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Genome maintenance functions of the INO80 chromatin remodeller

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Chromatin modification is conserved in all eukaryotes and is required to facilitate and regulate DNA-templated processes. For example, chromatin manipulation, such as histone post-translational modification and nucleosome positioning, play critical roles in genome stability pathways. The INO80 chromatin-remodelling complex, which regulates the abundance and positioning of nucleosomes, is particularly important for proper execution of inducible responses to DNA damage. This review discusses the participation and activity of the INO80 complex in DNA repair and cell cycle checkpoint pathways, with emphasis on the *Saccharomyces cerevisiae* model system. Furthermore, the role of ATM/ATR kinases, central regulators of DNA damage signalling, in the regulation of INO80 function will be reviewed. In addition, emerging themes of chromatin remodelling in mitotic stability pathways and chromosome segregation will be introduced. These studies are critical to understanding the dynamic chromatin landscape that is rapidly and reversibly modified to maintain the integrity of the genome.

This article is part of the themed issue 'Chromatin modifiers and remodellers in DNA repair and signalling'.

1. Characterization of chromatin remodellers

Manipulation of chromatin structure occurs via a variety of mechanisms including post-translational modification of histones, alteration of nucleosome composition and nucleosome repositioning. In particular, changes in nucleosome composition and position require the energy from ATP hydrolysis to disrupt the high-affinity contacts between DNA and histones. The ATP-dependent chromatin-remodelling complexes that facilitate such dramatic nucleosome rearrangements are evolutionarily conserved and share homology within their respective ATPase subunits as members of the Snf2 family of helicases, named after the first ATPase subunit characterized in the yeast SWI/SNF chromatin remodeller [1]. These remodellers are further classified into distinct SWI/SNF, ISWI, INO80 and CHD subfamilies largely due to the structural organization of helicase domains and unique flanking domains, such as canonical motifs that bind histone post-translational modifications [2].

The distinct enzymatic activities of these remodellers are the subject of continuing research. Thus far, a broad range of nucleosome manipulations have been identified *in vitro* and include DNA and histone binding, DNA translocation, nucleosome sliding, histone exchange and histone ejection (for review, refer to [3]). The chromatin products resulting from these reactions can be extremely varied and tailored specifically for different DNA-templated processes.

Like most chromatin modifiers, remodellers were originally characterized as transcriptional regulators, where nucleosome reconstruction and repositioning influence recruitment and processivity of the transcriptional machinery. For example, the previously introduced sucrose non-fermenting gene *SNF2* was first identified in a yeast screen for transcriptional regulators of carbon metabolism genes [4,5]. Similarly, the INOsitol-requiring *INO80* gene, encoding the ATPase subunit of the INO80 complex [6], was originally identified in a screen that revealed genes required for expression of genes in phospholipid metabolism pathways [7].

The efforts to characterize chromatin remodellers as transcriptional regulators were driven by both the biological importance of chromatin manipulation in transcription and also the strong focus within the research community to understand the epigenetic requirements during activation and repression of gene expression. This focus largely began with the identification and characterization of a known transcription activator as a histone acetyltransferase [8]. Many subsequent research efforts focused to identify other post-translational modifications, such as deacetylation and (de)methylation, in order to elucidate the dynamic transcriptional chromatin landscape.

However, a hint to the importance of chromatin remodellers in DNA damage response pathways came with the characterization of the *Saccharomyces cerevisiae* INO80 chromatin-remodelling complex [6], where the authors identified roles for INO80 in both *in vitro* transcription and *in vivo* damage responses. Specifically, *ino80Δ* cells lacking the *INO80* gene have reduced fitness in the presence of ultraviolet (UV) light, hydroxyurea and methyl methanesulfonate, which induce nucleotide-excision repair, replication stress and double-strand break (DSB) repair, respectively. These initial investigations of the INO80 complex provided a platform for future investigations of chromatin-remodelling in genome stability pathways. (Refer to [9]for more details on the roles of chromatin remodellers in DNA repair.)

2. Composition of the *Saccharomyces cerevisiae* INO80 complex

Since its initial discovery, the *S. cerevisiae* INO80 chromatin-remodelling complex has been found to regulate transcription [6,10,11], replication [12–14], DNA damage responses [15–17], telomere regulation [18] and mitotic stability [19,20]. Yeast genetic analyses have identified distinct functions for INO80 subunits in a variety of DNA damage response pathways, such as repair, recombination and cell cycle checkpoint regulation [15,21–23]. In mammalian systems, the conserved INO80 chromatin-remodelling complex has roles in genome stability, disease pathogenesis and embryonic stem cell identity [24–28]. These studies exemplify the functional diversity of the INO80 complex in different cellular pathways [29]. Moreover, they highlight the need for regulatory mechanisms that direct its activity among, and within, these processes. Ample opportunities for regulation of chromatin remodelling exist at the level of individual subunits that may direct the activities of the remodeller in distinct cellular processes.

The composition and structure of the multi-subunit 1.3 MDa *S. cerevisiae* INO80 complex has been revealed through biochemical and electron microscopy analysis (for review, refer to [30]). The complex is composed of 15 subunits [6] that comprise four structurally distinct and biochemically separable subunit modules that assemble along the Ino80 ATPase [31,32]. For example, the Actin-related protein 8 (Arp8) module consists of Arp8, Arp4, Actin, Taf14 and Ies4. Interestingly, of the 10 *S. cerevisiae* Arps, four are cytoplasmic with cytoskeleton functions, while the remaining six are in chromatin-remodelling complexes. These Arp subunits are critical for ATP-dependent chromatin-remodelling function [33]. Specifically, Arp4, Arp8 and Arp5 are required for, or facilitate, *in vitro* chromatin remodelling [31,34]. The Arp8 module assembles within the helicase-SANT–associated domain of the Ino80 ATPase [31,35] and is important for nucleosome recognition, ATP hydrolysis and nucleosome sliding *in vitro* [31,34,36–39].

The N-terminal domain of Ino80 ATPase assembles the Nhp10 module consisting of Nhp10, Ies1, Ies3 and Ies5 subunits that are less conserved among different species [31,40], yet some of these subunits have directed functions in DNA damage recognition [15] and telomere stability [18]. Another hint to distinct involvement of the INO80 complex in DNA damage responses is the identification of the Rvb1 and 2 modules, which are AAA+ helicases with homology to bacterial RuvB helicase involved in Holliday junction migration [6,41,42]. Their presence in the INO80 complex suggests conserved genome maintenance functions. However, these genes are essential, thus their role in the INO80 complex remains understudied. Nevertheless, the presence of these Rvb1 and 2 subunits is unique to the INO80 subfamily of complexes. Their association is dependent on the large 'insertion' or 'spacer' region that splits the ATPase domain of the Ino80 subunit [43,44], a primary distinguishing characteristic of the INO80 subfamily.

Lastly, the Arp5 module that consists of both Arp5 and Ies6 is structurally found within close proximity to the Ino80 ATPase domain [31,32], thus connecting Arp5-Ies6 to critical enzymatic components of the INO80 complex. Not only is the insertion region of the Ino80 ATPase important for Rvb1 and 2 recruitments, but it is also needed for Arp5 module assembly into the INO80 complex [43–45]. Owing to its importance in the chromatin-remodelling function of the INO80 complex, the Arp5-Ies6 module affects nucleosome positioning [46], replication [13], transcriptional regulation [11,47], mitotic stability [19] and DNA damage responses [15,48–50]. *In vitro*, this module is needed for INO80-mediated ATP hydrolysis, nucleosome sliding and histone exchange that reconstructs nucleosomes by removing the Htz1 variant (H2AZ in mammals) [31,32,34]. Interestingly, this Arp5-Ies6 module forms an abundant and distinct subcomplex *in vivo* [51]. Furthermore, the module can activate INO80-mediated activity *in vitro* through de novo assembly into an INO80 complex that lacks Arp5-Ies6 [44], suggesting that assembly of distinct modules of the INO80 complex may be a form of regulation for inducible function *in vivo*.

3. γ-H2AX is involved in the recruitment of INO80 to repair sites

A critical component in determining the role of the INO80 complex in DNA damage responses was revealed when the complex was found to bind phosphorylated H2AX at sites surrounding DNA breaks [15,16,52]. DNA DSBs caused by genotoxic stress are particularly dangerous lesions that can result in mutations caused by error-prone repair, or cell death if left unrepaired. Phosphorylated H2AX is commonly referred to as γ-H2AX, because of its rapid accumulation on the genomes of cells treated with gamma radiation that induce DNA DSBs [53,54].

H2AX is phosphorylated by ataxia-telangiectasia (A-T) mutated (ATM) and A-T and RAD3-related (ATR) kinases *in vivo* and *in vitro* [55,56]. ATM and ATR (Tel1 and Mec1 in yeast) are essential regulators of DNA damage responses (for review, refer to [57,58]). These kinases have an expansive network of substrates in genome stability pathways, such as the tumour suppressor p53 and Checkpoint Kinase 2, Chk2

(Rad53 in yeast) [59]. Mutations in ATM/ATR result in disorders that are characterized by DNA damage sensitivity and cancer predisposition [60,61]. (Refer to [62] for more details on the roles of ATM in DNA repair.)

H2AX is a histone variant in mammals with a high degree of homology with canonical H2A. The main sequence deviation is located in the carboxyl termini, which contains an ATM/ATR consensus target sequence (SQE) at serine 129. H2AX is found in approximately 10% of nucleosomes in mammals [54], while the canonical histone H2A is orthologous to the mammalian H2AX variant and ubiquitously present throughout the genome. γ-H2AX accumulates in large megabase regions around DSBs in mammals and serves as a signal and docking site for several DNA damage response proteins (for review, refer to [63]). In yeast, mutation of the phosphorylation site in H2A results in decreased fitness following production of DSBs [64]. H2AX deficiency in mammalian cells also results in decreased survival upon exposure to ionizing radiation, as well as increased chromosomal translocations, and cancer predisposition in mice [65–68].

The two major DSB repair pathways are homologous recombination (HR) and non-homologous end joining (NHEJ) [69]. The Nbs1 subunit of the Mre11- Rad50-Nbs1 complex binds γ-H2AX at break sites and mediates single-stranded DNA resection of the DNA end [70]. During HR, the *RAD52* epistasis group (Rad50, Rad51, Rad52, Rad54 and Rad55) promotes homology search, strand invasion and synapsis between the invading DNA strand and donor DNA to form Holliday junctions. Cohesin also binds γ-H2AX to assist in pairing of sister chromatids for gene conversion [71,72]. DNA repair is complete once DNA synthesis has finished and the Holliday junction is resolved.

HR is inherently error-free and the preferred repair pathway in yeast, probably due a genome densely composed of genic loci. However, error-prone NHEJ often occurs in larger mammalian genomes with an abundance of non-coding regions. During NHEJ, genetic alterations can be induced around break sites because a homologous donor is not used [69]. Specifically, the Ku70–Ku80 complex tethers and ligates the broken DNA end back together through a mechanism that often results in deletion of several nucleotides. Importantly, regardless of the DNA repair pathway, dramatic reconstruction of the chromatin environment is required to facilitate these repair steps. (Refer to [73]for more details on manipulation of chromatin during DSB repair.)

4. The INO80 complex participates in DNA repair

An invaluable model system used to examine the participants and mechanisms of DSB repair is the well-defined *S. cerevisiae* system that can create a single DSB site at the *MAT* locus [74]. This system exists normally in yeast to induce mating type switching at the *MAT* locus with a homologous donor sequence of the opposite mating type. This system can be used in DNA repair assays by placing the HO endonuclease that cleaves the *MAT* locus under an inducible promoter. Furthermore, repair can be directed to HR or NHEJ specifically, depending on the presence or absence of a recombination donor sequence [74,75]. Thus, a targeted DSB can occur within minutes after endonuclease induction, and repair kinetics can be monitored with precise accuracy.

This system was used to identify the association and function of the INO80 complex at DNA break sites. Specifically, the Nhp10 module was shown to bind γ-H2AX and mediate recruitment of the INO80 complex to sites of DSBs [15,16,52]. However, recently the dependence of γ-H2AX as an absolute prerequisite for INO80 recruitment has been challenged and proposed to be due to cell cycle kinetics of different experimental strains [76]. Arp5 recruitment at break sites is indeed cell cycle–dependent with enhanced association in G2/M phase, compared with G1 phase [76]. Furthermore, recruitment of the Arp5 subunit is also facilitated by production of the Rad51 single-stranded DNA filament that is involved in homologous donor search, adding to the evidence that the INO80 complex is an essential component of the HR pathway [76].

The inducible *MAT* locus DNA break system was also used to determine that INO80 complex influences the proximal eviction of both γ-H2AX- and H2AZ-containing nucleosomes surrounding DSBs. H2AZ is another H2A histone variant that facilitates DNA repair by creating a flexible and permissive chromatin environment for histone modification and recruitment of repair proteins [77]. Loss of H2AZ in yeast leads to increased sensitivity to DNA-damaging agents [78,79] and defective repair of DSBs [80]. (For more details on the role of H2AZ in DNA damage responses, refer to [81].)

Specifically, deletion of *ARP8*, which reduces the *in vitro* chromatin-remodelling activity of the INO80 complex [34], or deletion of *NHP10*, which decreases the recruitment of the INO80 complex to the DSB [15], results in defective nucleosome eviction in chromatin proximal to the DSB and in the region of the homologous donor locus [82–84].

This process of nucleosome eviction has recently been linked to histone degradation that increases both the flexibility of the chromatin fibre and mobility within the nucleus [85]. Large-scale movement of chromatin regions within the interphase nucleus probably increases the chances of encountering a homologous donor for error-free DNA repair [86]. Indeed, monitoring of fluorescently tagged loci proximal to an inducible DSB has identified a role for the INO80 complex in chromatin mobility during the response to DNA damage [48,49,85,87]. (Refer to [88] for more details on the influence of chromatin remodelling in chromatin mobility following production of DSBs.)

Impaired nucleosome eviction at DNA break sites concomitantly influences end resection and recruitment of repair and checkpoint factors to the processed DNA end. For example, mutants of the INO80 complex have defects in the association of the Mre11 nuclease and DNA resection as measured by the production of single-stranded DNA [16,84], an observation that is confirmed in mammalian cells [89]. Other chromatin remodellers, namely Fun30 and the RSC remodellers, also participate in DNA resection and have redundant roles with the INO80 complex [90]. Although it appears that INO80 is more important for resection proximal to the break site, while Fun30 facilitates distal DNA resection [90]. This is consistent with the observation that the INO80 complex associates within 3 kb of the break site [15,16].

The subsequent recruitment of DNA damage response factors to resected DNA, such as Rad51 repair protein and the Mec1 checkpoint kinase, is strongly reduced in an *arp8* mutant strain [82–84]. A recent study in yeast revealed that the defects in Rad51 recruitment and post-synaptic filament formation are associated with reduced H2AZ eviction of the *arp8* mutant [91]. The INO80-dependent removal of H2AZ during HR has also been confirmed in mammalian cells [92]. Collectively, these

studies demonstrate that the importance of INO80 complex is closely linked to nucleosome eviction of both canonical and H2AZ-containing nucleosomes. Consequently, mutations or deletions of INO80 chromatin-remodelling subunits result in defective DNA repair. Specifically, INO80 mutants have deficiencies in both NHEJ and HR pathways in *S. cerevisiae* [16,84,93], mammals [27,92] and plants [94,95].

As previously mentioned, the original biochemical characterization of the INO80 complex revealed that *ino80Δ* cells are hypersensitive or have reduced fitness in the presence of multiple DNA-damaging agents, not just ones that create DSBs [6]. Accordingly, the INO80 complex has also been found to be important for manipulation of the chromatin environment to facilitate UV damage repair [50,96].

Indeed, the INO80 complex regulates multiple genome maintenance pathways. For example, INO80 influences replication [12–14] and replication-associated processes, including: the inducible response to replication stress [17,79,97]; and during collisions between the replication and transcription machinery [98]. (Refer to [88,99] for more details regarding the involvement of chromatin manipulation during replication.)

5. The INO80 complex influences DNA damage checkpoint pathways

Checkpoint pathways function cooperatively with DNA repair pathways by altering cell cycle kinetics, which allow for repair of damaged DNA and re-entry into the cell cycle [100]. As previously described, DNA resection is needed during the HR pathway to form a Holliday junction. In addition, the production of single-stranded DNA is required for the recruitment and activation of the previously introduced checkpoint Mec1 kinase that phosphorylates H2AX [55,56,101]. Subsequent amplification of γ-H2AX around DNA damage sites serves to recruit other checkpoint proteins, such as the *S. cerevisiae* Rad9 (53BP1 in mammals), which, along with Mec1, assists in the activation of downstream checkpoint factors [102–104].

Because INO80 influences the dynamics of γ-H2AX and H2AZ around DSBs, alterations in checkpoint responses in mutants of the INO80 complex may stem from defects in the association of checkpoint proteins, such as Mec1 [84]. Indeed, it has been shown that INO80 and SWR1 antagonistically regulate the abundance of γ-H2AX and H2AZ around DSBs [105]. Defects in this regulation result in inability to adapt to a persistent DSB in *S. cerevisiae*. This process, called checkpoint adaptation is a rare event in which the cell divides despite the presence of a persistently unrepaired DSB and initial Rad9-mediated cell cycle arrest [106].

The INO80 complex has also been found to be involved in replication checkpoint responses, specifically. Chromatin modulation is a crucial step in DNA replication, particularly when challenged with replicative stress that impedes the progression of the replication fork [107]. Stalled replication forks arise when the replication machinery encounters a DNA lesion or when nucleotide levels are low. If the damage is left unrepaired, or if nucleotide levels are not restored, disassembly of the replication machinery can occur concomitantly and can result in DNA breaks (for review, refer to [100]). The S-phase DNA damage response attempts to resolve the DNA lesion by activating cell cycle checkpoint arrest and assembling repair proteins at the DNA lesion. Fitness defects and checkpoint alterations occur in mutants of the yeast INO80 complex in response to replication stress, such as depleted dNTP levels and DNA crosslinks caused by alkylating agents [13,97,105,108,109]. Furthermore, global genetic screens in *S. cerevisiae* implicate the INO80 complex in replicative damage response pathways [22,110].

A critical subunit of the *S. cerevisiae* INO80 complex that regulates cell cycle checkpoint responses is Ies4, which contains five serines within Mec1/Tel1 consensus sites in the N-terminus. Indeed, the Ies4 subunit of the INO80 complex is directly phosphorylated by the Tel1 kinase *in vitro* and *in vivo* following treatment with alkylating agents [97]. Ies4 phosphorylation subsequently modulates DNA replication checkpoint responses without significantly altering repair processes. In cells with mutations that prevent Ies4 phosphorylation and deletion of the *TOF1* checkpoint factor, which mediates the replication checkpoint response [111,112], recovery from replication stress is dramatically impaired [97]. Furthermore, phospho-micking mutants of Ies4 display heightened and prolonged S-phase checkpoint activation following exposure to genotoxic stress.

Subsequent studies revealed that the checkpoint kinase Rad53 binds phosphorylated Ies4 and protects it from protease-mediated degradation while also enhancing its *in vitro* kinase activity [113]. Mutation of helicase domain in the Ino80 ATPase subunit modestly diminishes Rad53 activity, thus it appears that ATP-dependent chromatin remodelling is not required for Rad53 activation. As a result, it is proposed that Ies4 provides a scaffold for Rad53 and potentiates its activity at DNA repair sites. These results demonstrate that the INO80 chromatin remodeller can alter the function of non-histone proteins. Similar functions have been observed for SWI/SNF-mediated activation of the Mec1 checkpoint kinase [114].

Additional studies provide corroborating evidence that the INO80 complex normally functions to attenuate DNA replication checkpoint activation and facilitate efficient recovery [108,109]. Specifically, the INO80 complex cooperates with the ISWI chromatin-remodelling complex to regulate the checkpoint response to hydroxyurea that depletes dNTP pools during replication. In double mutants of the INO80 and ISW1 complexes, persistent problems with replication fork integrity were not identified. However, a direct interaction was identified between these chromatin remodellers and RPA [108], a protein that accumulates on single-stranded DNA at stalled replication forks and signals for recruitment of checkpoint factors [115]. Thus, it has been proposed that INO80 and ISWI chromatin remodellers function redundantly to facilitate removal of RPA at replication forks, thus attenuating checkpoint activation and expedite recovery. Again, these results suggest that the INO80 chromatin remodeller can influence DNA damage responses through modulation of non-histone substrates.

6. The INO80 complex regulates mitotic stability

Not only is the INO80 chromatin remodeller involved in genome maintenance through DNA repair and cell cycle checkpoint regulation, but it is also involved in mitotic stability pathways. Proper chromosome segregation during mitosis ensures the faithful transmission of genetic information to daughter cells. Global genetic screens in yeast show that the

INO80 subfamily is involved in chromosome segregation pathways [116,117]. Mechanistic studies demonstrate that mutants of the INO80 complex exhibit increased abundance of histone H2AZ at pericentromeric regions [19]. The alteration of chromatin structure around centromeres correlates with defects in chromosome segregation and polyploidy [19]. In addition, *ARP8* deletion in the *S. cerevisiae* INO80 complex results in decreased association of the sister chromatid cohesion component Ctf18 (chromosome transmission fidelity 18) to chromatin and increased rates of sister chromatin separation during mitosis compared with wild-type cells [20]. Subunits of the INO80 complex, such as Arp4, complex bind directly to centromeres [118]. Mutation of *ARP4* in *S. cerevisiae* causes defects in the assembly of kinetochore components, such as the histone H3 variant chromosome segregation protein 4 (Cse4), resulting in mitotic cell cycle arrest [118]. Furthermore, certain mutations in histone H2A cause polyploidy that can be suppressed by overexpression of Arp4 [119].

Recently, chromatin remodellers have also been implicated in microtubule function. Human Ino80 has been shown to colocalize with the spindle *in vivo* and bind tubulin *in vitro* [120]. The *S. cerevisiae* complex co-purifies with tubulin [121]. Additionally, homologues of Rvb1 in Drosophila (Pontin) and mammals (RUVBL1) influence spindle assembly and organization of microtubule arrays in Xenopus extracts [122]. While these roles in microtubule function seem distant from previously defined roles in chromatin remodelling, it is unlikely to be restricted to the INO80 chromatin remodeller, as SWI/SNF complexes co-purify with tubulin [123] and genetically interact with γ-tubulin mutants [124]. Both ISWI and CHD4 chromatin remodellers bind microtubules in a RanGTP-dependent manner and are needed for microtubule bundling, spindle positioning and chromosome segregation [125,126].

Microtubules may simply serve as cytoplasmic sequestration factors for remodellers, as has previously been demonstrated for transcription factors [127–129]. However, because chromatin-remodelling factors affect microtubule polymerization and spindle dynamics, it may be that like checkpoint factors, microtubules and/or microtubule-associated proteins are also regulated by chromatin remodellers. This, in fact, may be another way to coordinate cell cycle dynamics during DNA damage responses.

7. Future directions

Important outstanding questions remain regarding the roles of INO80 in genome maintenance pathways. Specifically, despite multiple studies demonstrating that the INO80 complex is phosphorylated by ATM/ATR kinases [97,98,130], it is not yet known how these modifications modulate INO80 activity. In addition, as previously revealed, the activities of the INO80 complex are regulated by the inositol signalling pathway [131]. Inositol signalling is initiated by a range of external stimuli, such as growth factors and hormones, and regulates a number of crucial cellular functions, including cell growth, apoptosis and differentiation [132]. Thus, the INO80 complex may be regulated by multiple signalling pathways, including checkpoint responses and small molecules, in response to DNA damage.

As mentioned, assembly of the Arp5-Ies6 subunit module into the INO80 complex can induce chromatin-remodelling activity [44,51]. Thus, alteration of complex organization may regulate INO80's function *in vivo* during DNA repair and checkpoint processes. Combinatorial assembly of chromatin-remodelling subunits is critical to the composite activity of the complex. In fact, different assemblies of mammalian BAF (yeast SWI/SNF) complexes regulate development of the nervous system [133] and pluripotency of embryonic stem cells [134]. Hints of this dynamic regulation of the INO80 complex can be found in chromatin organization and transcriptional studies. Specifically, Arp5 appears to have a function independent of its associated chromatin-remodelling complex, as the mutant alleles of *arp5* impart phenotypes that are more severe than mutant *ino80* alleles in *Arabidopsis* [94,95]. Furthermore, localization of individual subunits varies across promoters and gene bodies and also contribute to different nucleosome positioning activities [46,135]. The INO80 complex participates in diverse genome stability activities and pathways. Thus, the knowledge of regulatory mechanisms that rapidly induce and reverse INO80's functions in DNA damage responses will be critical to our understanding of genome maintenance.

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