SIRT7 clears the way for DNA repair

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Histone modification by reversible lysine acetylation is a key regulatory mechanism in chromatin and nuclear signaling, whose deregulation is linked to aging, cancer, and other diseases. New work by Vazquez et al (2016) uncovers a role for the sirtuin family deacetylase SIRT7, which controls epigenetic maintenance of oncogenic gene expression programs, mitochondrial homeostasis, and ribosome biogenesis, in promoting genomic stability and DNA repair via site-specific deacetylation of a damage-associated histone mark, H3K18Ac.

See also: BN Vazquez et al (July 2016)

DNA is susceptible to damage from both environmental agents and cell intrinsic sources, and unrepaired or misrepaired damage is implicated in aging-related pathology and cancer. DNA double-strand breaks (DSBs) are particularly dangerous lesions. Defects in their repair can lead to mutations, DNA rearrangements, cell death, or senescence. The major DSB repair pathways in mammalian cells are non-homologous end joining (NHEJ) and homologous recombination-mediated repair (HR). Both pathways involve factors that detect damage, determine repair pathway choice, or activate downstream signaling (Smeenk & van Attikum, 2013). There is growing appreciation that chromatin regulation at sites of DNA damage plays pivotal roles in DNA repair and damage signaling. Changes in post-translational histone modifications—such as phosphorylation, acetylation, or methylation—at DSBs can increase chromatin accessibility or provide docking sites for damage signaling or repair factors. Thus, complex networks of interactions involving histone marks, their modifying enzymes, and downstream modification readers contribute to dynamic chromatin changes that are necessary for recognition and repair of damaged DNA (Smeenk & van Attikum, 2013).

SIRT7 is a member of the sirtuin family of NAD⁺-dependent lysine deacetylase enzymes, which play diverse roles in aging, metabolism, and disease processes (Chalkiadaki & Guarente, 2015). Studies over the past 5 years have identified roles for SIRT7 in regulating epigenetic and cellular homeostasis through deacetylation of histones and other nuclear proteins (Fig 1B). In chromatin, SIRT7 selectively deacetylates a specific histone residue, lysine 18 of histone H3 (H3K18Ac), to repress transcription at specific promoters. SIRT7-dependent H3K18Ac deacetylation inhibits a tumour-suppressive gene network that stabilizes the malignant state of cancer cells (Barber et al, 2012). SIRT7 has pleiotropic effects on the protein translation machinery, in part through transcriptional repression of ribosomal protein genes by H3K18Ac deacetylation. This can alleviate protein folding stress and, in mice, protect against fatty liver pathology and hematopoietic stem cell aging (Shin et al, 2013; Mohrin et al, 2015). SIRT7 also deacetylates the non-histone protein GABPβ1, a master transcriptional regulator of mitochondrial genes, to prevent aging- or stress-related mitochondrial dysfunction (Ryu et al, 2014). Finally, SIRT7 is enriched in nucleoli, where it deacetylates components of RNA polymerase I and the U3 snoRNP (small nucleolar RNP) complex to promote rRNA biogenesis (Chen et al, 2013, 2016). Thus, SIRT7 can impact on aging and disease biology through diverse effects on transcriptional and translational programs.

In this issue of The EMBO Journal, Vazquez and colleagues describe chromatin regulation at DSBs as a new role for SIRT7. They report that SIRT7 promotes DNA repair by H3K18Ac deacetylation at break sites, and this triggers recruitment of NHEJ repair factors. Moreover, new analysis of SIRT7-deficient mice revealed genomic instability and phenotypes suggestive of premature aging, which the authors propose may result from defective DSB repair.

SIRT7 is one of three nuclear mammalian sirtuins; the other two, SIRT1 and SIRT6, have been previously shown to promote DNA repair by inducing chromatin changes at DSBs and regulating the activity of DNA repair factors (Chalkiadaki & Guarente, 2015). Indeed, SIRT6 deficiency leads to shortened life span and aging-related phenotypes, some of which may result from defective DNA repair. By contrast, a direct role for SIRT7 in DNA repair has not yet been described, and DNA damage-related changes were not reported in SIRT7 mutant mice (Vakhrusheva et al, 2008; Shin et al, 2013). In the current study, Vazquez et al (2016) generated new strains of SIRT7 mutant mice. These mice exhibited partial embryonic lethality and shortened life span of those mice that were born. Analysis of these mice confirmed several previously reported phenotypes in other SIRT7 mutant mouse models, but also uncovered new effects of SIRT7 loss. Mutant mice had fatty liver and kyphosis, as well as phenotypes associated with premature aging including hematopoietic stem cell (HSC) dysfunction, leukopenia, and increased markers of cellular senescence (Fig 1C).

Strikingly, the SIRT7 mutant mice and cells showed many signs of defective DSB repair, both under baseline conditions and in response to ionizing radiation (IR). These signs include increased IR sensitivity, DSB accumulation, activation of ATM-dependent DNA damage response signaling, and H2AX.

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SIRT7 has been shown to regulate DNA repair by the non-homologous end joining (NHEJ) pathway, which is important for DSB repair in a NHEJ reporter. In addition, SIRT7 deficiency led to decreased immunoglobulin class switch recombination, a process that requires NHEJ. By contrast, several readouts of HR were unaffected in SIRT7-deficient cells.

To gain further insight into the mechanisms through which SIRT7 influences DSB repair, Vazquez et al. (2016) focused on 53BP1 signaling. 53BP1 is a large protein with many peptide binding modules and is targeted to chromatin through numerous interactions, including recognition of DSB-associated histone modifications (Panier & Boulton, 2014). Unexpectedly, however, no alterations in the known mechanisms of 53BP1 targeting were observed in SIRT7-deficient cells. Instead, the authors uncover a novel mechanism, in which 53BP1 recruitment to DSBs is linked to H3K18Ac deacetylation by SIRT7. First, they show that SIRT7 associates dynamically with chromatin at DSBs to deacetylate H3K18Ac, and SIRT7 deficiency leads to increased H3K18Ac levels both globally after IR and locally at site-specific DSBs. Vazquez et al. (2016) then provide evidence that H3K18Ac deacetylation by SIRT7 at DSBs is specifically required for recruitment of 53BP1. They use multiple approaches to show that overexpression of a mutant that mimics the deacetylated state (H3K18R) fully restores DSB-dependent phosphorylation (a chromatin marker of DSBs). The authors then provide multiple lines of evidence suggesting that SIRT7 is important for DSB repair by NHEJ, but not by HR. They show that SIRT7-deficient cells have defects in the DSB recruitment of 53BP1, a key regulator of chromatin signaling from DSBs that promotes NHEJ while preventing HR-mediated repair (Panier & Boulton, 2014). Importantly, reconstitution of SIRT7 levels with wild-type enzyme but not a catalytically inactive mutant was able to restore formation of 53BP1 DSB foci, indicating that the enzymatic activity of SIRT7 is required for the targeting of 53BP1 to DSBs. In addition, SIRT7 deficiency led to defective DSB repair in a NHEJ reporter assay and to reduced immunoglobulin class switch recombination, a process that requires NHEJ. By contrast, several readouts of HR were unaffected in SIRT7-deficient cells.

Figure 1. SIRT7, a regulator of epigenetic and cellular homeostasis.

(A) Model of SIRT7 function in DNA repair: SIRT7 is recruited by PARP1 to DSBs, where it deacetylates H3K18Ac. H3K18Ac deacetylation allows DSB recruitment of 53BP1 and activation of DNA repair by NHEJ. (B) Cellular functions of SIRT7 that may contribute to mouse loss-of-function phenotypes. SIRT7 is found in the nucleus and highly enriched in the nucleolus, where it promotes rRNA transcription and processing. In the nucleoplasm, H3K18Ac deacetylation by SIRT7 represses transcription of tumor-suppressive genes (which stabilizes cancer cell phenotypes) and ribosomal protein genes (which alleviates ER stress). In addition, H3K18Ac deacetylation at DSBs promotes DNA repair. SIRT7 also deacetylates the non-histone protein GABPβ1, which maintains mitochondrial homeostasis. (C) SIRT7 knockout mouse phenotypes reported by Vazquez and colleagues.
recruitment of 53BP1 in SIRT7-deficient cells. These findings suggest models in which H3K18 acetylation prevents recognition of adjacent sequences by 53BP1, and upon DNA damage needs to be cleared away by SIRT7-mediated deacetylation to allow for 53BP1 recruitment (Fig 1A).

Together, these findings establish for the first time a role for SIRT7 in DNA repair and elucidate a novel DBS chromatin signaling pathway that links damage-associated H3K18Ac deacetylation to activation of NHEJ repair. Moreover, defects in this pathway might contribute to aging-associated phenotypes observed in SIRT7 mutant mice. However, the findings also raise numerous questions for future investigation. For example, while the histone H3K18 mutational studies directly link SIRT7 to 53BP1 recruitment, several observations suggest that SIRT7 could impact on DNA repair and genomic stability through mechanisms beyond NHEJ. Indeed, Vazquez et al (2016) observe defects in SIRT7-deficient mice and cells—such as increased replication stress and mutation accumulation in an in vivo mutagenesis assay—that could point to defects in other genome stability pathways. Moreover, SIRT7-dependent deacetylation of H3K18Ac could lead to changes in chromatin structure and thereby affect many repair processes.

It is also likely that SIRT7 has additional histone and non-histone substrates, including other histone marks or DNA repair factors. Recent studies have shown that some mammalian sirtuin enzymes can catalyze deacetylation of longer chain fatty acyl modifications on histones or other proteins, such as myristoylation, succinylation, and crotonylation (Feldman et al, 2013). The physiologic relevance of these modifications is just beginning to be explored, and proteomic studies may uncover novel modifications that are regulated by SIRT7. Other known functions of SIRT7 might also indirectly affect DNA repair, and their loss might contribute to the defective genome maintenance and aging-like phenotypes of SIRT7-deficient mice. For example, the DNA damage-dependent mobilization of SIRT7 to DSBs leads to a transient reduction of nuclear SIRT7 levels; this decline in the nuclear functions of SIRT7 could underlie some of the DNA damage-dependent effects of SIRT7.

Vazquez et al (2016) also show that the association of SIRT7 with DSBs and its depletion from nucleoli upon DNA damage are dependent on PARP1, a chromatin-associated protein with roles in multiple DNA repair pathways as well as chromatin regulation of transcription. Does PARP1 specifically recruit SIRT7 for DSB repair, or can it also target SIRT7 to function in other contexts? Conversely, how are other functional consequences of 53BP1 activation affected by SIRT7 loss? Since 53BP1 is proposed to favor NHEJ over HR, can SIRT7 inactivation actually increase DSB repair by HR?

Finally, the importance of SIRT7 in DNA repair suggests that it might have tumor-suppressive functions. However, high SIRT7 expression is observed in many cancers, and previous work showed that SIRT7 is important for epigenetic stabilization of the transformed state of cancer cells (Barber et al, 2012). Thus, SIRT7 may have opposing effects on early stages of cancer initiation versus cancer progression.

In this study, Vazquez and colleagues provide the most detailed analysis to date of SIRT7-deficient mice and suggest that these mice undergo aspects of premature aging (Fig 1C). Some of these phenotypes are not directly linked to defects in SIRT7-dependent DBS repair and presumably result from other mechanisms (Fig 1B). SIRT7 already has several known cellular functions that can be linked to aging biology, including regulation of translation, mitochondrial homeostasis, and ER stress. As the list of molecular targets and cellular functions of SIRT7 continues to expand, it will be interesting to examine how deregulation of these pathways contributes to aging and disease.

**References**


