitive defects
  - Usually succumb to atherosclerosis
- Caused by mutations in *LMNA* encoding the A-type lamins (LaA)[3]
  - ~90% of cases caused by autosomal dominant splicing defect
  - More rare recessive mutations of residues within the Ig-fold of LaA exist at the predicted BAF-Lamin binding interface (green mutations)



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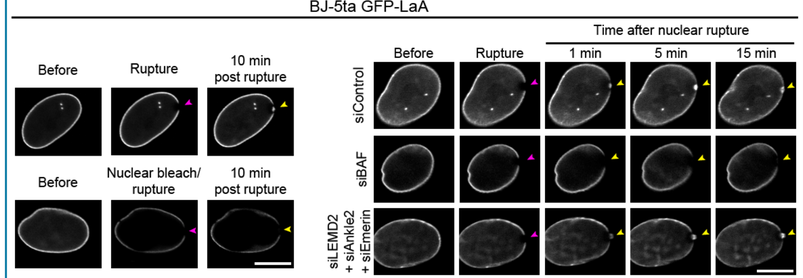
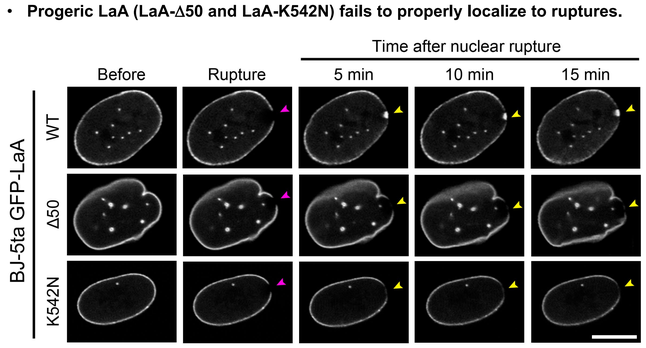
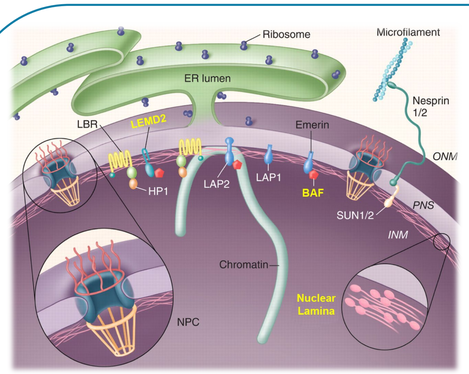
- **A mobile population of LaA accumulates at ruptures in a BAF-dependent manner.**



- **Progeric LaA (LaA-Δ50 and LaA-K542N) fails to properly localize to ruptures.**



Nuclear Envelope and Nuclear Rupture



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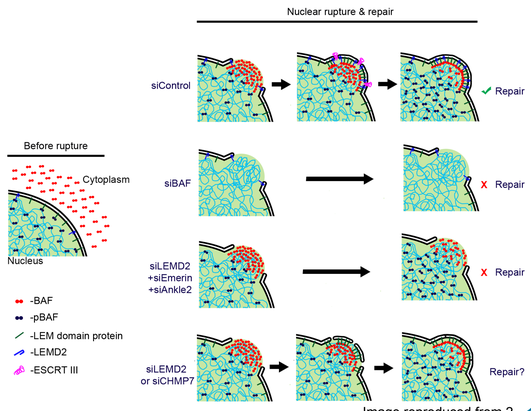
- The nuclear envelope is an extension of the endoplasmic reticulum (ER) that is composed of two layers:
  - Inner nuclear membrane (INM) and outer nuclear membrane (ONM)
- Proteins along the INM have roles in the organization of chromatin and regulation of gene expression.
  - Among these proteins are BAF and LEMD2
- Lamins assemble filaments to form the nuclear lamina, a protein scaffold underlying the INM.

- BAF rapidly and transiently mobilizes to sites of nuclear rupture.
- BAF in the cytoplasm is recruited to nuclear ruptures primarily by binding DNA exposed at the rupture site.
- LEM proteins and membranes are recruited to nuclear ruptures by BAF.
- BAF is required for the repair of nuclear ruptures
- Substantial loss of LEM proteins prevents repair of ruptures



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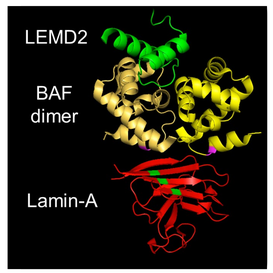
Unifying Hypothesis for Mechanism of Progeria



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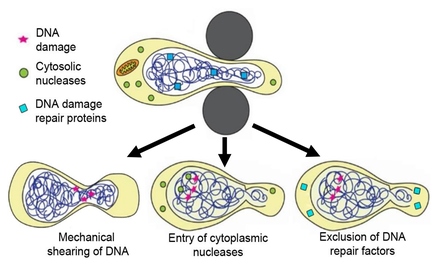
- BAF dimers can bridge LEM-proteins and A-type lamins at the nuclear envelope
- All three progeria-associated proteins reside in the same complex and localize at nuclear ruptures
- Recessive mutations in LaA (green) and BAF (purple) exist in the BAF-Lamin binding interface



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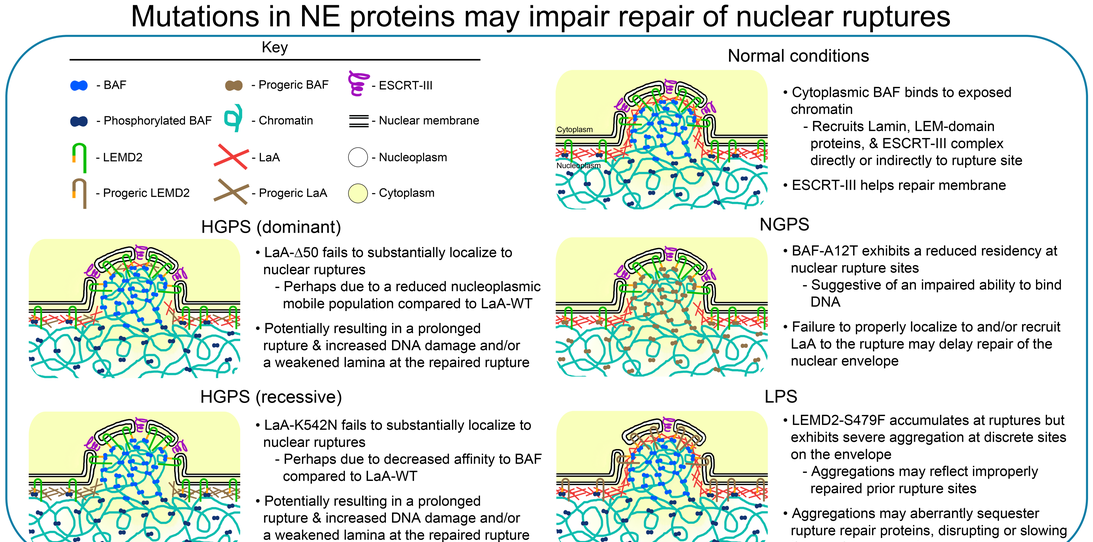
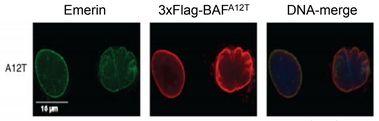
- Nuclear rupture induces DNA damage, however the mechanism of how this DNA damage occurs is unknown[7].
- DNA damage could be occurring through DNA shearing, loss of repair factors, and/or influx of cytosolic nucleases
- DNA damage leading to cellular senescence is a commonly proposed mechanism of progeria

Mutations in NE proteins may impair repair of nuclear ruptures



Nestor-Guillermo Progeria Syndrome (NGPS)

- Defined as a chronic progeria[4]
  - Longer survival
  - Common aging phenotypes
  - Severe osteolysis
  - No cardiac complications
- Caused by mutation in *BANF1*[4]
  - C.34G>A [p.A12T]
  - Autosomal recessive
  - BAF-A12T has DNA binding defect
- Abnormally shaped nuclei



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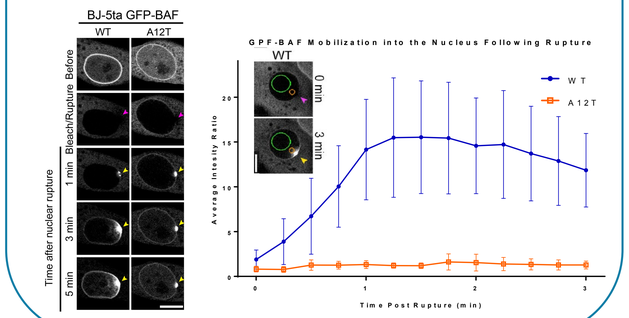
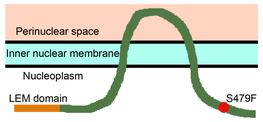
- **BAF-A12T behaves like a DNA-binding mutant during nuclear rupture.**

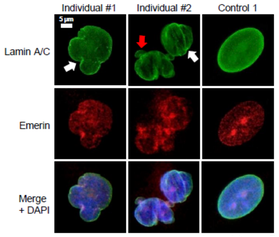


LEMD2 Progeria Syndrome (LPS)

- Caused by mutation in *LEMD2*[5] c.1436C>T [p.S479F]
  - Autosomal Dominant



- Early progeria-like appearance
  - Longer survival
- Abnormally shaped nuclei



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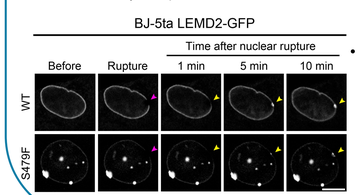

- **LEMD2-S479F accumulates at rupture sites but exhibits severe aggregation at discrete sites on the envelope**
  - **Aggregations may reflect improperly repaired prior rupture sites**

Future Directions

- Evaluate progeric proteins' effects on nuclear leakage and nuclear envelope repair post nuclear rupture
- Investigate whether nuclear rupture is a source of enhanced DNA damage and senescence in progeria

References

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Acknowledgments

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