Ubiquitin and SUMO in DNA repair at a glance

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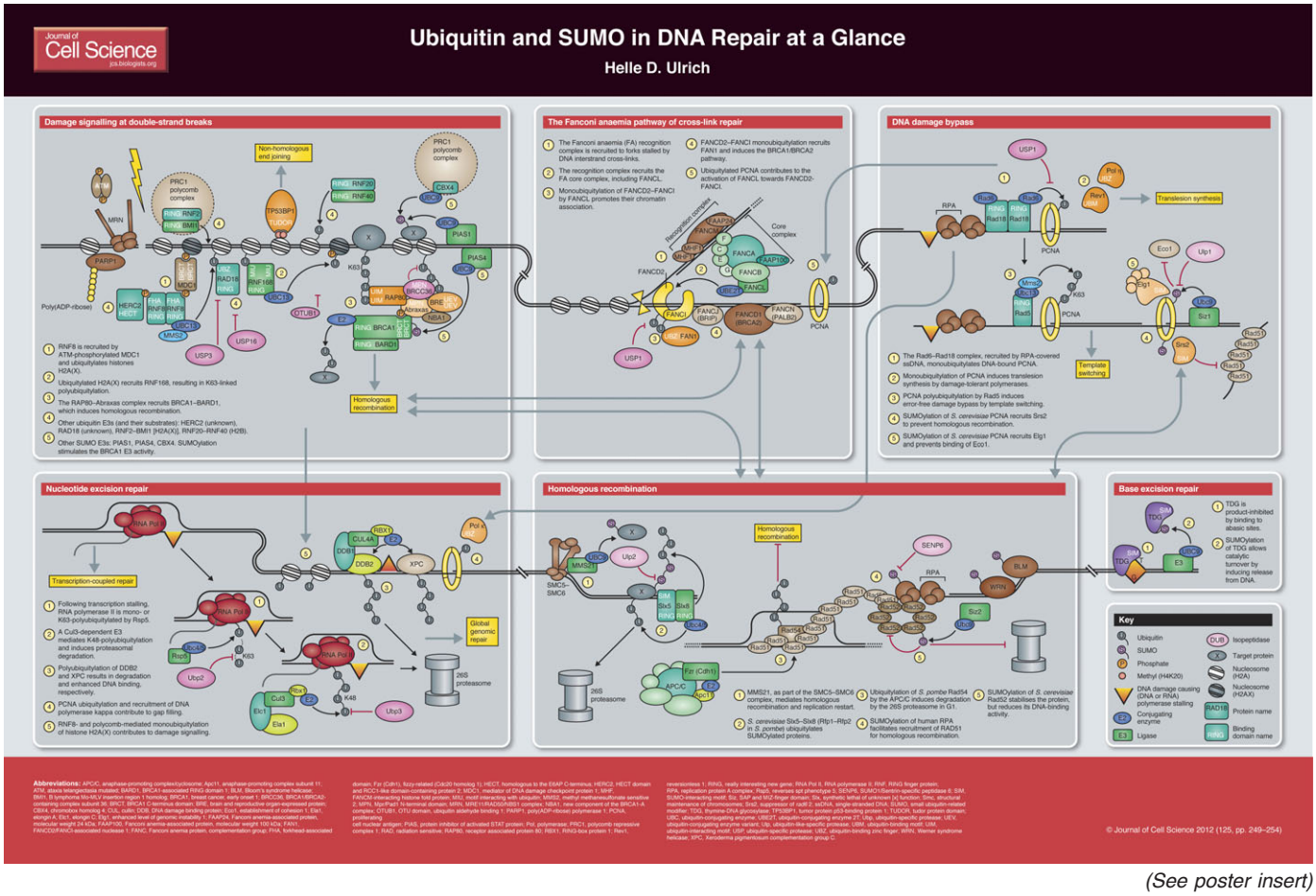
The task of preserving the stability of the genetic information of a cell is characterised by several important requirements (Hoeijmakers, 2009). First, genome maintenance is a largely cell-autonomous function, as each cell within an organism is obliged to prevent or repair injury of its own genome. Second, insults that endanger genome stability require a rapid response because damage to the genetic material quickly affects essential cellular functions by interfering with gene expression. Third, any response needs to be reversibly tuned to the physiological state of the cell, in particular its stage within the cell cycle. Last, but not least, mechanisms for the protection of genome integrity have to react flexibly to a large variety of damaging agents to which a cell may be exposed.

Considering these characteristics of DNA repair, it is not surprising that post-translational modifications with members of the ubiquitin family, such as ubiquitin itself and small ubiquitin-related modifier (SUMO), have been identified as key contributors to genome maintenance. The notion that ubiquitin and SUMO can rapidly and reversibly change the properties, stability or localisation of their target proteins without the need for de novo protein synthesis makes them ideal regulators for fine-tuning DNA repair and damage response pathways. Their general action as modulators of protein function goes far beyond their contribution to regulated proteolysis, for which ubiquitin first became famous (Glickman and Ciechanover, 2002).

In this Cell Science at a Glance article and the accompanying poster, I will summarise the contributions of ubiquitin and SUMO to the major pathways of genome maintenance. Several excellent reviews on this topic have been published over the past years, which give insight into the relevant mechanisms involved (Al-Hakim et al., 2010; Bergink and Jentsch, 2009; Huang and D'Andrea, 2006; Ulrich and Walden, 2010). Here, I will place more emphasis on the crosstalk between individual repair pathways and the specific contributions of selected proteins involved in ubiquitin and SUMO conjugation to the processes involved. For information about the general principles of protein ubiquitylation and SUMOylation, the reader is referred to pertinent reviews in this field (Glickman and Ciechanover, 2002; Kerscher et al., 2006).



(See poster insert)

The response to DNA double-strand breaks

DNA double-strand breaks (DSBs) represent perhaps the most dangerous type of DNA lesion because they have dramatic effects on all DNA transactions, including proper segregation of chromosomes during cell division (Hoeijmakers, 2009). In order to initiate repair, a series of phosphorylation events, namely the phosphorylation of the histone variant H2AX and mediator of DNA-damage checkpoint 1 (MDC1) by the checkpoint kinase ataxia telangiectasia mutated (ATM), leads to the sequential recruitment of several E3 ubiquitin ligases in higher eukaryotes, as detailed below (Bekker-Jensen and Mailand, 2011; Panier and Durocher, 2009; Tang and Greenberg, 2010). These enzymes promote extensive ubiquitylation of histone H2A and other, yet unknown, chromatin-associated proteins in a cascade that eventually results in the localisation of another RING-finger ubiquitin ligase, BRCA1 (for breast cancer 1, early onset), as well as the checkpoint protein TP53BP1 (for tumor protein p53 binding protein 1), to the break. Whereas BRCA1 is essential for initiating DSB repair by homologous recombination, TP53BP1 has been associated with repair by non-homologous end-joining (Hiom, 2010).

The mechanistic details of TP53BP1 recruitment to DSBs are poorly understood. The protein binds to methylated histones, and it is unclear how the damage-induced ubiquitylation cascade elicits this signal for chromatin association of TP53BP1. By contrast, the signalling pathway leading to BRCA1 recruitment has now been roughly elucidated. Although there are indications that the pathway is not entirely linear, the prevailing concept is based on the recognition of post-translational modifications, such as phosphate or ubiquitin moieties, by dedicated domains in the respective effector proteins, which themselves trigger the recruitment of additional enzymes for modification of other chromatin components. Specifically, phosphorylated H2AX (γ-H2AX) is recognised by tandem BRCA1 C-terminal (BRCT) motifs on MDC1. Following phosphorylation by ATM, MDC1 is then able to interact with the forkhead-associated (FHA) domains of the RING-finger E3 RNF8 (Huen et al., 2007; Kolas et al., 2007; Mailand et al., 2007). The ubiquitin moieties conjugated by RNF8 and its cognate ubiquitin-conjugating enzyme (E2) UBC13 (officially known as ubiquitin-conjugating enzyme E2N, UBE2N) to histones H2A and H2AX, and possibly other chromatin-bound proteins, are thought to be recognised by a second RING-finger E3, RNF168, through its 'motifs interacting with ubiquitin' (MIU) domains (Doil et al., 2009; Stewart et al., 2009). RNF168, together with UBC13, catalyses the formation of polymeric chains, linked through lysine (K) 63 of ubiquitin, that in turn recruit the adapter protein RAP80 (receptor associated protein 80, also known as UIMC1) through its ubiquitin-interacting motifs (UIM). The dimeric BRCA1–BARD1 complex is eventually recruited through the interaction of the BRCA1 tandem BRCT motifs with the phosphorylated abraxas protein (also known as FAM175A), which is itself part of a multisubunit scaffold complex (Kim et al., 2007; Liu et al., 2007; Sobhian et al., 2007; Wang et al., 2007). Although it is clear that BRCA1 is an important mediator of DNA DSB repair through homologous recombination, its relevant substrate proteins and cognate E2 enzyme(s), the structure of the resulting ubiquitin conjugates and the physiological consequences of these modifications are not yet fully understood (Hiom, 2010).

In addition to BRCA1, several other ubiquitin E3s participate in the cascade, although their roles are less well defined. On one hand, RAD18, a RING-finger E3 best known for its function in DNA damage bypass (see below), acts downstream of RNF8, presumably by being recruited to chromatin by means of a ubiquitin-binding zinc finger (UBZ) domain (Huang et al., 2009). Intriguingly, the binding of RAD18, but not its E3 ligase activity, is required for proper homologous recombination. On the other hand, HERC2, a large HECT domain family E3 protein, associates with the FHA domain of RNF8 and seems to promote interaction with UBC13 in an as yet unknown way (Bekker-Jensen et al., 2010). Finally, a number of polycomb group proteins, which mediate transcriptional repression through modulation of chromatin structure, have recently been shown to contribute to the recruitment of both BRCA1 and TP53BP1 through H2A and H2AX ubiquitylation (Gieni et al., 2011). These include the RING-finger proteins BMI1 and RNF2 (also called RING1B or RING2), which form a heterodimeric ubiquitin E3. Although the mechanism by which the complex is initially recruited is a matter of debate – it might involve the MRN (MRE11–RAD50–NBS1) damage recognition complex and/or poly-(ADP)-ribosylation (Chou et al., 2010; Ismail et al., 2010) – sustained localisation at the site of DSBs seems to require signalling by the ATM or ataxia-telangiectasia-related (ATR) kinases, H2AX phosphorylation and its ubiquitylation by RNF8 (Ginjala et al., 2011).

Negative regulation of ubiquitylation in the context of DSB repair is exerted by a number of deubiquitylating enzymes (DUBs) (Al-Hakim et al., 2010), namely BRCC36 (for BRCA1/BRCA2-containing complex, subunit 3), ubiquitin specific peptidases (USP) 3 and 16 as well as OTUB1 (for OTU domain, ubiquitin aldehyde binding 1). BRCC36 is part of the RAP80 complex and exhibits a preference for K63-polyubiquitin chains (Sobhian et al., 2007). USP3 and USP16 have both been shown to act on histone H2A and seem to downregulate the pathway at the stage of RNF8 (Cai et al., 1999; Doil et al., 2009; Joo et al., 2007; Nicassio et al., 2007), whereas OTUB1 acts further downstream and might inhibit the action of UBC13 in a non-catalytic manner (Nakada et al., 2010). The negative influence of DUBs on the formation of damage-induced BRCA1 and TP53BP1 foci indicates that cells maintain a fine balance between ubiquitylation and deubiquitylation to regulate DSB repair.

In addition to ubiquitylation, the post-translational modifications at DSBs also involve SUMOylation, which is mediated by the SUMO E3 PIAS1 and PIAS4 proteins (for protein inhibitor of activated STAT), which both associate with the single SUMO E2 UBC9 (also known as UBE2I) (Galanty et al., 2009; Morris et al., 2009). One of the substrates appears to be BRCA1 itself, whose catalytic activity is boosted by SUMO modification. Hence, SUMOylation of the ubiquitin E3 BRCA1 represents an interesting example of crosstalk between the two modifiers. In addition, the polycomb protein Pc2 (officially known as CBX4), which acts as a SUMO ligase on a number of substrates, including itself (Wotton and Merrill, 2007), is also recruited to chromatin in a damage-dependent manner (Chou et al., 2010). There are clearly additional physiologically relevant targets, whose SUMOylation is important during DSB repair, but these remain to be identified.

Apart from the direct involvement in the recruitment of repair factors, histone ubiquitylation is known to affect chromatin on a structural level, which is particularly important for the activation of transcription. In higher eukaryotes, this involves the relaxation of chromatin through monoubiquitylation of histone H2B by the heterodimeric RING finger E3 complex RNF20–RNF40 (Fierz et al., 2011; Weake and Workman, 2008). Very recently, it has been discovered that RNF20–RNF40-dependent H2B ubiquitylation is also required for efficient DSB repair, presumably by the same mechanism of chromatin decompaction (Moyal et al., 2011). As a consequence, inhibition of this modification causes defects in the recruitment of repair factors that are involved in both homologous recombination and non-homologous end-joining processes. Interestingly, this H2B-dependent contribution appears to be independent of the signalling

pathway that involves RNF8-mediated H2A ubiquitylation.

Homologous recombination and replication fork restart

As discussed above, the ubiquitylation and SUMOylation cascades elicited at DSBs culminate in the recruitment of factors that initiate the two major pathways for the repair of such lesions (i.e. homologous recombination through recruitment of BRCA1 and non-homologous end-joining through TP53BP1). Whereas this particular signalling pathway is restricted to higher eukaryotes, SUMO also modifies several core recombination factors in both higher and lower eukaryotes. Among its prominent targets is RAD52, which promotes formation of the recombinogenic RAD51 filament. In budding yeast, SUMOylation by the E3 Siz2 stabilises Rad52 (Sacher et al., 2006) while at the same time also reducing the DNA-binding and single-strand annealing activities of this protein (Altmannova et al., 2010). SUMOylation of replication protein A (RPA), a single-stranded binding complex that is essential for recombination, replication and repair, has been detected in yeast and mammalian cells (Burgess et al., 2007; Dou et al., 2010). In mammals, this modification facilitates the recruitment of RAD51 and has been shown to be counteracted by the SUMO-specific isopeptidase SENP6 (Dou et al., 2010).

As SUMOylation is often less dependent on specific ligases than ubiquitylation, the cognate E3s have not been well defined for all SUMO targets. On the basis of the phenotypes of the respective deletion mutants, it is clear that all three major SUMO E3s in budding yeast, Siz1, Siz2 and Mms21, participate in the modification of relevant substrates. Whereas the two yeast members of the PIAS family, Siz1 and Siz2, associate with DNA through SAP (for SAF-A/B, Acinus and PIAS) domains (Okubo et al., 2004), Mms21 is recruited to DNA through its association with the Smc5–Smc6 complex, a cohesin-like assembly with an important function in homologous recombination and replication fork restart in both yeast and humans (Potts and Yu, 2005; Zhao and Blobel, 2005). Although the importance of these SUMO ligases to genome maintenance by means of homologous recombination is undeniable, many of the relevant target proteins, as well as the mechanisms by which they affect the function of these targets, have yet to be elucidated.

In addition to protein modification by SUMO, the regulation of DNA repair by homologous recombination also involves ubiquitin. In fission yeast, this modifier acts in its ‘classical’ way by inducing the degradation of the recombination factor Rad54 during the G1 phase of the cell cycle, which is consistent with a downregulation of recombination activity at this stage (Trickey et al., 2008). In this case, ubiquitin is attached by the anaphase promoting complex/cyclosome (APC/C), an E3 protein involved in cell cycle regulation that acts together with its G1-specific regulator Fzr (fizzy related, also referred to as Cdh1 and Hct1).

An interesting crosstalk between ubiquitin and SUMO was uncovered by the identification of a set of ubiquitin ligases that recognise SUMOylated proteins as their substrates by means of SUMO-interaction motifs (SIMs) (Prudden et al., 2007; Sun et al., 2007; Uzunova et al., 2007; Xie et al., 2007). In yeast, one of these SUMO-targeted ubiquitin ligases, the heterodimeric Slx5–Slx8 complex in *S. cerevisiae* (Rfp1/2–Slx8 in *S. pombe*), acts as a regulator of homologous recombination, although its mechanism of action and its relevant substrate proteins remain to be identified. Bulk removal of high-molecular-mass SUMO targets might contribute to this DNA repair process (Uzunova et al., 2007).

Homologous recombination plays a major role not only in DNA DSB repair but also in promoting the restart of stalled or collapsed replication forks. In this aspect, the SUMO system again appears to be particularly important. Although it is very likely that not all SUMOylated proteins that are relevant to this process have been identified, appropriate targets include members of the family of RECQ helicases: BLM (Bloom syndrome, RecQ helicase-like) and WRN (Werner syndrome, RecQ helicase-like) in higher eukaryotes, and Sgs1 in budding yeast (Branzei et al., 2006; Eladad et al., 2005; Kawabe et al., 2000). How SUMO affects the activities of these proteins and the subsequent restart of replication forks, however, has not been fully elucidated.

Bypassing DNA damage during replication

Homologous recombination is just one way of dealing with DNA damage during replication. It applies to a variety of situations, including those where replication fork progression is impeded by strand breaks or interstrand crosslinks. Small lesions, such as adducts in the template DNA, which cannot be processed by the replicative polymerases, represent more subtle disturbances to fork progression and can be resolved by different processes (Friedberg, 2005). One solution to this problem, which results in error-free bypass, is template switching through a recombination event. Alternatively, specialised, error-prone DNA polymerases that can accommodate abnormal structures in their active sites can be employed in a process referred to as translesion synthesis (TLS) (Lehmann et al., 2007). Both strategies contribute to cellular damage resistance, but they also require strict regulation, as they might themselves induce genomic instability by means of larger genome rearrangments or point mutations, respectively.

Control over both bypass pathways is mediated by ubiquitylation of the sliding clamp protein proliferating cell nuclear antigen (PCNA) (Ulrich, 2009). Monoubiquitylation at K164 by a complex containing the E3 RAD18 and the E2 RAD6 enhances the affinity of a series of damage-tolerant polymerases for PCNA and thus facilitates TLS (Bienko et al., 2005; Stelter and Ulrich, 2003). Conjugation of additional ubiquitin moieties by the RING-finger E3 Rad5 and the heterodimeric E2 Ubc13–Mms2 results in a K63-linked polyubiquitin chain, which in yeast is a prerequisite for the error-free template-switching pathway (Hoege et al., 2002). In addition, the enzymes involved in polyubiquitylation have been implicated in some aspects of TLS (Gangavarapu et al., 2006; Pages et al., 2008). Intriguingly, higher eukaryotes encode two homologues of Rad5, helicase-like transcription factor (HLTF) and histone linker PHD RING helicase (SHPRH), which apparently act non-redundantly on different types of DNA damage (Lin et al., 2011). How PCNA polyubiquitylation induces template switching is not at all understood. There is even controversy about whether the downstream events initiated by the modification involve the full set of homologous recombination factors or whether a simple fork reversal might be sufficient to align the stalled primer terminus with the alternative template. Interestingly, however, both ubiquitin-dependent TLS and template switching can occur in manner that is uncoupled from the replication fork, within post-replicative gaps, which argues against the predominant use of fork reversal as a means to initiate error-free damage bypass (Daigaku et al., 2010; Karras and Jentsch, 2010).

Budding yeast PCNA is also modified by SUMO (Hoege et al., 2002). In contrast to ubiquitylation, this reaction is not damage-dependent, but occurs constitutively during replication, and also changes the affinity of the clamp for its interaction partners. Specifically, SUMOylation enhances the binding of an anti-recombinogenic helicase, Srs2, which prevents the formation of unscheduled Rad51 filaments and thereby enables the ubiquitin-dependent bypass pathway to act under conditions of DNA damage (Papouli et al., 2005; Pfander et al., 2005). Recognition of SUMOylated PCNA by Srs2 is mediated by a SIM in the C-terminus of Srs2. At the same time, PCNA SUMOylation inhibits the binding of Eco1, which is involved

in the establishment of chromatid cohesion (Moldovan et al., 2006), and induces the recruitment of an alternative clamp loader, Elg1, again through a number of SIMs, which influences genome stability in a poorly defined way (Parnas et al., 2010). Intriguingly, the human homologue of Elg1, ATAD5, was found to promote deubiquitylation of PCNA independently of SUMO, by localising a complex of the ubiquitin-specific peptidase 1 (USP1) and the USP1 accessory factor 1 (UAF1) to ubiquitylated PCNA (Lee et al., 2010). SUMOylation of PCNA was also observed in chicken DT40 cells and in *Xenopus laevis* egg extracts (Arakawa et al., 2006; Leach and Michael, 2005); however, its functions in these system have not been determined and are unlikely to involve a vertebrate Srs2 homologue. Hence, the SUMO-dependent crosstalk with homologous recombination might be specific to budding yeast.

The Fanconi anaemia pathway for interstrand crosslink repair

Repair of DNA interstrand cross-links (ICL) is particularly important for genome stability and survival, as these lesions impair strand separation not only for the purpose of replication but also for transcription. In general, ICL repair requires either homologous recombination or a combination of nucleotide excision repair and TLS. Higher eukaryotes have developed a special processing system for ICLs, the Fanconi anaemia pathway, which is named after a hereditary disease associated with defects in this process (Alpi and Patel, 2009).

The monoubiquitylation of a heterodimeric complex of the FANC (for Fanconi anemia, complementation group) proteins FANCD2 and FANCI, whose modification triggers their localisation to chromatin, is central to the Fanconi anaemia pathway (Garcia-Higuera et al., 2001; Sims et al., 2007; Smogorzewska et al., 2007). Ubiquitylation is mediated by the Fanconi core complex, whose main component is FANCL, a RING-finger E3 that cooperates with the E2 UBE2T. A complex of other chromatin-associated proteins, the so-called recognition complex, with FANCM as its central DNA-binding component, functions in directing the core complex to the appropriate sites. The events downstream of ubiquitylation are not entirely clear, but similar to the ubiquitylation cascade at DSBs described above, they result in an activation of the BRCA1/2 pathway (Wang, 2007). It has recently been shown that the FANCD2/FANCI-associated nuclease 1 (FAN1) is recruited to monoubiquitylated FANCD2 by means of a UBZ domain, which might account, at least in part, for the function of FANCD2 ubiquitylation (Kratz et al., 2010; Liu et al., 2010; MacKay et al., 2010; Smogorzewska et al., 2010).

Intriguingly, the Fanconi anaemia pathway overlaps not only with the BRCA1 pathway that operates at DSBs but also exhibits substantial crosstalk with RAD18-dependent damage bypass. On one hand, PCNA and FANCD2 are deubiquitylated by the same DUB, USP1 (Huang et al., 2006). On the other hand, it has been recently found that PCNA monoubiquitylation is actually a prerequisite for FANCD2 ubiquitylation, potentially by resulting in the recruitment and direct stimulation of FANCL by ubiquitylated PCNA (Geng et al., 2010; Park et al., 2010; Song et al., 2010). Hence, activation of the Fanconi anaemia pathway seems to be intimately coupled to TLS as a coordinated approach to processing lesions during replication.

Nucleotide excision repair

Nucleotide excision repair (NER) is initiated independently of DNA replication on bulky lesions that distort the helix, and involves the excision of the region around the lesion as a single-stranded oligonucleotide and filling of the resulting gap by re-synthesis. A sub-pathway of NER called global genome repair (GGR) operates throughout the genome. In humans, damage recognition is mediated by XPC (for xeroderma pigmentosum, complementation group C) and – in the case of UV-induced pyrimidine dimers – the UV-damage-specific DNA-damage-binding (DDB) protein complex, which comprises DDB1 and DDB2 (Sugasawa, 2010). Whereas DDB2 binds to the damaged DNA, DDB1 forms part of a multimeric cullin-based E3 protein, the DDB1–CUL4 complex. This E3 polyubiquitylates XPC and DDB2. Whereas DDB2 ubiquitylation results in proteasomal degradation, XPC remains stable, indicating that the modification serves regulatory purposes (Sugasawa et al., 2005). By contrast, the XPC-related protein Rad4 from budding yeast is ubiquitylated and degraded upon DNA damage (Lommel et al., 2002). However, the details of how proteolytic and non-canonical ubiquitylation regulate GGR remain controversial. Even a non-catalytic role for the 19S proteasome cap in this process has been postulated (Russell et al., 1999).

As an alternative to GGR, damage recognition on the transcribed strand of expressed genes can be accomplished by RNA polymerase II, in a process called transcription-coupled repair (TCR). Although ubiquitin or SUMO have not been directly implicated in this reaction, ubiquitylation and subsequent proteasomal degradation of the large subunit of the polymerase itself has been recognised as an important way of resolving transcription complexes that are stalled by DNA damage (Svejstrup, 2010). The budding yeast HECT-like E3 Rsp5 (and its human homologue NEDD4) together with the E2s Ubc4 and Ubc5 mediate monoubiquitylation of the polymerase (Anindya et al., 2007; Beaudenon et al., 1999). Rsp5 can also produce K63-linked chains on RNA polymerase II. However, these appear to be subject to removal by the DUB Ubp2 (Harreman et al., 2009). Further ubiquitylation of the polymerase by a cullin3-based E3 complex results in K48-linked chains, which induce proteasomal degradation of the enzyme (Harreman et al., 2009; Ribar et al., 2007). It has also been shown that a second DUB, Ubp3, is involved in deubiquitylation of the polymerase (Kvint et al., 2008).

Both GGR and TCR converge on the filling of single-stranded gaps that result from the excision of the damaged stretch. Intriguingly, although these gaps are presumably free of lesions, PCNA monoubiquitylation and recruitment of the damage-tolerant DNA polymerase κ have been reported to contribute to the efficient repair of these lesions in humans (Ogi et al., 2010). In yeast, however, NER appear to be independent of TLS by this kind of polymerase. In addition, ubiquitylation of histone H2A by RNF8 and polycomb proteins have been implicated in the reaction (Bergink et al., 2006; Marteijn et al., 2009), suggesting parallels in the signalling pathways at DSBs and during NER.

Base excision repair

Whereas NER resolves bulky lesions, small adducts such as alkylation or oxidative damage are processed by the base excision repair (BER) pathway, which is initiated by a series of lesion-specific glycosylases that excise damaged bases. The resulting abasic site is processed further by incision of the DNA backbone, followed by removal of the sugar-phosphate moiety and re-synthesis of the correct nucleotide. Although ubiquitylation has not been heavily implicated in this pathway yet, a prominent example of SUMO modification illustrates how this modification of a protein can change the properties of its targets in terms of its intramolecular interactions. Thymine-DNA glycosylase (TDG) acts on G–T mismatches in double-stranded DNA, but the enzyme is product-inhibited by strongly binding to the abasic site. In this situation, SUMOylation of TDG promotes catalytic turnover by inducing the release of the enzyme from DNA (Hardeland et al., 2002). This is mediated by a large conformational change in the enzyme (Steinacher and Schar, 2005). Accordingly, the crystal structure of a SUMO-modified TDG domain shows a conformation incompatible

with DNA binding (Baba et al., 2005). Non-covalent SUMO binding might also contribute to the stimulation of catalytic turnover (Takahashi et al., 2005). Finally, the modification might also coordinate the intracellular localisation of TDG as well as the hand-over of the enzyme to the downstream factor, the apurinic and apyrimidinic endonuclease 1 (APE1) (Hardeland et al., 2002).

Conclusions

Although the list of ubiquitin and SUMO targets and conjugation factors involved in the maintenance of genome stability is far from complete, the examples given here illustrate the diversity of mechanisms by which members of the ubiquitin family are known to act. Both modifiers can initiate protein degradation, but they often function in a non-proteolytic manner, either by recruiting downstream effectors through dedicated recognition domains or by directly mediating changes in the properties or catalytic activities of their target proteins. Particularly intriguing is the degree of crosstalk between the individual pathways of damage processing. In addition to overlaps in the conjugation or deconjugation factors or the modification targets, there are instances where one particular modification event promotes or activates a subsequent reaction. This principle is evident in the SUMO-targeted ubiquitin ligases, but also in the activation of the BRCA1 ubiquitin ligase by its own SUMOylation and in the activation of the FANCL ubiquitin ligase by PCNA ubiquitylation. Overall, the variety of ubiquitin- and SUMO-mediated influences on DNA replication and repair reflects very well the flexibility by which our cells react to insults to their genetic information, and these processes highlight the paramount importance of the mutual interactions between the modifiers and DNA itself. As expected, most of the ubiquitylation and SUMOylation reactions occur directly on chromatin. The modifications in turn can induce changes in the affinity of the target proteins for DNA, as observed with sumoylated Rad52 or TDG. Alternatively, they might exert a direct influence on chromatin structure, such as with ubiquitylated histone H2B. It has become clear, however, that we still lack mechanistic insight into the consequences of ubiquitin and SUMO modification for many, if not most of their targets. Further studies are therefore likely to continue the discovery of new principles of how the two modifiers contribute to genome maintenance.

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A high-resolution version of the poster is available for downloading in the online version of this article at jcs.biologists.com. Individual poster panels are available as JPEG files at http://jcs.biologists.org/lookup/suppl/doi:10.1242/jcs.091801/-/DC1

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