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Review Article

Function of transcription factors at DNA lesions in DNA repair

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ABSTRACT

Cellular systems for DNA repair ensure prompt removal of DNA lesions that threaten the genomic stability of the cell. Transcription factors (TFs) have long been known to facilitate DNA repair via transcriptional regulation of specific target genes encoding key DNA repair proteins. However, recent findings identified TFs as DNA repair components acting directly at the DNA lesions in a transcription-independent fashion. Together this recent progress is consistent with the hypothesis that TFs have acquired the ability to localize DNA lesions and function by facilitating chromatin remodeling at sites of damaged DNA. Here we review these recent findings and discuss how TFs may function in DNA repair.

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DNA damage and repair: the participation of TFs

Cellular DNA is constantly damaged from DNA lesions arising at a frequency of several breaks per cell per day [1]. Among the most notorious DNA damage-inducing agents are so called reactive oxygen species (ROS) – by-products of cellular oxidative metabolism. Also exogenous sources of radiation such as UV or ionizing radiation can cause damage to the DNA. Depending on

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the nature of the damage (e.g. single bases, nucleotide dimers, single or double strand breaks) specialized DNA repair pathways are responsible for detecting and removing damaged regions [1]. The specificity of DNA repair pathways largely relates to the ability of dedicated DNA damage sensor proteins to detect a given lesion and then orchestrate repair by recruiting downstream-operating factors [2]. In this review we primarily focus on transcription factors (TFs) that have been identified to function in nucleotide excision (NER) and double strand break (DSBs) repair pathways. NER is the major pathway responsible for removal of bulky DNA lesions arising by the action of UV irradiation, chemotherapeutic drugs and certain environmental mutagens [3] (see Fig. 1a for details). DSBs are life-threatening lesions whose repair engages a network of multiple DNA repair pathways. A majority of DSBs are repaired by two independent repair pathways: non-homologous end joining (NHEJ) and homologous recombination (HR) [2] (see Fig. 1b for details).

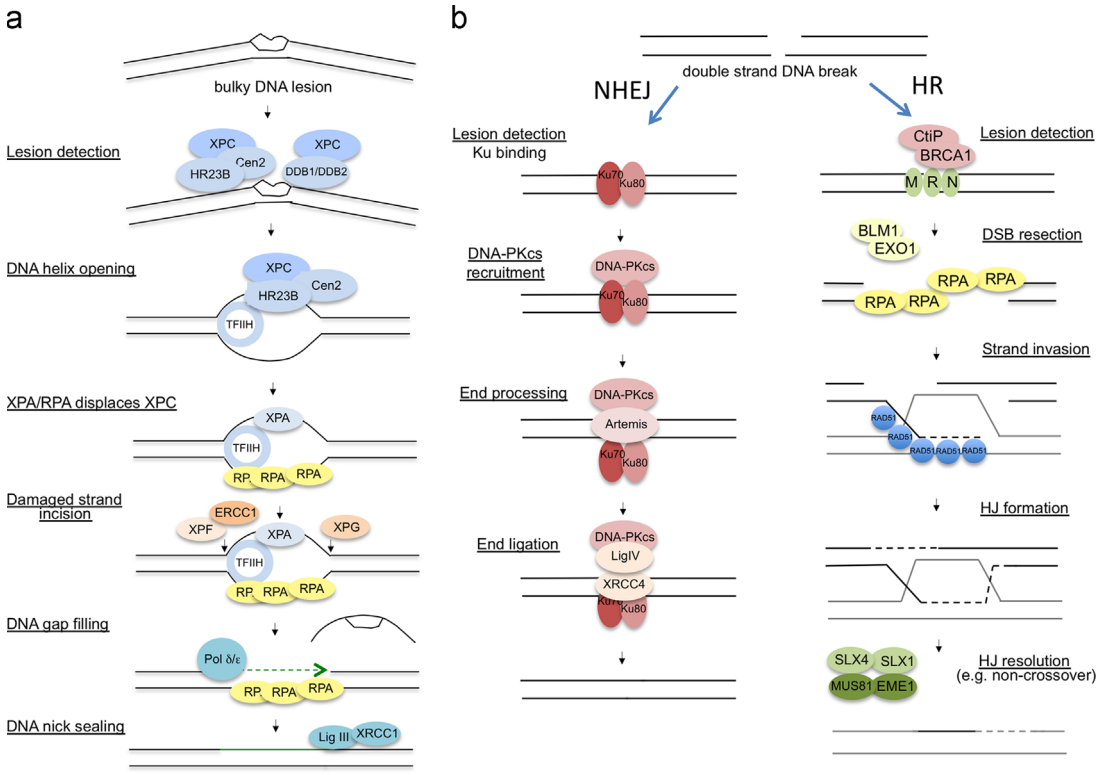

Fig. 1 – DNA repair pathways showing involvement of transcription factors (TFs). (a) NER pathway is responsible for the removal of a variety of bulky DNA lesions, such as thymidine dimers, from the DNA. NER involves the orchestrated recruitment and action of more than 30 proteins. This figure shows global-genome NER mechanism (only key factors are shown for simplicity). Global NER is initiated by the recognition of a helix-distorting lesion by the XPC-HR23B-Cen2 protein complex (some lesion types require DDB1/DDB2 complex for efficient recognition and XPC recruitment). The XPC-HR23B-Cen2 complex stably bound to the DNA lesion allows the recruitment of the TFIIH complex. Once TFIIH is recruited to the damaged site, its DNA helicases catalyze the opening of the DNA around the lesion, which allows the recruitment of XPA. Replication protein A (RPA) binding to single-stranded DNA further stabilizes this structure and participates in the recruitment of the two DNA endonucleases, XPG and XPF-ERCC1. The activities of these structure-specific endonucleases cut the damaged DNA strand and induce the excision of the damaged segment. The DNA re-synthesis machinery that catalyzes the synthesis of missing DNA follows the excision step. The repair process is finished by a DNA ligase (LigIII). (b) DSB repair (only key factors are shown for simplicity). DNA double strand breaks (DSBs) are typically repaired via homologous recombination (HR; see below) or non-homologous end joining (NHEJ) pathways. NHEJ (left panel) is considered the main pathway for DSB repair in mammalian cells as it can operate in any phase of the cell cycle and in contrast to homologous recombination does not require a sister chromatid for completion of the repair. NHEJ is initiated by binding of DNA-PK regulatory subunit (Ku70/Ku80 heterodimer) to free DNA ends followed by recruitment of DNA-dependent kinase catalytic subunit protein (DNA-PKcs) to DSBs. This assembly results in DNA-PK kinase activation. DNA-PK complex (Ku70/Ku80/DNA-PKcs) serves as a platform that holds both DNA ends together and orchestrates DNA processing and ligation. The latter steps of NHEJ require additional proteins including Artemis (end-processing nuclease), XLF/Cerunnos and XRCC4/LigIV complex (ligase) that seal the processed DNA break. In case of homologous recombination (HR) type of DSB repair (right panel) MRN complex (composed of MRE11, RAD50 and NBS1 proteins) mediates the initial stages of DSB resection together with CtIP and BRCA1. Extensive DSB resection and formation of RPA-coated ssDNA ends are induced by EXO1 and BLM. Displacement of RPA from the ssDNA ends and assembly of RAD51 filaments leads to strand invasion into homologous DNA sequences. D-loop structures formed after strand invasion can be cleaved by MUS81/EME1 or other activities to generate crossover or non-crossover events, respectively.

For the purpose of this review we define TFs as sequence specific DNA binding factors that have been associated with the process of transcriptional regulation, and exclude adapters and accessory proteins that regulate transcription in DNA sequence-independent fashion. There are examples of numerous proteins that can function both in transcription and DNA repair. A recent review [4] covered the functions of core DNA repair factors in transcriptional regulation, so here we focus on the alternative question: the direct role of TFs in DNA repair.

TFs regulate target gene transcription either positively or negatively by binding to specific sequences termed response elements (RE in Fig. 2a) found in gene promoters and enhancers. TFs typically harbor a DNA binding domain (DBD in Fig. 2a) that dictates sequence-specific DNA binding, and at least one transactivation (AF in Fig. 2a) or repressor domain [5–7]. Transactivation and repressor domains mediate gene activation (Fig. 2a) and repression via interaction with so-called co-activators and co-repressors, respectively. The recruitment of such co-regulators to target genes leads to local chromatin alterations, often via the modification of histones, and either induced or repressed gene expression (Fig. 2a). It is rather evident that TFs can regulate DNA repair indirectly by controlling the activity of genes encoding key components of the DNA repair systems [8]. For example, genes encoding core NER factors are typically under transcriptional control and are strongly induced after DNA damage [9]. Interestingly, in recent years an increasing number of studies have revealed that several TFs also regulate DNA repair directly and can function as integral components of the repair machinery itself. DNA damage-inducing insults (irradiation, chemotherapy drugs) promote translocation of some TFs directly to DNA lesions, where they actively facilitate DNA repair (Fig. 2b). TFs in DNA repair have thus far been mainly associated with DSB and NER repair (Table 1) but it seems likely that also other DNA repair pathways utilize TFs as key mediators.

DNA repair regulated directly by TFs at DNA lesions

Recruitment of many DNA repair factors to double strand breaks can be observed by immunofluorescence assays as formation of

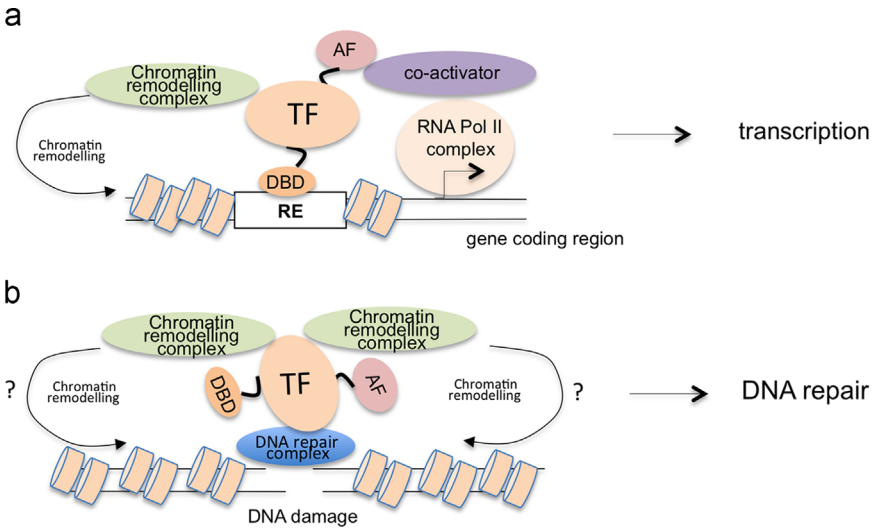

Fig. 2 – Regulation of transcription and DNA repair by transcription factors (TFs). (a) TFs regulate gene expression (only positive regulation of transcription by TFs is shown for simplicity). TFs utilize their DNA binding domain (DBD) to bind to DNA response elements (RE) located in gene promoters and enhancers. The transactivation domain (AF) facilitates the recruitment of adapter proteins (co-activator) that enable the stabilization of basal transcriptional machinery (RNA Pol II complex) at the gene transcriptional start sites (arrow). TFs can also recruit chromatin-remodeling complexes that facilitate chromatin changes at the promoter to enable transcription. (b) TFs directly regulate DNA repair. TFs are recruited to DNA lesions by binding to specialized DNA repair proteins. At DNA lesions TFs are presumably able to facilitate the DNA repair process by allowing for efficient chromatin remodeling and access of DNA repair machinery. Note that unlike in the context of transcriptional regulation the recruitment of TFs to DNA lesions occurs in DNA sequence in an independent fashion.

Table 1 – Key features of transcription factors (TFs) directly regulating DNA repair.

TF name	Mechanism of TF translocation to DNA lesions	DNA repair pathway	Which DNA-damage activated kinase targets the TF?	Phosphorylated residue	Sequence-specific DNA binding required for DNA repair?	Refs.
ATF2	?	?	ATM	Ser490, Ser498	no	[13]
E2F1	TopBP1 interaction	DSB, NER	ATM/ATR	Ser31	no	[20,43]
NR4A	Requires PARP1	DSB, NER	DNA-PK	Ser337 (NR4A2)	no	[33,34]
Sp1	?	DSB	ATM	Ser101	no	[36]

large nuclear foci termed "DSB repair foci" [10]. This is possible for those DNA repair factors that spread on chromatin surrounding DSBs such as MRN complex components. The initial formation of DSB foci depends on ATM kinase mediated phosphorylation of the variant histone H2AX. H2AX phosphorylated on ser139 – called gamma-H2AX or γH2AX – provides a platform for recruitment of additional DNA repair components to chromatin flanking DSBs (Fig. 3) [10]. It is important to mention that, for example, NHEJ core components are present at DSBs in small quantities and cannot be visualized as discrete nuclear foci [11].

ATF2 is a transcription factor belonging to the so-called AP1 family of stress responsive transcriptional activators and has previously been implicated in DNA repair by its ability to regulate a large set of genes functioning in DNA repair [12]. Importantly, however, ATF2 also seems to act directly in DNA damage response at DNA lesions. Thus, immediately following DNA damage, ATF2 localizes to DNA DSBs, as revealed by the formation of DNA-damage induced DSB foci containing phospho-ATF2 [13]. Although it remains unclear if ATF2 actively promotes DNA repair, this observation was a first example of a TF capable of translocation directly to DNA lesions [13]. Several additional examples of TFs translocating directly to DNA damage sites have been reported since this initial observation, as summarized in Table 1.

E2F1 is one of the additional TFs that translocates to sites of DNA repair. E2F1 is mostly known for its central role in the regulation of cellular proliferation and apoptosis. However, E2F1 is also induced in response to various DNA-damaging agents, including ionizing radiation, UV radiation, and a number of chemotherapeutic drugs [14,15]. Moreover, as shown by ultraviolet (UV) laser micro-irradiation and immunofluorescence staining, E2F1 accumulates at sites of DNA damage [16]. Somewhat surprisingly the E2F1's DNA-binding domain seems to be dispensable for the localization to DNA lesions. The recruitment to UV-damaged DNA requires the activity of DNA damage-activated kinases (ATM and ATR) that phosphorylate E2F1. Interestingly, E2F1 deficiency impairs the recruitment of core NER factors (such as XPC and XPA) to DNA lesions although their level of expression is unaffected. In addition, mutation eliminating the DNA-binding capacity of E2F1 does not influence its function in NER DNA repair. These observations thus indicate a non-transcriptional role for E2F1 in stimulating NER-factor recruitment to sites of DNA repair [16]. E2F1 has subsequently been associated also with DSB repair and accumulates at DSB foci where it forms a complex with MRN complex component NBS1 [17]. The important role of E2F1 in the DSB repair is emphasized by the demonstration that E2F1 deficiency impairs NBS1 foci formation and NBS1 phosphorylation in normal human cells. Moreover, interaction of E2F1 with NBS1 is increased by DNA damage-inducing radiation, suggesting that E2F1 promotes NBS1 assembly at DNA damage sites. GCN5, a histone 3, lysine 9 (H3K9) acetyltransferase, has been identified as a co-activator interacting with E2F1 and is essential in mediating its transcriptional activity [18]. E2F1 also associates with GCN5 in response to UV radiation and recruits GCN5 to sites of DNA damage [19] suggesting that E2F1 promotes NER by stimulating H3K9 acetylation and increased chromatin accessibility at sites of DNA repair [19]. Notably, E2F1 is so far the only TF for which the mechanism of translocation to DSB lesions has been relatively well characterized in experiments showing that the DNA topoisomerase II-beta proteins (TopBP1) interacts with the E2F1 N-terminal domain and enables E2F1 recruitment to DNA lesions [20]. The involvement of E2F1 in DNA repair is specific to E2F1 since E2F1 homologs, E2F2, E2F3 or E2F4, do not interact with TopBP1 and are also not phosphorylated by ATM.

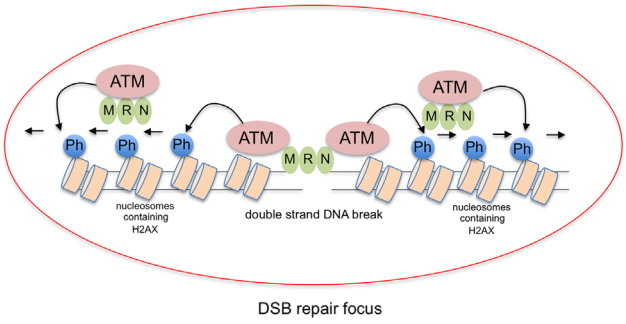

Fig. 3 – ATM-mediated and MRN-dependent spread of variant histone H2AX phosphorylation in the chromatin flanking DSBs initiates the DSB repair focus formation. MRN complex initially binds DSBs and facilitates ATM kinase activation. ATM is the main kinase responsible for H2AX histone phosphorylation (in some cases also ATR and DNA-PK kinases can contribute to H2AX phosphorylation), which spreads away from the DSB (there are multiple mechanisms of ATM retention on chromatin – here only MRN complex is presented for simplicity). H2AX histone phosphorylated on serine 139 is called gamma H2AX (γH2AX) and serves as a platform for further DNA repair complex recruitment.

The direct function of E2F1 in DNA repair has recently been illustrated in a mouse knock-in model, in which ATM/ATR serine 29 phosphorylation site in E2F1 was exchanged for an alanine. This resulted in defective repair from UV-induced damage and increased incidence of cancer. Interestingly the transcriptional regulation of E2F1 target genes remained unaltered in primary keratinocytes derived from the mutant mice substantiating the independent key roles for E2F1 in transcription and DNA repair, respectively [21].

Nur77 (NR4A1), Nurr1 (NR4A2) and Nor1 (NR4A3) are orphan members of the nuclear receptor family that can function as ligand-independent transcription factors [22,23]. A distinguishing feature of the NR4A-family of nuclear receptors is that they are rapidly induced by various acute stimuli and are functioning in adaptive and stress-responsive physiological functions. In addition NR4As have important roles in cellular differentiation into mid-brain dopamine neurons and cells of the hematopoietic lineage [24–30]. NR4A proteins have recently been identified as tumor suppressors in myeloid cells and NR4A loss-of-function results in acute myeloid leukemia in mice [28,31]. Interestingly, loss-of-function of NR4As has also been associated with increased DNA damage in myeloid and other cell types [31,32]. How these proteins promote DNA repair was until recently unclear, but since NR4A TFs can function as conventional transcription factors it seemed likely that their participation in DNA repair is indirect and occurs via target gene transcriptional regulation. Contrary to these assumptions; however, more recent work has established that also these TFs influence DNA repair directly as components of the DNA repair machinery [33,34]. By searching for NR4A-interacting proteins DNA-dependent protein kinase catalytic subunit (DNA-PKcs) was identified as a major NR4A2 associated protein. Further experiments revealed that NR4A proteins promote DNA DSB repair in a process that is independent of their function in transcription.

Instead, in cells exposed to DNA damage, NR4As rapidly translocate directly to DNA repair foci by a mechanism requiring the activity of poly(ADP-ribose) polymerase-1 (PARP-1) [33,34]. At DSBs NR4As are phosphorylated by DNA-dependent protein kinase (DNA-PK) and act directly to promote DNA end-ligation. DNA-PK phosphorylates serine 337 on NR4A and phosphorylated NR4A then accumulates on DNA repair foci. Furthermore, substitution of serine 337 for an alanine (S337A) impairs the function of NR4A in DNA repair, likely as a result of prolonged association with DNA-PKcs that somehow disrupts the repair process. At DNA repair foci NR4As co-localise with well-known DNA repair proteins such as γH2AX, DDB2 and XPC (see Figs. 3 and 1 respectively for functional description of these factors). An intact C-terminal helix 12, a region that is an essential structural component in the ligand binding domain in other nuclear receptors, is important for proper NR4A localization to repair foci, but in the absence of an intact helix 12, localization to repair foci can be restored by histone deacetylase inhibition [34]. These findings therefore define NR4As as entirely novel components of DNA damage response, identified a functionally relevant substrate of DNA-PK, and showed that the DNA repair capacity of a cell can be enhanced by increasing the levels of NR4A [33]. Two additional and independent studies have also found that NR4As contribute to DSB DNA repair [31] and NER [32], but without mechanistic explanation. Taken together these observations provide further support that TF-mediated chromatin remodeling can contribute to the proper assembly of DNA repair complexes at DNA lesions *in vivo*.

Sp1, is a ubiquitously expressed transcription factor that also translocates directly to DNA lesions. ATM kinase phosphorylates Sp1 in response to ionizing radiation and oxidative stress (H_2O_2 exposure) [35]. Phosphorylated Sp1 localizes to ionizing radiation-induced foci with γH2AX, and chromatin immunoprecipitation showed that Sp1 resides in close proximity to DNA lesions [36]. Depletion of Sp1 impaired repair of DNA breaks introduced by site-specific endonuclease. An N-terminal fragment of Sp1 that is not transcriptionally active but harbors ATM kinase phosphorylation sites can localize to DSB foci and rescue the DNA repair deficit resulting from Sp1 depletion. Thus, Sp1 is important in DSB repair via a mechanism that is independent of its function in transcriptional regulation [36].

Finally, a number of additional TFs, including NF-κB and FOXO3a, may be directly involved in DNA repair; however; additional work is required to further elucidate their mechanistic roles in these processes [37,38].

Function of TFs in DNA repair

Different tissues are variably exposed to DNA-damaging conditions. For example neurons have a high rate of oxidative metabolism, generating large quantities of reactive oxygen species that damage DNA, and skin cells are exposed to high doses of UV radiation and need to cope with UV-related DNA damage. Interestingly, TFs that have been associated with DNA repair are regulated in response to extracellular stimuli and stress-related signaling, properties that presumably are relevant in DNA repair. For example, NR4A orphan receptors are highly inducible in response to a variety of stimuli such as mitogens or DNA damaging oxidative stress [39]. Recent work suggests that skin cells adapt to increased ultraviolet (UV) radiation by raising the efficiency of NER DNA repair by a mechanism that depends on NR4A proteins [40]. Accordingly, UV irradiation stimulates keratinocytes to produce and secrete melanocyte-stimulating hormone (α-MSH). α-MSH binds to melanocortin-1 receptor (MC1R) on the surface of melanocytes, elevates intracellular cAMP levels, NR4A gene expression [39,41] and NR4A-stimulated NER [40,42]. As mentioned above, E2F1 is also involved in adaptive UV-induced NER [43]. Thus, both E2F1 and NR4A TFs may be central components in an inducible DNA repair pathway that provides an additional level of protection to UV-sensitive cells. Since many TFs are critical mediators of cell type-specific adaptive responses it seems likely that several TFs have been recruited as core DNA repair components because of their involvement in adaptation to stressful insults that are also associated with DNA damage.

What is the role of TFs at DNA repair foci? Several mechanisms for how TFs influence DNA repair are possible, but available data suggest that their capacity to alter chromatin structure is critical, and has been supported by experiments utilizing an in vitro system in which DNA repair was studied on chromatinized DNA substrates [44]. An artificial TF (Gal4-VP16) and the retinoid acid receptor (RAR) can alter chromatin accessibility around their binding sites and they also facilitate DNA repair by a mechanism that is independent of transcription since blocking PolII or depleting transcriptional co-regulators (such as TBP) did not affect the efficiency of DNA lesion removal. In contrast, DNA binding seemed to be required for effective DNA repair and lesions located far away from the TF DNA binding which reduced the efficiency of DNA repair [44]. It therefore seems likely that TFs capable of relaxing chromatin also have the capacity to utilize this activity to facilitate DNA repair in close proximity to their normal DNA binding sites [44]. Thus, TF binding to their normal response elements in the vicinity of regulated genes may provide an additional level of DNA surveillance at key gene regulatory promoter and enhancer regions [45]. The idea that chromatin remodeling underlies TF involvement in DNA repair is clearly consistent with the data on E2F1 and NR4A functions in DNA repair. As mentioned earlier the GCN5 histone acetyltransferase can increase chromatin accessibility and collaborates with E2F1 at DNA lesions [43]. Furthermore proper localization of mutant NR4A2 to DNA lesions during NER reaction could be restored by artificial chromatin relaxation [34]. The importance of establishing proper chromatin structure for efficient DNA repair may thus explain why it has been evolutionary advantageous to recruit specific TFs, including E2F1, NR4A and Sp1, as global DNA repair components. One can assume that this ability has been acquired by the establishment of novel protein–protein interactions such as the interaction between E2F1 and TopBP1 proteins, a specialized DNA replication and repair factor that localizes to DNA lesions [20]. Thus, TFs that regulate global DNA repair have acquired the ability to localize to DNA lesions where they potentially utilize their chromatin-modifying activities to facilitate the repair process.

Concluding remarks

Future studies based on structure-function relationships, in part by utilizing point mutations in TFs participating in DNA repair, will help to unravel the precise molecular mechanisms governing their participation in DNA repair, e.g. how they localize to DNA

repair sites. We propose that the key to understanding TF function in DNA repair will come from understanding how TFs collaborate with chromatin remodeling complexes and how such interactions contribute to the repair process. As there is an evidence that TFs also directly regulate DNA replication [46] an emerging theme may be that TFs are utilized in many key nuclear processes where their effects on chromatin states are advantageous.

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