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POSTER 124

C. elegans as a Nestor Guillermo Progeria Syndrome Model

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Abstract
Nestor-Guillermo Progeria Syndrome (NGPS) is a premature ageing illness that affects a variety of tissues, leading to growth retardation, severe skeletal defects and scoliosis. The syndrome is caused by a single amino acid substitution (A12T) in BAF1 (Barrier to Autointegration Factor 1). BAF1 is a highly conserved chromatin binding protein implicated in nuclear envelope (NE) breakdown, assembly and repair as well as chromatin compaction. Its NE localization is interdependent of lamins and LEM-domain proteins (LAP2, emerin, and MAN1) and contributes to chromatin organization although BAF1 is also present in the nucleoplasm.
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 NE levels of lamin/LMN-1 and emerin/EMR-1 are reduced in *baf-1(G12T)* mutants, whereas errors in chromosome segregation are increased. The *baf-1(G12T)* mutation reduces fertility and lifespan and accelerates age-dependent nuclear morphology deterioration. Moreover, we found that *baf-1(G12T)* mutants are hypersensitive to NE perturbations, particularly to modifications affecting lamin/LMN-1.
Like other progerias, NGPS-derived fibroblasts feature malformed nuclei. Importantly, a set of genes whose depletion alleviates the nuclear associated defects was unveiled by CRISPR-mediated gene knockout in NGPS fibroblasts. When orthologs were silenced by RNAi in *C. elegans*, several reduced the embryonic lethality of sensitized *baf-1(G12T)* mutants. This represents a first and encouraging list of candidate genes to be further explored for the development of NGPS therapies.