NURD keeps chromatin young

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Progerin, a mutated form of lamin A, causes the premature ageing disease Hutchinson-Gilford progeria syndrome and is also involved in normal ageing. Progerin accumulation leads to distinct chromatin-related defects and the NURD complex appears to affect ageing-related chromatin defects.

Ageing involves various cellular and molecular alterations and studying their molecular basis is often difficult. The childhood ageing disease Hutchinson-Gilford progeria syndrome (HGPS)[1,2] is caused by a shortened isoform of the nuclear intermediate filament protein lamin A (progerin) and it provides a unique model system to study cellular ageing mechanisms[3]. On page 1261 of this issue, Pegoraro *et al.* have now investigated the underlying reasons for defects in chromatin structure and function during premature ageing in HGPS and normal ageing[4].

HGPS and normal ageing cells share many cellular features, including loss of heterochromatin foci, reduced levels of heterochromatin-associated histone modifications and heterochromatin proteins, increased transcription of satellite III repeats and elevated levels of DNA damage[5–9]. Alterations in chromatin structure and function during ageing have been documented for many years. For example, there is a decline in the level of histone acetylation[10], aberrations in global compaction of chromatin[11] and reduced chromatin accessibility[12]. More recently, the molecular mechanisms underlying ageing-related chromatin changes have begun to emerge, including evidence for a role of the Wnt signalling pathway[13] and several sirtuins[14,15] that link ageing and chromatin with the energy and metabolism of a cell.

Despite these advances, the causes of chromatin defects in progeroid (prematurely ageing) and normally ageing cells remained obscure. Pegoraro *et al.* now report that RBBP4 (retinoblastoma binding protein 4) and RBBP7 (retinoblastoma binding protein 7) interact specifically with wild-type lamin A, but not with progerin. Both RBBP4 and RBBP7 are significantly depleted in cells of HGPS patients and their reduced levels correlate with chromatin aberrations characteristic of HGPS cells. Ectopic expression of progerin causes a similar reduction in RBBP4/7 levels, demonstrating its dominant-negative effect.

An important question is whether the depletion of RBBP4/7 is sufficient for inducing progeroid-like chromatin defects. If so, it might be at least one of the much sought-after mechanisms leading to ageing-related chromatin defects. When both proteins were depleted, cells showed the chromatin-related defects of progeroid cells, including the loss of heterochromatin HP1γ and H3K9 methylation, elevated levels of satellite III transcription and significantly increased DNA damage. By examining cells at various time points, the authors found that chromatin defects emerged three days after RBBP4/7 depletion, whereas DNA damage appeared at five days post depletion. Although previous studies suggested that the ageing-related chromatin defects are caused by DNA damage[16], Pegoraro *et al.* now demonstrate that DNA damage occurs only after the chromatin defects, suggesting that DNA damage cannot be an upstream event in ageing cells. These observations also strongly suggest that reduced levels of RBBP4/7 are directly linked to the ageing-related chromatin defects of HGPS cells.

The authors next determined which of the three complexes that share the RBBP4/7 proteins is the rogue one. By examining the protein levels of the different subunits of the different complexes, the authors demonstrated that only the NURD complex, which in addition to RBBP4/7 contains the HDAC1, MTA3, CHD3 and CHD4 proteins, is significantly depleted in HGPS cells. Remarkably, in normal cells, knockdown of each of the different subunits of the NURD complex phenocopies the aberrant chromatin-related defects of HGPS or RBBP4/7-depleted cells, suggesting that RBBP4/7 exert their effects in HGPS cells through the NURD complex.

But is the NURD complex also involved in the process of normal cellular ageing? It seems to be. Comparing primary skin fibroblasts derived from young and old donors revealed reduced levels of RBBP4/7 and HDAC1 in the 'older' cells. Taken together, these important findings by Pegoraro *et al.* suggest that, in addition to being a hallmark of normal ageing, reduced levels of the subunits of NURD can cause the progression of ageing-related phenotypes (Fig. 1).

This study raises new questions. For example, how do the different components of the NURD complex inflict chromatin defects? The relatively mild reduction in HDAC1 activity in HGPS cells hints that reduced deacetylation is only part of the story. Similarly, it is not clear what roles the chromatin remodelling proteins CHD3 and CHD4 have in HGPS and normal ageing. A major open question in the field is what causes the ageing-related cellular defects. One hypothesis is that the accumulation of DNA damage throughout the life of an organism, whether yeast or human, alters chromatin structure and nuclear architecture[17]. However, as indicated above, the study by Pegoraro *et al.* suggests otherwise. They convincingly show that chromatin defects precede DNA damage when cells are depleted of NURD components. If NURD depletion indeed mimics accelerated cellular ageing accurately, as suggested by the current study, the DNA damage hypothesis will require revisiting. In the new model, global changes in chromatin structure and depletion of heterochromatin marks will lead to the accumulation of DNA damage through yet unknown mechanisms.

Another major challenge is to understand how ageing affects gene expression programs. In cellular senescence, for example, proliferation-associated genes are silenced by the formation of senescence-associated heterochromatin foci (SAHF)[18] and the accumulation of HMGA (high mobility group A) proteins at proliferation-related genes, inhibiting their transcription[19]. As NURD is a chromatin remodelling complex, it would be interesting to determine whether NURD is involved in cellular senescence and SAHF regulation, whether it associates with specific ageing-related genes and

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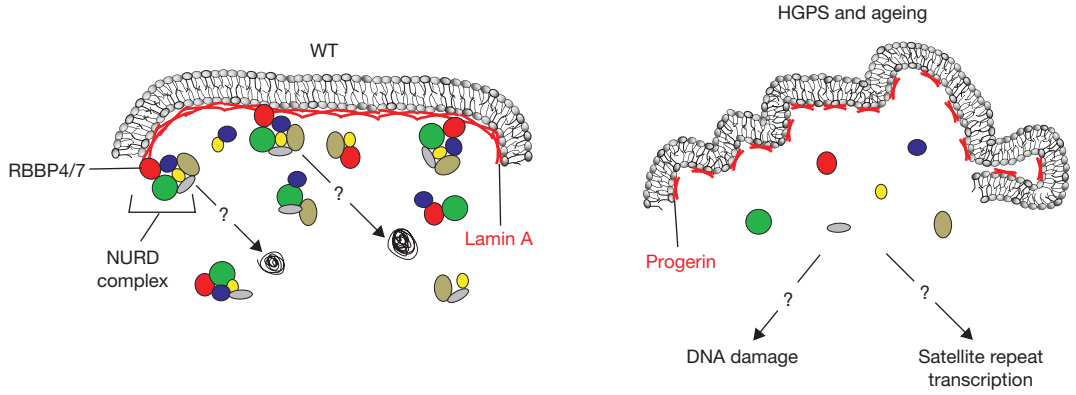

Figure 1 Progerin expression leads to NURD depletion. In young, healthy cells (left), wild-type (WT) lamin A (red stripes) binds the NURD complex through interaction of its carboxy-terminal region with RBBP4/7 (red circle). This interaction is important for maintaining heterochromatin foci, H3K9 and HP1γ (black coils), through unknown mechanisms. In HGPS and ageing cells (right), progerin (shorter red stripes; note that the nuclear lamina itself is changed, but probably not broken), which gradually replaces wild-type lamin A, cannot bind RBBP4/7 and components of the NURD complex are significantly depleted, causing loss of heterochromatin, increased transcription of satellite III repeats and increased DNA damage through unknown mechanisms.

whether its genome-wide distribution changes during ageing and cellular senescence.

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A motor driving PTEN

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To fulfil its lipid phosphatase function, PTEN must be in close proximity to the plasma membrane where its substrates reside. PTEN translocation to the plasma membrane is an active process that is mediated by the myosin-based transport machinery. MyosinV controls PTEN membrane association and thus, PTEN-mediated cell growth in neurons.

PTEN (phosphatase and tensin homologue deleted on chromosome 10) is a tumour suppressor that antagonizes the function of PI(3)K (phosphatidylinositol-3 kinase). By catalysing the conversion of PtdIns(3,4,5)P_3 (phosphatidylinositol 3,4,5-triphosphate) to PtdIns(4,5)P_2 (phosphatidylinositol 4,5-bisphosphate), PTEN prevents the accumulation of PtdIns(3,4,5)P_3 in the plasma membrane and thereby inhibits PI(3)K signalling. Due to several essential roles of PI(3)K signalling in regulating cell growth, survival and migration, mutations in *PTEN* are associated with a broad spectrum of cancers and *PTEN* has been listed as the second most frequently mutated tumour suppressor gene in human cancers, surpassed only by *p53* (ref. 1). In addition, individuals with *PTEN* germline mutations are prone to developing brain disorders, including macrocephaly, seizures, Lhermitte-Duclos disease and autism[2]. Therefore, regulation of both the *PTEN* gene and PTEN protein has been extensively studied. The discovery of a new molecular mechanism that regulates PTEN function could provide a new window of opportunity for developing novel therapies for PTEN-associated diseases.

One interesting puzzle about PTEN regulation that has not been fully solved is the control of its subcellular localization. Immunostaining demonstrates that intracellular localization can be both cytoplasmic and nuclear, with only a few specific examples where PTEN shows obvious membrane localization[1,3,4]. These observations are confounding as PTEN contains lipid-binding domains and membrane association is essential for its lipid phosphatase activity[5]. How then is PTEN translocated to the proximity of the plasma membrane and activated when exposed to its substrates? On page 1191 of this issue, an elegant study by Eickholt and colleagues demonstrates an active role for the myosinV motor in transporting PTEN to

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