

Introduction



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Chromatin modifiers and remodellers in
DNA repair and signalling

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Following the seminal unravelling of the double helical structure of DNA by Watson, Crick and colleagues in 1952, work of equal significance and similarly recognized by a Nobel Prize led to the appreciation that DNA is an unstable structure subject to damage from chemical attack by agents arising endogenously or exogenously, and from metabolic transactions, such as replication and transcription [1,2]. The past 50 years has seen mounting recognition of the enormous significance of DNA damage response (DDR) pathways in protecting against the harmful effects of this damage, and particularly our understanding of the DNA repair processes [1]. Indeed, we now understand the importance these pathways play in cancer avoidance, in protection against ageing and in ensuring normal development [3,4]. We now have a good understanding of the basic DNA repair processes, at least when considering their action on naked DNA. However, in a cellular setting, our DNA is organized within a chromatin environment, which can represent a diverse range from open to closed conformations of distinct types. Our DNA sequences can be unique or repetitive. And there are ongoing DNA transactions, which can profoundly influence the DNA repair processes. Thus, a current focus of research is to understand how chromatin is modified and reorganized to allow optimal DNA repair and interplay between the DDR and metabolic processes such as transcription and replication.

Our goal in this themed issue is to review our current understanding of the epigenetic changes that arise in the vicinity of DNA double strand breaks (DSBs) and the chromatin remodelling complexes employed to reorganize chromatin. While the focus lies on DSBs, we include a consideration of how DNA damage influences transcription/replication as well as how chromatin is remodelled to allow replication since an evaluation of these interfacing processes is integral to our understanding of the processes arising following DNA damage. This area of research is still at an early stage. It is highly dynamic and, like all current research, confusion and conflicting data sometimes precede clarity—and the underlying mechanisms remain poorly defined. In this introductory report, we summarize the goals of this theme issue and consider the current questions, insights and apparent contradictions.

The ataxia telangiectasia mutated kinase (ATM) is the central orchestrator of the DDR to DSBs [5]. ATM has long been recognized as a central regulator of processes, such as cell cycle checkpoint arrest, that enhance the opportunity for optimal DSB repair [6]. Recent studies have extended this notion to include roles in inhibiting transcription specifically in the DSB vicinity [7,8]. Critically, however, more recent studies have unearthed the central role that ATM plays in orchestrating chromatin changes at a DSB. Indeed, while ataxia telangiectasia (A-T), a disorder caused by mutations in ATM, was originally considered to be a DNA repair disorder and later a checkpoint disorder, it could now be argued to be a disorder that fails to appropriately orchestrate DSB-induced chromatin changes, helping to explain its more significant role in higher compared with lower organisms [9–15]. In our opening article, Goodarzi and colleagues [16] set the scene by reviewing the complex nature of the chromatin changes regulated by ATM at a DSB. The route by which ATM effects epigenetic changes at a DSB has been emerging for several years. The process starts by ATM-dependent

phosphorylation of H2AX, with this signal being read and transduced via MDC1 binding to promote or expose additional histone modifications including ubiquitination, SUMOylation and methylation [17,18]. Importantly, these histone modifications exert two somewhat distinct endpoints; firstly, histone modifications can directly effect the recruitment of DDR proteins, such as BRCA1 and 53BP1, and secondly, coupled with direct ATM-dependent phosphorylation of DDR proteins, they can lead to the recruitment or modification of chromatin remodelling complexes. Goodarzi and colleagues [16] review insight into the mechanism of the ATM-dependent processes regulating chromatin reorganization where detailed knowledge is available. Wilson & Durocher [19], in our second review, discuss how the distinct histone modifications can be read to influence recruitment of DDR proteins. They discuss the characterized domains at a mechanistic and structural level, revealing important insight into the 'reading' signatures and the downstream consequences. Such 'reading' encompasses roles for BRCT, Tudor and ubiquitin binding domains in binding to phosphorylation, methylation and ubiquitin modifications but their interplay with readers of, for example, acetylation, provides a network of balances. Extending this theme, Miller and colleagues [20] focus on bromodomain (BRD) proteins, discussing how they 'read' histone acetylation and the route by which they promote chromatin remodelling. Indeed, BRD-containing proteins are central to several chromatin remodelling complexes, providing an interface with the reviews that focus more on chromatin remodelling.

While modification of histone variant forms, such as H2AX, H2AZ and H3.3, has been recognized for some time to play critical roles in chromatin organization after DNA damage or during transcription, the N-terminal tail of H4, which has well conserved lysine residues primed for acetylation at the amino group, is becoming increasingly recognized as a central factor regulating the DDR [21,22]. Acetylation of the H4 tail can also directly influence chromatin organization through charge-regulated histone interactions. Moreover, as discussed in our second review [19], histone acetylation can serve to block or restrict other modifications on the same or nearby residues. Dhar *et al.* [23] provide a focused review on the N-terminal tail of H4 considering the processes influencing lysine acetylation, how it influences chromatin organization and the downstream impact on repair.

The ubiquitin-dependent molecular unfoldase/segregase, p97, also known as VCP in vertebrates and Cdc48 in lower eukaryotes, has emerged as another route by which epigenetic modifications can influence chromatin remodelling at the sites of DNA damage, as well as during transcription and repair [24]. p97 is an AAA+ ATPase, which uses ATP to unfold or segregate ubiquitinated substrates, targeting them for proteasome-mediated degradation and relieving their impact on chromatin structure. p97-mediated protein degradation can directly impact upon DSB repair, such as the targeted removal of DNA-bound Ku, but can also interface and cooperate with chromatin remodelling complexes to reorganize chromatin structure after DNA damage. Somewhat distinctively, p97 can also regulate the inhibition and recovery of transcription at the sites of DNA damage via the removal of arrested RNA polymerase II. Ramadan and colleagues [25] provide a review of the emerging understanding of roles of p97 during DNA DSB repair.

While the phosphorylation, ubiquitylation and acetylation modification machinery has been well examined, SUMO modifiers, 'reader' motifs and interacting proteins have been less

well characterized, although there is clear evidence that SUMOylation occurs during the DDR and directly influences DSB repair [17]. Garvin & Morris [26] focus on these aspects of SUMOylation in their review, providing a nice addition to the reviews discussed above.

Chromatin remodelling enzymes use the energy derived from the hydrolysis of ATP to alter the structure or composition of chromatin. The enzymes can be divided into families based on their domain organization, and most remodelling enzymes are found within multisubunit complexes. While they all share a related catalytic subunit, each remodelling enzyme (or complex) leads to different outcomes, such as nucleosome repositioning, histone eviction, or histone subunit exchange [27]. This specificity in mode of action is generated by the accessory domains and subunits attached to the motor proteins.

One remodelling complex, INO80, has been shown to play numerous important roles in the maintenance of genome stability, with many of the insights generated in work done using budding yeast as a model system. The review from Morrison [28] focuses on the role of INO80 in mediating the checkpoint response to replicative stress, which highlights the importance of individual subunits of these complexes, since a key player in this activity is the non-catalytic Ies4 subunit of INO80. In addition, she discusses a mitotic role for INO80, which impacts on the fidelity of chromosome segregation.

In a review from Poli and colleagues [29] the central role of INO80 in mediating the complex interplay between replication, transcription and DDRs is discussed. The authors point out that this is no doubt a contributing factor to the known impact of INO80 on development and disease in higher eukaryotes. In addition, this review brings up an important concept related to the role of remodellers in DDRs: that of chromosome mobility. It is perhaps intuitive that an increase in chromosome mobility might facilitate the manipulation required to carry out repair, but it was more surprising that some breaks are moved to the nuclear periphery during the repair process. The contribution of INO80 to these events is discussed.

Highly complementary with this review is one from Chiolo and colleagues [30], which examines the challenges associated with DSB repair in heterochromatin. This review focuses primarily on work on *Drosophila*, where movement of DNA breaks arising in heterochromatin is required for repair, but the authors also highlight elements of the cellular responses that are intriguingly conserved in other organisms. In addition, they also consider the distinction between expansion of heterochromatin and mobilization of the break to a new location, and discuss the dynamic nature of heterochromatin proteins in this process.

While INO80 plays a central role in DDRs, many more chromatin remodelling enzymes have also been implicated. Clearly, the different enzymes contribute distinct functions to the process of repair, and understanding why so many are needed and what each one is doing is of great importance. This is the subject of the review by Rother & van Attikum [31], who cover the current state of knowledge around nine remodellers with known functions in DNA repair. How each of these is recruited to the right place at the right time, which step in the repair process is promoted by each, and how the complexes talk to each other are still very open questions.

As discussed above, the chromatin changes required to optimize DSB repair must be evaluated in the context of other DNA transactions, of which transcription is, arguably, the most important process. Recent findings have revealed

that RNA Pol II-dependent transcription is arrested in the vicinity of a DSB in a manner that requires chromatin remodeling, which may itself influence the DSB repair process [7,8,32]. Yasui and colleagues [33] provide a review of the chromatin changes involved in that process. As discussed in this review, emerging evidence indicates that there is a repair process that occurs in regions open for transcription interfacing transcriptional arrest and repair, akin to the distinction between transcription coupled repair and global genome repair at UV photoproducts. An emerging topic in the field of DNA repair is the contribution of transcription and RNA to the repair process [34–36]. In particular, DNA-RNA hybrids or R-loops can present a source of DNA damage but equally can profoundly influence the repair process. Sebastian & Oberdoerffer [37] provide a timely review of the influence of RNA on genome maintenance. Although less focused on chromatin, this review is significant in overviewing the evidence for how RNA or R-loops can drive transcription-associated DNA damage as well as potentially providing a template to optimize DSB repair. Insight into this novel aspect of DSB formation and repair must be evaluated in future considerations of chromatin changes at damage sites, particularly given recent evidence that RNA can be transcribed in an end-templated manner [38].

The very early studies on A-T provided seminal evidence for a role of ATM (although the causal genetic defect was uncharacterized at that time) in arresting replication in the presence of DSBs [13]. We still have only a poor understanding of how ATM influences replication and, more significantly, the chromatin changes required to promote replication. As a step towards addressing this critical topic, Bellush & Whitehouse [39] have discussed DNA replication in the context of a chromatin environment, considering origin licensing, origin firing and the replication process itself. Although somewhat distinct from our focus on DSB repair, an evaluation of replication in a chromatin environment reveals the role of factors, including chromatin remodelling complexes, that may also participate in DSB repair as well as providing insight into the mechanism underlying this related process.

What emerges from these reviews is the magnitude and complexity of the changes that arise in the DSB vicinity, frequently with seemingly conflicting consequences. Important contributing factors to the range of responses are the influence of transcription, replication and other transactions involving the DNA molecule coupled with the nature of the pre-existing chromatin structure prior to DNA damage (e.g. unique or repetitive sequences, heterochromatic or euchromatic); there are also likely to be kinetic and distance related requirements for chromatin structure at a DSB. Studies employing a site-specific DSB have shown that there are temporal changes in chromatin structure, with early but transient chromatin expansion followed by extensive and persistent condensation [40,41]. Nevertheless, others have provided evidence that these changes occur in the opposite order. Namely, there is an initial stage of recruitment of repressive complexes such as HP1, H2AZ and the NuRD complex, followed by a shift to a more open structure involving acetylation of the H4 tail compaction with subsequent chromatin relaxation [42,43]. This apparent contradiction may be due to the different scales measured in the different approaches (for example, immunofluorescence compared with chromatin immunoprecipitation). Indeed, it seems likely that chromatin relaxation, histone sliding or eviction will be required immediately adjacent to the DSB to facilitate repair while a compacted environment may be required more distal to the DSB to restrict

translocation formation. An important goal for future work will be to determine how the modifications and chromatin dynamics change in a temporal and location-dependent manner, as well as how they are influenced by ongoing DNA transactions.

Similarly, the data regarding the role of upstream signalling factors do not lend themselves well to a straightforward single model. This is almost certainly due to the fact that not all events will take place at every break. The location, timing, and complexity of the break are just a few of the factors that might influence which events are carried out and in what order.

Another critical question is about how the pre-existing chromatin environment influences pathway usage so that the cell uses the optimal choice. The core process of DNA non-homologous end-joining (c-NHEJ) represents a compact process, demanding little chromatin opening. There may, in fact, be a significant benefit from a highly compacted environment distal to a DSB undergoing c-NHEJ to restrict the possibility of translocation events, which can potentially occur readily by c-NHEJ owing to the lack of requirement for sequence homology for rejoining. Homologous recombination (HR), in contrast, necessitates extensive end-resection and histone changes if branch migration also occurs and the extensive homology requirements restrict the opportunity for translocation formation. However, paradoxically, the extensive chromatin changes necessitated by HR may be a significant factor restricting its usage in higher organisms, where the precise epigenetic code is complex but critical, since the precision of this code needs to be reconstituted after the completion of repair. Recent studies have suggested that, at least in late S/G2 phase, HR is exploited to repair DSBs within transcriptionally active regions, a possibility that appears rational given the potential enhanced accuracy of HR compared with NHEJ [44]. As discussed in the review by Chiolo and colleagues [30], there is also evidence, though with less obvious rationality, that DSBs within repeat sequences may be preferably repaired by HR. If correct, then what determines how the optimal pathway is chosen and how do these signals interface with damage-induced chromatin modifications?

If HR repairs transcription-associated DSBs in late S/G2 phase, then what happens to such DSBs in G1 phase? Recent studies have revealed that the slow component of DSB repair in G0/G1 phase cells occurs via a resection-mediated process of c-NHEJ [45], which arises in a manner akin to HR in late S/G2 phase cells [46]. This process will most likely require a greater degree of chromatin relaxation than the fast process of c-NHEJ, which occurs without the requirement for resection nucleases. Significantly, many of the reporter constructs for NHEJ are likely to monitor this resection-mediated NHEJ process, since resection-independent c-NHEJ will predominantly reconstitute the restriction site. Thus, an important future question is how damage-induced chromatin modifications and chromatin remodelling influence the usage of these two forms of c-NHEJ (resection-independent or resection-dependent) versus HR (dependent upon extensive resection). However, to address such questions it is vital to understand the factors influencing which repair pathway is optimally used, which may itself be determined by pre-existing (i.e. non-DNA damage-induced) chromatin modifications or structure.

Collectively, our reviews demonstrate the significance of the nucleosome as a central hub that organizes the recruitment of repair and signalling factors in a coordinated fashion to achieve optimal DSB repair. Such optimal DSB repair may

itself, however, be determined, at least in part, by the chromatin environment prior to DNA damage. The optimal DSB repair process at these distinct sites has possibly been evolutionarily determined by the route limiting genomic instability. This encompasses a range of endpoints including the avoidance of junctional deletions or missense mutations, translocations and longer term epigenetic changes in the DSB vicinity. Moreover, the ability to interface DSB repair with the arrest and subsequent recovery of DNA transactions, such as repair and replication, is clearly important. This likely involves a complex network of changes in chromatin

structure that arise in a temporal- spatial- and context-dependent manner. The future challenge lies in unravelling this complex web.

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Editor biographies



Professor Penny Jeggo obtained her PhD in the laboratory of Dr Robin Holliday at the National Institute for Medical Research (NIMR) in London. After two post-doctoral fellowships, Penny returned to NIMR in 1980 and commenced her independent work on the damage responses to radiation exposure in mammalian cells. In 1989 Penny moved to the Cell Mutation Unit in Sussex and in 2001 became a founding member of the Genome Damage and Stability Centre at the University of Sussex. Penny isolated X-ray sensitive mammalian mutants that proved to be defective in DNA double strand break (DSB) repair owing to defects in DNA non-homologous end-joining. Using these mutants, the Jeggo laboratory identified Ku80 as the first gene conferring radioresistance in mammalian cells. In collaborative work, she showed that DNA non-homologous end-joining functions during immune development. This work predicted that there might be radiosensitive immunodeficiency (RS-SCID) patients with mutations in DNA non-homologous end-joining genes. Collaborating with clinicians in UK immunodeficiency centres, such patients were identified in 2001. The Jeggo laboratory has identified further DNA repair disorders and studied the contribution of DNA repair to

human health. Penny is interested in radiation protection and has contributed to several committees considering the impact of radiation exposure on human health. Penny is a fellow of the Academy of Medical Sciences, and received the Bach and Alexander Award in 2011, UK's Genome Damage and Stability Network Award and the Sylvanus Thompson Award in 2013.



Jessica Downs is the Professor of Epigenetics and Genome Stability at the Institute of Cancer Research in London. She did her PhD at the Gurdon Institute at Cambridge University followed by a postdoctoral position studying DNA repair. In 2002, Jessica was awarded the Jenner Fellowship from the Lister Institute of Preventive Medicine, which she used to establish her own lab in the Biochemistry Department at Cambridge University, followed by a move to the Genome Damage and Stability Centre. In 2016, Jessica relocated the lab to the Institute of Cancer Research to join the Division of Cancer Biology. Research in the Downs lab is aimed at understanding the impact of chromatin structure and epigenetic regulation on DNA damage responses and the maintenance of genome stability.



Professor Susan M. Gasser is a Swiss biochemist who studied biophysics at the University of Chicago, and completed her PhD at the University of Basel in Biochemistry. After studying human mitotic chromosomes at the University of Geneva, she began her own research on chromatin and chromosome organization in budding yeast, combining genetics, microscopy and biochemical approaches, at the Swiss Institute for Experimental Cancer Research in Epalinges/Lausanne. After 15 years, she returned to the University of Geneva as Professor of Molecular Biology and, in 2004, she was recruited as Director of the Friedrich Miescher Institute for Biomedical Research in Basel, where she also holds the chair of Molecular Biology at the University of Basel. Susan Gasser studies how nuclear and chromosomal context establishes and maintains heritable patterns of gene expression. From the telomere position effect in yeast, to the inheritance of repressed tissue-specific genes in *Caenorhabditis elegans*, her studies have examined how the spatial organization of heterochromatin in the nucleus contributes to heritable gene silencing. In parallel to these studies, the Gasser laboratory optimized live imaging techniques to pioneer the analysis of chromatin dynamics with time-lapse fluorescence imaging. This brought her to the study of chromatin

remodellers, among which figured INO80, particularly in the context of replication stress and double strand break repair. Dr Gasser was elected to the Académie de France, EMBO and the Swiss Academy of Medical Sciences, and received the INSERM International Prize in 2011, the FEBS | EMBO Women in Science Award in 2012, and the Weizmann Institute Women in Science award in 2013.

References

- Kunkel TA. 2015 Celebrating DNA's repair crew. *Cell* **163**, 1301–1303. (doi:10.1016/j.cell.2015.11.028)
- Lindahl T, Modrich P, Sancar A. 2016 The 2015 Nobel prize in chemistry the discovery of essential mechanisms that repair DNA damage. *J. Assoc. Genet. Technol.* **42**, 37–41.
- Hoeijmakers JH. 2009 DNA damage, aging, and cancer. *N Engl. J. Med.* **361**, 1475–1485. (doi:10.1056/NEJMra0804615)
- Canugovi C, Misiak M, Ferrarelli LK, Croteau DL, Bohr VA. 2013 The role of DNA repair in brain related disease pathology. *DNA Repair (Amst)* **12**, 578–587. (doi:10.1016/j.dnarep.2013.04.010)
- Shiloh Y. 2014 ATM: expanding roles as a chief guardian of genome stability. *Exp. Cell Res.* **329**, 154–161. (doi:10.1016/j.yexcr.2014.09.002)
- Jeggio P, Lavin MF. 2009 Cellular radiosensitivity: how much better do we understand it? *Int. J. Radiat. Biol.* **85**, 1061–1081. (doi:10.3109/09553000903261263)
- Kakaroukas A, Ismail A, Chambers AL, Riballo E, Herbert AD, Kunzel J, Loblrich M, Jeggo PA, Downs JA. 2014 Requirement for PBAF in transcriptional repression and repair at DNA breaks in actively transcribed regions of chromatin. *Mol. Cell* **55**, 723–732. (doi:10.1016/j.molcel.2014.06.028)
- Shanbhag NM, Rafalska-Metcalf IU, Balane-Bolivar C, Janicki SM, Greenberg RA. 2010 ATM-dependent chromatin changes silence transcription in cis to DNA double-strand breaks. *Cell* **141**, 970–981. (doi:10.1016/j.cell.2010.04.038)
- Taylor AMR, Harnden DG, Arlett CF, Harcourt SA, Lehmann AR, Stevens S, Bridges BA. 1975 Ataxia-telangiectasia, a human mutation with abnormal radiation sensitivity. *Nature* **258**, 427–429. (doi:10.1038/258427a0)
- Cornforth MN, Bedford JS. 1985 On the nature of a defect in cells from individuals with ataxia-telangiectasia. *Science* **227**, 1589–1591. (doi:10.1126/science.3975628)
- Kastan MB, Zhan Q, El-Deiry WS, Carrier F, Jacks T, Walsh WV, Plunkett BS, Vogelstein B, Fornace AJ. 1992 A mammalian cell cycle checkpoint pathway utilizing p53 and GADD45 is defective in ataxia-telangiectasia. *Cell* **71**, 587–597. (doi:10.1016/0092-8674(92)90593-2)
- Beamish H, Williams R, Chen P, Lavin MF. 1996 Defect in multiple cell cycle checkpoints in ataxia-telangiectasia postirradiation. *J. Biol. Chem.* **271**, 20 486–20 493. (doi:10.1074/jbc.271.34.20486)
- Painter RB, Young BR. 1980 Radiosensitivity in ataxia-telangiectasia: a new explanation. *Proc. Natl Acad. Sci. USA* **77**, 7315–7317. (doi:10.1073/pnas.77.12.7315)
- Lavin MF. 2008 Ataxia-telangiectasia: from a rare disorder to a paradigm for cell signalling and cancer. *Nat. Rev. Mol. Cell Biol.* **9**, 759–769. (doi:10.1038/nrm2514)
- Price BD, D'Andrea AD. 2013 Chromatin remodeling at DNA double-strand breaks. *Cell* **152**, 1344–1354. (doi:10.1016/j.cell.2013.02.011)
- Berger ND, Stanley FKT, Moore S, Goodarzi AA. 2017 ATM-dependent pathways of chromatin remodelling and oxidative DNA damage responses. *Phil. Trans. R. Soc. B* **372**, 20160283. (doi:10.1098/rstb.2016.0283)
- Jackson SP, Durocher D. 2013 Regulation of DNA damage responses by ubiquitin and SUMO. *Mol. Cell* **49**, 795–807. (doi:10.1016/j.molcel.2013.01.017)
- Fradet-Turcotte A *et al.* 2013 53BP1 is a reader of the DNA-damage-induced H2A Lys 15 ubiquitin mark. *Nature* **499**, 50–54. (doi:10.1038/nature12318)
- Wilson MD, Durocher D. 2017 Reading chromatin signatures after DNA double-strand breaks. *Phil. Trans. R. Soc. B* **372**, 20160280. (doi:10.1098/rstb.2016.0280)
- Chiu L-Y, Gong F, Miller KM. 2017 Bromodomain proteins: repairing DNA damage within chromatin. *Phil. Trans. R. Soc. B* **372**, 20160286. (doi:10.1098/rstb.2016.0286)
- Xu Y, Ayrapetov MK, Xu C, Gursoy-Yuzugullu O, Hu Y, Price BD. 2012 Histone H2A.Z controls a critical chromatin remodeling step required for DNA double-strand break repair. *Mol. Cell* **48**, 723–733. (doi:10.1016/j.molcel.2012.09.026)
- Paull TT, Rogakou EP, Yamazaki V, Kirchgessner CU, Gellert M, Bonner WM. 2000 A critical role for histone H2AX in recruitment of repair factors to nuclear foci after DNA damage. *Curr. Biol.* **10**, 886–895. (doi:10.1016/S0960-9822(00)00610-2)
- Dhar S, Gursoy-Yuzugullu O, Parasuram R, Price BD. 2017 The tale of a tail: histone H4 acetylation and the repair of DNA breaks. *Phil. Trans. R. Soc. B* **372**, 20160284. (doi:10.1098/rstb.2016.0284)
- Meerang M *et al.* 2011 The ubiquitin-selective segregase VCP/p97 orchestrates the response to DNA double-strand breaks. *Nat. Cell Biol.* **13**, 1376–1382. (doi:10.1038/ncb2367)
- Torreclilla I, Oehler J, Ramadan K. 2017 The role of ubiquitin-dependent segregase p97 (VCP or Cdc48) in chromatin dynamics after DNA double strand breaks. *Phil. Trans. R. Soc. B* **372**, 20160282. (doi:10.1098/rstb.2016.0282)
- Garvin AJ, Morris JR. 2017 SUMO; a small, but powerful, regulator of double-strand break repair. *Phil. Trans. R. Soc. B* **372**, 20160281. (doi:10.1098/rstb.2016.0281)
- Clapier CR, Iwasa J, Cairns BR, Peterson CL. 2017 Mechanisms of action and regulation of ATP-dependent chromatin-remodelling complexes. *Nat. Rev. Mol. Cell Biol.* **18**, 407–422. (doi:10.1038/nrm.2017.26)
- Morrison AJ. 2017 Genome maintenance functions of the INO80 chromatin remodeler. *Phil. Trans. R. Soc. B* **372**, 20160289. (doi:10.1098/rstb.2016.0289)
- Poli J, Gasser SM, Papamichos-Chronakis M. 2017 The INO80 remodeler in transcription, replication and repair. *Phil. Trans. R. Soc. B* **372**, 20160290. (doi:10.1098/rstb.2016.0290)
- Christopher CP, Laetitia D, Grzegorz Z, Irene C. 2017 And yet, it moves: nuclear and chromatin dynamics of heterochromatic double-strand break. *Phil. Trans. R. Soc. B* **372**, 20160291. (doi:10.1098/rstb.2016.0291)
- Rother MB, van Attikum H. 2017 DNA repair goes hip hop: SMARCA and CHD chromatin remodellers join the break dance. *Phil. Trans. R. Soc. B* **372**, 20160285. (doi:10.1098/rstb.2016.0285)
- Ui A, Nagaura Y, Yasui A. 2015 Transcriptional elongation factor ENL phosphorylated by ATM recruits polycomb and switches off transcription for DSB repair. *Mol. Cell* **58**, 468–482. (doi:10.1016/j.molcel.2015.03.023)
- Watanabe R, Kanno S-ichiro, Mohamadi Roushandeh A, Ui A, Yasui A. 2017 Nucleosome remodelling, DNA repair and transcriptional regulation build negative feedback loops in cancer and cellular ageing. *Phil. Trans. R. Soc. B* **372**, 20160473. (doi:10.1098/rstb.2016.0473)
- Chakraborty A, Tapryal N, Venkova T, Horikoshi N, Pandita RK, Sarker AH, Sarker PS, Pandita TK, Hazra TK. 2016 Classical non-homologous end-joining pathway utilizes nascent RNA for error-free double-strand break repair of transcribed genes. *Nat. Commun.* **7**, 13049. (doi:10.1038/ncomms13049)
- Ohle C, Tesorero R, Schermann G, Dobrev N, Sinning I, Fischer T. 2016 Transient RNA-DNA hybrids are required for efficient double-strand break repair. *Cell* **167**, 1001–1013 e1007. (doi:10.1016/j.cell.2016.10.001)
- Tresini M *et al.* 2015 The core spliceosome as target and effector of non-canonical ATM signalling. *Nature* **523**, 53–58. (doi:10.1038/nature14512)
- Sebastian R, Oberdoerffer P. 2017 Friend or foe: RNA in (epi)genome maintenance. *Phil. Trans. R. Soc. B* **372**, 20160288. (doi:10.1098/rstb.2016.0288)
- Francia S, Cabrini M, Matti V, Oldani A, d'Adda di Fagnana F. 2016 DICER, DROSHA and DNA damage response RNAs are necessary for the secondary recruitment of DNA damage response factors. *J. Cell Sci.* **129**, 1468–1476. (doi:10.1242/jcs.182188)
- Bellush JM, Whitehouse I. 2017 DNA replication through a chromatin environment. *Phil. Trans. R. Soc. B* **372**, 20160287. (doi:10.1098/rstb.2016.0287)
- Khurana S *et al.* 2014 A macrohistone variant links dynamic chromatin compaction to BRCA1-dependent genome maintenance. *Cell Rep.* **8**, 1049–1062. (doi:10.1016/j.celrep.2014.07.024)
- Burgess RC, Burman B, Kruhlak MJ, Misteli T. 2014 Activation of DNA damage response signaling by

- condensed chromatin. *Cell Rep.* **9**, 1703–1717. (doi:10.1016/j.celrep.2014.10.060)
42. Gursoy-Yuzugullu O, House N, Price BD. 2016 Patching broken DNA: nucleosome dynamics and the repair of DNA breaks. *J. Mol. Biol.* **428**, 1846–1860. (doi:10.1016/j.jmb.2015.11.021)
43. Baldeyron C, Soria G, Roche D, Cook AJ, Almouzni G. 2011 HP1alpha recruitment to DNA damage by p150CAF-1 promotes homologous recombination repair. *J. Cell Biol.* **193**, 81–95. (doi:10.1083/jcb.2011101030)
44. Clouaire T, Legube G. 2015 DNA double strand break repair pathway choice: a chromatin based decision? *Nucleus* **6**, 107–113. (doi:10.1080/19491034.2015.1010946)
45. Biehs R, Steinlage M, Barton O, Juhasz S, Kunzel J, Spies J, Shibata A, Jeggo PA, Lobrich M. 2017 DNA double-strand break resection occurs during non-homologous end joining in G1 but is distinct from resection during homologous recombination. *Mol. Cell* **65**, 671–684.e675. (doi:10.1016/j.molcel.2016.12.016)
46. Beucher A *et al.* 2009 ATM and artemis promote homologous recombination of radiation-induced DNA double-strand breaks in G2. *EMBO J.* **28**, 3413–3427. (doi:10.1038/emboj.2009.276)