Title: A-type lamins have perturbed targeting to nuclear ruptures in nuclear envelope-associated progerias

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Brief Abstract: Mutations in three genes encoding nuclear envelope (NE) proteins, LMNA, BANF1, and LEMD2, result in accelerated aging syndromes known as progerias. These proteins interact with each other to accomplish various cellular processes. One of these processes is the repair of interphase nuclear ruptures to ensure the efficient reconstitution of the nuclear-cytoplasmic barrier. Previously, we have shown that barrier-to-autointegration factor (BAF) localizes to sites of nuclear rupture and is required for recruiting NE-repair machinery, including the LEM-domain proteins, ESCRT-III complex, and membranes. Here, we show that a mobile, nucleoplasmic population of A-type lamins is recruited to ruptures in a BAF-dependent manner via BAF's association with the Ig-like β fold domain. Progeria-associated lamin A (LaA) mutations inhibit the recruitment of LaA to nuclear ruptures through differing mechanisms. Additionally, a progeria-associated BAF mutant targets to nuclear ruptures; however, it is unable to recruit A-type lamins. Together, these data support a model where defective A-type lamins recruitment to nuclear ruptures could be a shared mechanism of NE-associated progeria, perhaps by enhancing propensity for nuclear rupture and/or by compromising nuclear rupture repair, contributing to progeria phenotypes.