P104/B35 The role of Barrier to Autointegration Factor BAF-1 in chromatin organisation and premature ageing

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BAF-1 (Barrier to Autointegration Factor) is a highly conserved chromatin binding protein implicated in nuclear envelope (NE) breakdown, assembly and repair as well as chromatin compaction. It acts as a homodimer and is found in the nucleoplasm and enriched at the NE, where its localisation is interdependent on lamins and LEM-domain proteins (LAP2, emerin, and MAN1). Strikingly, a single amino acid substitution in human BAF (A12T) causes Nestor-Guillermo Progeria Syndrome (NGPS). This premature ageing illness affects a variety of tissues, leading to growth retardation, severe skeletal defects and scoliosis.

We have modified the *baf-1* locus in *Caenorhabditis elegans* to mimic the human NGPS mutation (*baf-1(G12T)*) to elucidate why a mutation in an essential protein expressed throughout development triggers the appearance of symptoms ~2 years after birth. We report that lifespan and NE levels of lamin/LMN-1 and emerin/EMR-1 are reduced in *baf-1(G12T)* mutants, whereas errors in chromosome segregation are increased. Interestingly, the *baf-1(G12T)* mutation makes animals temperature sensitive in terms of brood size and fertilisation capacity. Moreover, we found that *baf-1(G12T)* mutants are hypersensitive to NE perturbations, particularly to modifications affecting lamin/LMN-1.

To explore if the NGPS mutation affects BAF-1's association with chromatin, we determined the binding profiles for wild type and mutant BAF-1 through tissue-specific DamID. Globally, the profiles for the two proteins are very similar, but we also identified discrete genomic regions with altered association to BAF-1. We are currently correlating these observations with tissue-specific changes in gene expression.