CELL CYCLE
2020, VOL. 19, NO. 18, 2260–2269
https://doi.org/10.1080/15384101.2020.1801190

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REVIEW

The E2F1 transcription factor and RB tumor suppressor moonlight as DNA repair factors

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ABSTRACT

The E2F1 transcription factor and RB tumor suppressor are best known for their roles in regulating the expression of genes important for cell cycle progression but, they also have transcription-independent functions that facilitate DNA repair at sites of damage. Depending on the type of DNA damage, E2F1 can recruit either the GCN5 or p300/CBP histone acetyltransferases to deposit different histone acetylation marks in flanking chromatin. At DNA double-strand breaks, E2F1 also recruits RB and the BRG1 ATPase to remodel chromatin and promote loading of the MRE11-RAD50 -NBS1 complex. Knock-in mouse models demonstrate important roles for E2F1 post-translational modifications in regulating DNA repair and physiological responses to DNA damage. This review highlights how E2F1 moonlights in DNA repair, thus revealing E2F1 as a versatile protein that recruits many of the same chromatin-modifying enzymes to sites of DNA damage to promote repair that it recruits to gene promoters to regulate transcription.

ARTICLE HISTORY
Received 26 May 2020
Revised 19 June 2020
Accepted 6 July 2020

KEYWORDS
E2F1; ATM/ATR; TopBP1; GCN5; p300/CBP; BRG1

Introduction

Agents that cause DNA damage, including certain chemicals and radiation, can induce the genetic mutations that underlie cancer but also provide a strategy for treating cancer. Thus, understanding how cells respond to DNA damage is important for understanding both the causes of cancer and the biological responses to many cancer therapeutics. The ATM, ATR, and DNA-PK kinases recognize DNA damage and relay this information throughout the cell to regulate transcription, cell cycle progression and DNA repair [1]. The phosphorylation of target proteins by these kinases, along with signals from other DNA damage sensors, like poly-(ADP-ribose) polymerase 1 (PARP1), results in the efficient recruitment of appropriate DNA repair enzymes to repair different types of DNA damage. An important component of the response to DNA damage is the dynamic modification of chromatin structure at sites of damage that must be coordinated with DNA repair [2–5].

Dozens of sequence-specific, DNA-binding transcription factors have been reported to localize to laser-induced DNA damage tracks [6]. Although recruitment of these transcription factors to sites of DNA damage is likely sequence-independent, the DNA-binding domains of many of these transcription factors are still required for their enrichment at sites of DNA damage [6]. Exceptions include E2F1, ATF2, NR4A, and SP1, which localize to sites of DNA damage independently of their DNA binding domains but may require phosphorylation by ATM, ATR or DNA-PK [7–13]. Loss-of-function experiments demonstrate that E2F1, ATF2, NR4A and SP1 each play important roles in DNA damage response signaling and/or in enhancing DNA repair efficiency, independent of transcription [7,8,12,14]. How these transcription factors directly regulate DNA damage response signaling and repair is largely unknown.

E2F1 has a well-established role in regulating the periodic expression of genes important for cell proliferation [15]. An important regulator of E2F1 is the RB tumor suppressor, which directly

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binds E2F1 and a subset of other E2F family members. The interaction with RB switches these E2F family members from transcriptional activators to transcriptional repressors. E2F factors can bind RB both in its unphosphorylated form and following RB mono-phosphorylation by cyclin D-CDK4/6 complexes [16]. When RB is hyperphosphorylated by CDK2 during the late G1 and S phases of the cell cycle, E2F factors are released to stimulate the transcription of target genes. Thus, E2F transcriptional activity is tightly controlled by RB during the cell cycle and in non-proliferating cells. Mutations that disrupt this regulation are a hallmark of cancer [17].

In this review, we discuss how E2F1 is converted from a regulator of transcription into a regulator of DNA repair through post-translational modifications induced in response to DNA damage. We also discuss how the RB tumor suppressor protein cooperates with E2F1 at DNA double-strand breaks (DSBs) to promote DNA end-resection and homologous recombination (HR) repair. This expands the known genome maintenance functions of RB and reveals a potential vulnerability of cancer cells lacking RB. E2F1 emerges as a paradigm for factors that regulate both transcription and DNA repair by recruiting the same chromatin-modifying enzymes and directing the same changes to chromatin structure at both gene promoters and at sites of DNA damage.

Regulation of E2F1 in response to DNA damage

In response to DNA damage, both ATM and ATR can phosphorylate E2F1 at a site (serine 31 in humans) that is not conserved in other E2F family members [18]. When phosphorylated at this site, the 14-3-3τ protein binds to and stabilizes E2F1 by inhibiting its ubiquitination and degradation [19]. In response to agents that cause DSBs, E2F1 is phosphorylated by ATM and this is associated with the induction of apoptosis through the transcriptional activation of target genes such as *TP73* [18–20]. In contrast, in response to ultraviolet (UV) radiation, E2F1 is phosphorylated by ATR, which is associated with neither the induction of apoptosis nor the transcriptional activation of *TP73* [21,22]. Phosphorylation of E2F1 also leads to the formation of a complex containing TopBP1 that suppresses E2F1 transcriptional activity [23].

TopBP1 contains nine BRCT domains and binds to E2F1 through a phospho-specific interaction between its sixth BRCT domain (BRCT6) and the E2F1 serine 31 motif [11]. This interaction was one of the first examples of a BRCT domain binding to a phosphorylated protein motif, now recognized as a general feature of BRCT domains [24,25]. Other TopBP1 BRCT domains bind to phosphorylated motifs on other DNA damage response factors, including RAD9, 53BP1 and MDC1, which helps to recruit TopBP1 to damaged DNA [26,27]. In turn, TopBP1 oligomerization at sites of DNA damage allows the BRCT6 domain to bind and recruit phosphorylated E2F1 [11,28]. Notably, E2F1 localization to damaged DNA requires the ATM/ATR phosphorylation site but not the DNA binding or transcriptional activation domains of E2F1 [9,11].

Localization of E2F1 at sites of UV-induced DNA damage is associated with the efficient recruitment of nucleotide excision repair (NER) factors like XPA and XPC [9,29]. Likewise, localization of E2F1 at DSBs is associated with the recruitment and/or retention of DNA repair factors such as NBS1, MRE11, RPA and RAD51 [14,30,31]. In both cases, the absence of E2F1 results in inefficient DNA repair [14,32]. A knock-in mutation (S29A in mice) that prevents phosphorylation of E2F1 by ATM/ATR, also prevents its accumulation at sites of DNA damage, impairs the recruitment of DNA repair factors, and reduces the efficiency of repair of both UV photoproducts and DSBs [21,33].

RB forms one or more complexes with E2F1 in response to DNA damage. These complexes are associated with not only the transcriptional repression of cell cycle-related genes but also, and unexpectedly, the transcriptional activation of pro-apoptotic genes like *TP73* and *CASP7* [20,34,35]. RB stabilizes phosphorylated E2F1 and the E2F1-TopBP1 interaction that occurs in response to ionizing radiation (IR) [33]. This is consistent

with earlier reports that the interaction between RB and E2F1 protects E2F1 from ubiquitination and proteasomal degradation [36,37]. Moreover, the binding of RB to E2F1 recruits RB to DSBs, whereas the loss of RB prevents E2F1 accumulation at DSBs [33]. Thus, E2F1 and RB are mutually dependent on each other for their localization to DSBs. Further, loss of RB, like loss of E2F1, results in defective DSB repair, particularly by the HR pathway [33,38–40].

In sharp contrast to DSB repair, the loss of RB enhances the kinetics of repair for UV-induced DNA photoproducts, possibly through the upregulation of *XPC* and other NER-related genes due to the deregulation of E2F activity [41–43]. In agreement with these findings, we were unable to detect recruitment of RB to sites of UV-induced DNA damage under the same conditions in which we observed E2F1 co-localization with DNA photoproducts and NER factors [9]. This suggests that in response to UV there is an RB-independent mechanism that stabilizes both phosphorylated E2F1 and the TopBP1-E2F1 interaction. The differential impact of RB loss on HR repair and NER has important implications for therapeutic sensitivities and vulnerabilities of cancers lacking RB [33,39,40].

E2F1 recruits GCN5 and induces H3K9 acetylation at UV-induced DNA damage

E2F1 stimulates transcription by recruiting a variety of histone acetyltransferases to gene promoters, leading to a more open chromatin conformation that allows the transcriptional machinery access to DNA [44–52]. As with transcription, DNA repair also requires remodeling of chromatin structure to provide the DNA repair machinery access to DNA. Pioneering studies by Smerdon and others demonstrated that chromatin structure becomes relaxed in response to UV radiation, that this process is important for efficient NER, and that chromatin structure is generally restored following repair [53,54]. This Access-Repair-Restore model has been refined by Almouzni and coworkers to describe the dynamic and active role of chromatin in DNA repair [4]. Not surprisingly, many of the histone modifying enzymes and nucleosome remodeling complexes involved in regulating gene transcription are also important for DNA repair; however, the mechanisms that target these proteins to sites of DNA damage are poorly understood.

We hypothesized that E2F1 might promote DNA repair through a mechanism similar to that used to regulate transcription, i.e. by recruiting proteins with chromatin-modifying activities to sites of DNA damage. Indeed, we found that the GCN5 acetyltransferase, which is known to cooperate with E2F1 in transcription [44,47], associates with E2F1 in response to UV irradiation and is recruited to sites of UV-induced DNA damage in an E2F1-dependent manner [32]. Moreover, both E2F1 and GCN5 are required for the induction of histone H3 lysine 9 acetylation (H3K9ac) at sites of UV-induced DNA damage, which is associated with chromatin relaxation and the efficient re-localization of NER factors XPC and XPA to damaged DNA [32].

As mentioned above, we made a knock-in mutant mouse allele, $E2f1^{S29A}$, that prevents E2F1 from being phosphorylated by ATM/ATR in response to DNA damage [21]. $E2f1^{S29A/S29A}$ knock-in cells have normal cell cycle checkpoint and apoptotic responses to UV and express E2F target genes, including those involved in DNA repair, at levels comparable to wild-type cells [21]. However, the E2F1 S29A mutation prevents both E2F1 and GCN5 from associating with UV-irradiated DNA and impairs H3K9 acetylation in UV damaged chromatin [21]. Preventing E2F1 and GCN5 enrichment at sites of UV-induced DNA damage correlates with reduced NER efficiency and increased numbers of epidermal cells with *p53* mutations [21]. Moreover, $E2f1^{S29A/S29A}$ mice are significantly more sensitive to UV-induced skin carcinogenesis, thus linking E2F1's ability to directly stimulate DNA repair with tumor suppression.

E2F1 and RB recruit p300 and CBP to DNA double-strand breaks to induce H3K18 and H3K56 acetylation

Like UV-induced DNA damage, other types of DNA damage also lead to dynamic changes in

chromatin structure that facilitate DNA repair. At DSBs, chromatin structure is transiently compacted and then relaxed, a process that is coordinated with DNA repair [55,56]. Given that GCN5 is enriched at DSBs, where it is associated with increased histone acetylation [57–60], we predicted that E2F1 would also recruit GCN5 to DSBs. In contrast to our expectations, we observed that loss of E2F1 had no effect on either the enrichment of GCN5 at a DSB or on the levels of H3K9ac in chromatin flanking the break.

Instead, we found that two other acetyltransferases, p300 and CBP, directly associate with E2F1 in response to IR and that E2F1 is required for their recruitment to DSBs [31]. Just as RB is required for stabilizing the TopBP1-E2F1 complex at DSBs, RB is also required for the recruitment of p300 and CBP to DSBs (Figure 1). E2F1- and RB-dependent recruitment of p300 and CBP to DSBs is associated with increased acetylation of histone H3 lysine 18 (H3K18ac) and histone H3 lysine 56 (H3K56ac) in flanking chromatin, rather than H3K9ac, as observed in response to UV damage [31,32]. The E2F1 S29A knock-in mutation, which blocks E2F1 phosphorylation and thus its interaction with TopBP1, also prevents p300/CBP recruitment and induction of H3K18ac and H3K56ac at DSBs [31].

These findings raise the question of how E2F1 is regulated in response to different types of DNA damage to ensure it recruits the proper acetyltransferase to correctly mark the chromatin flanking different forms of DNA damage. One clue comes from

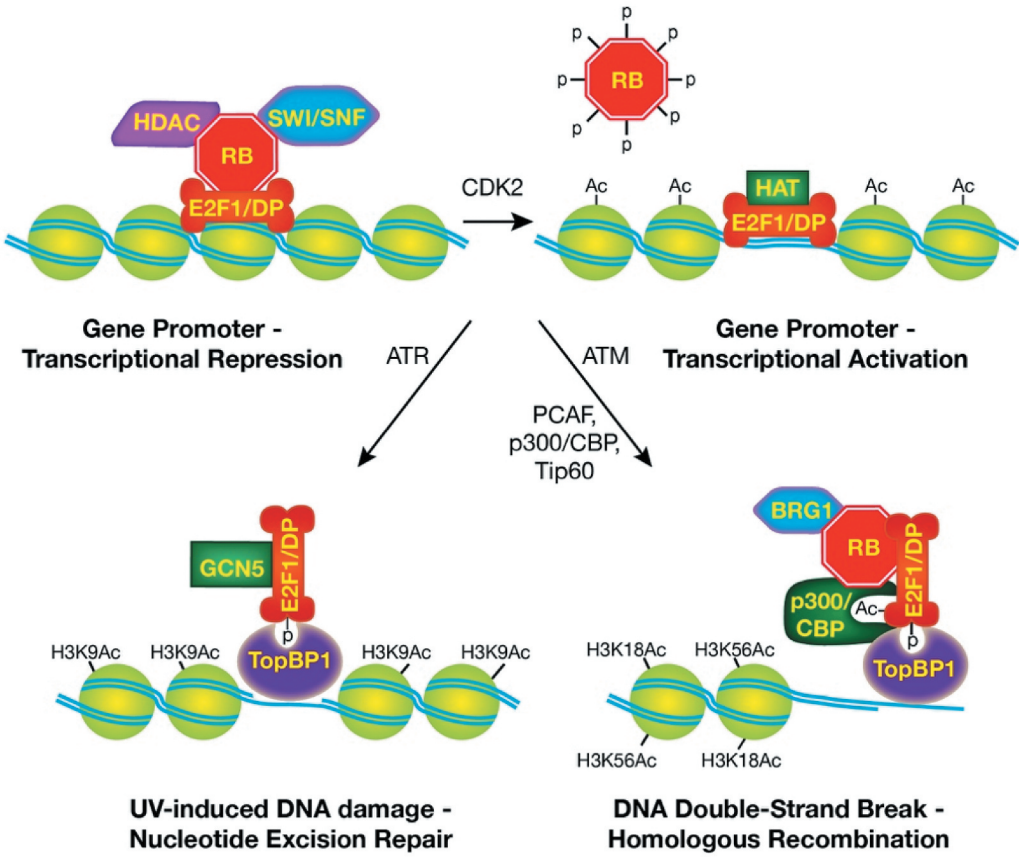

Figure 1. Regulation of E2F1 function during the cell cycle and in response to DNA damage. E2F1/DP dimers bind DNA sequences present in target gene promoters. When associated with RB, E2F1/DP can recruit chromatin-modifying enzymes to repress transcription (top left). RB is hyperphosphorylated and inactivated by CDK2 during cell cycle progression, which allows E2F1 to recruit histone acetyltransferases to activate transcription (top right). E2F1 is phosphorylated by either ATM or ATR in response to DNA damage, resulting in E2F1 localization to damaged DNA through an interaction with TopBP1. In turn, E2F1 recruits GCN5 to sites of UV-induced DNA damage to promote NER (bottom left). At DSBs, E2F1 is also acetylated and recruits p300/CBP, RB, and BRG1 to modify chromatin to facilitate HR repair (bottom right).

the finding that E2F1 is acetylated in response to agents that cause DSBs but not in response to UV radiation [22]. E2F1 is acetylated by one or more acetyltransferases, including PCAF, p300/CBP and Tip60, on three lysine residues located near its DNA binding domain [52,61,62]. Acetylation of E2F1 enhances its stability and in some contexts promotes the transcriptional activation of the pro-apoptotic gene *TP73* [22]. The importance of E2F1 acetylation for DNA repair was discovered only recently.

Protein acetylation can create binding motifs for bromodomains, which are frequently present in proteins that associate with chromatin to regulate transcription and/or DNA damage responses [63,64]. To determine whether acetylated E2F1 might interact with a bromodomain-containing protein, we screened a protein domain microarray. We identified the bromodomain of p300 as specifically interacting with an acetylated E2F1 peptide but not an unacetylated E2F1 peptide [31]. Follow-up studies demonstrated that the closely related bromodomain of CBP could also bind to acetylated E2F1, but not unacetylated E2F1.

The importance of the p300 and CBP bromodomains for recruiting these acetyltransferases to DSBs was demonstrated using a small molecule bromodomain inhibitor specific for p300/CBP [65]. Treatment of cells with this inhibitor did not affect the enrichment of E2F1 or RB at DSBs, but it did prevent both the recruitment of p300/CBP and the acetylation of H3K18 and H3K56 at sites of damage [31]. Further, knock-in mutations that block E2F1 acetylation caused similar effects; E2F1 and RB were recruited to sites of damage but p300 and CBP were not, resulting in a lack of H3K18 and H3K56 acetylation [31]. Thus, E2F1 acetylation, which occurs in response to DSB formation but not UV damage, helps to specify p300/CBP, rather than GCN5, as the acetyltransferases recruited to DSBs by E2F1 (Figure 1).

E2F1 post-translational modifications direct chromatin remodeling at DNA double-strand breaks to facilitate repair

BRG1, a core ATPase subunit of SWI/SNF (BAF/PBAF) nucleosome remodeling complexes, is also recruited to DSBs dependent on E2F1 and RB [33]. Like p300/CBP, BRG1 associates with phosphorylated E2F1 and RB in response to IR. Although the mechanism of this interaction is not established, mutation of the E2F1 acetylation sites prevents BRG1 from associating with the TopBP1-E2F1-RB complex [31]. E2F1 recruits both p300/CBP and BRG1 to E2F1 target gene promoters, and p300/CBP-mediated histone acetylation is thought to cooperate with BRG1-containing complexes to reduce nucleosome density at these promoters to stimulate transcription [48,66,67]. In the context of DNA repair, E2F1-dependent recruitment of p300/CBP and BRG1 is also associated with a reduction in nucleosome density, specifically in chromatin flanking DSBs [31,33].

The Tip60 acetyltransferase is also recruited to DSBs and is important for increasing histone H4 acetylation and destabilizing nucleosomes in chromatin flanking DSBs [68,69]. Unexpectedly, depletion of E2F1 or RB, or mutation of E2F1 at sites of phosphorylation or acetylation, also impairs recruitment of Tip60 and histone H4 acetylation at DSBs [31]. However, unlike p300/CBP and BRG1, Tip60 does not appear to physically associate with phosphorylated E2F1 in response to DNA damage. This suggests that E2F1- and RB-dependent chromatin remodeling is indirectly involved in the recruitment and/or retention of Tip60 at DSBs.

Knock-in mutations that block either the phosphorylation or acetylation of E2F1 also inhibit enrichment of the MRE11-RAD50-NBS1 (MRN) complex at an induced DSB, suggesting that efficient loading of MRN onto chromatin requires E2F1-mediated histone acetylation and nucleosome remodeling [31]. A direct interaction between NBS1 and E2F1 could also contribute to the recruitment and/or retention of MRN at DSBs [14,70]. Defective loading of MRN onto chromatin flanking a DSB may explain, in part, why depletion or mutation of E2F1 impairs DNA end-resection and HR repair [14,33]. The physiological relevance of E2F1-mediated chromatin remodeling at DSBs is illustrated by the finding that mice harboring knock-in mutations that block E2F1 phosphorylation or acetylation are hypersensitive to IR, a hallmark of defective HR repair [31,33].

Are there universal mechanisms for E2F1-mediated regulation of transcription and DNA repair?

As discussed above, E2F1 recruits p300/CBP and BRG1 to DSBs and to some gene promoters to induce histone acetylation and reduce nucleosome density. Depending on the specific locus where E2F1 recruits these factors, the resulting modifications to chromatin structure can facilitate either DNA repair or transcription. In some cases, such as during osteoblast differentiation, RB also participates in the recruitment of BRG1 and cooperates with p300 in the transcriptional activation of tissue-specific E2F1 target genes [71,72]. How RB participates in E2F1-dependent transcriptional activation is unclear. RB binding is thought to mask the C-terminal transcriptional activation domain of E2F1, thus preventing its interaction with histone acetyltransferases and other co-activators [45,73–75]. However, because the bromodomains of p300 and CBP interact with the N-terminal acetylation sites of E2F1, this could allow E2F1 to simultaneously associate with RB and either p300 or CBP. While this appears to be the mechanism by which E2F1 recruits both RB and p300/CBP to DSBs, it remains to be determined whether this mechanism is also used by E2F1-RB complexes to activate transcription.

In other contexts, E2F1 can regulate both transcription and DNA repair by recruiting GCN5 to induce H3K9 acetylation, relax chromatin structure, and increase access to the transcription or NER machinery, respectively [21,32,44,47]. The mechanism by which E2F1 associates with GCN5 in response to UV radiation is unclear. Mutational analysis of E2F1 indicates that neither the DNA binding domain nor the transcriptional activation domain are necessary for E2F1 to promote NER [9]. Instead, the Marked box domain of E2F1, which is located between the DNA binding and transcriptional activation domains, is required for E2F1 to enhance NER factor recruitment to sites of UV damage [9]. The Marked box domain is used by E2F1 to bind a number of partner proteins, including prohibitin and Jab1 [76,77]. Whether this domain also binds GCN5 in response to UV radiation remains to be determined. Regardless of the mechanism, taken together, these studies reveal E2F1 to be a versatile protein that performs multiple jobs as a transcription factor while also moonlighting as a regulator of DNA repair by recruiting the same chromatin-modifying enzymes to either target genes or different types of DNA damage.

The distinction between transcription factors and DNA repair factors is becoming blurry

The histone code model posits key roles for writers, erasers, and readers of histone post-translational modifications in regulating transcription and this model has been extended to include DNA repair and other process that require access to DNA in the context of chromatin [3,78,79]. However, mechanisms must exist for targeting the writers, erasers and readers of the histone code to specific sites in the genome, such as gene promoters and sites of DNA damage. The role of sequence-specific DNA binding proteins like E2F1 in recruiting components of the histone code machinery to gene regulatory elements is well known but how the histone code machinery is targeted to sites of DNA damage is less well understood. Some DNA damage recognition factors may recruit chromatin-modifying enzymes to sites of DNA damage through direct interactions. For example, damaged DNA binding protein 2 (DDB2/XPE) interacts with and recruits the acetyltransferase HBO1 to sites of UV-induced DNA damage, resulting in increased acetylation of histone H3K14 and H4 [80]. This DDB2-HBO1 pathway appears to cooperate with the E2F1-GCN5 pathway in relaxing chromatin structure to allow the NER machinery access to damaged DNA for efficient repair.

Interestingly, DDB2 moonlights as a transcriptional regulator by associating with gene promoters and recruiting different components of the histone code machinery [81–84]. In fact, DDB2 can bind to and cooperate with E2F1 to activate transcription [85,86]. Another DNA damage recognition factor, XPC, also moonlights as a regulator of transcription, including E2F1-dependent transcription [87–90]. XPC interacts with both E2F1 and GCN5 and co-localizes with them at a subset of active gene promoters [87]. Depletion of XPC reduces the expression of these target genes, concomitant with a decrease in H3K9ac at their promoters [87].

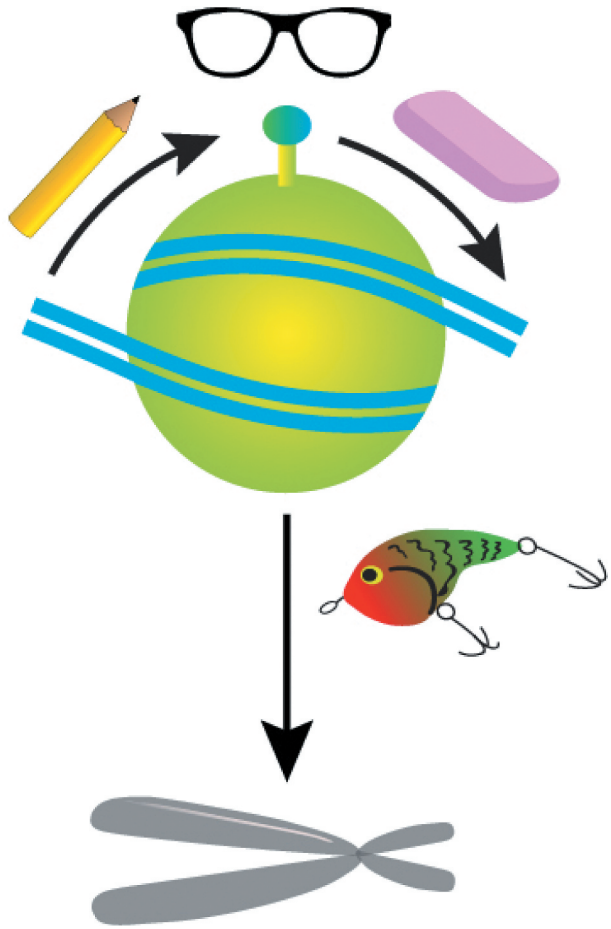

Figure 2. The fishing lure analogy. Some factors, like E2F1, lure various components of the histone code machinery to specific genomic loci to regulate multiple DNA-dependent cellular processes in the context of chromatin.

If E2F1 and XPC cooperate to regulate both transcription and DNA repair [29,32,87], then the distinction between a transcription factor and a DNA repair factor begins to break down. There is no term for factors like E2F1 and XPC that regulate both transcription and DNA repair through similar mechanisms involving the recruitment of chromatin modifying enzymes, like GCN5, to specific loci in the genome. We and others have used the term "chromatin accessibility factors" to describe the functions of E2F1 and p53 in relaxing chromatin structure for NER [91,92]. However, this term does not imply a uniform mechanism as E2F1 co-localizes with sites of UV-induced DNA damage, whereas p53 does not, indicating that E2F1 plays a more direct role in modifying chromatin structure at sites of UV damage [9,93]. Moreover, E2F1-mediated chromatin remodeling may be important for more than simply increasing chromatin accessibility to cellular machinery.

Perhaps a good analogy for factors like E2F1, DDB2 and XPC is that they act like fishing lures (Figure 2). Like a lure, E2F1, DDB2 and XPC can attract and catch various chromatin-modifying enzymes using multiple protein-protein interaction domains as hooks. They can then reel in these chromatin modifiers to specific genomic loci. Just as different lures can be selected to target different fish, E2F1 can be post-translationally modified to capture different prey to differentially modulate chromatin structure depending on the context. It is quite possible that other transcription factors that localize to DNA damage also lure the same set of chromatin-modifying proteins to both promoters and sites of DNA damage to regulate gene transcription and DNA repair, respectively. It will be interesting to determine whether other DNA repair factors that moonlight as transcriptional regulators, like BRCA1 [94–99], also recruit the same chromatin-modifying enzymes and direct the same chromatin modifications for both transcription and DNA repair.

Acknowledgments

We wish to thank Rebecca Deen and Briana Dennehey for help with manuscript preparation and editing, Joi Holcomb for figure graphics, and Jen Orona for her many years of technical and animal care support for our research program. Work described in this review was supported in part by grants from the Cancer Prevention and Research Institute of Texas (RP140222 to D.G.J.), the National Institutes of Health (CA079648 to D.G.J., CA214723 to D.G.J., and Cancer Core Support Grant CA016672), and institutional support from the Center for Cancer Epigenetics and the Center for Genetics and Genomics.

Disclosure statement

The authors declare no competing interests.

Funding

This work was supported by the Division of Cancer Epidemiology and Genetics, National Cancer Institute [CA214723].

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