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Functional links between transcription, DNA repair and apoptosis

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Abstract. DNA damage initiates damage response pathways, cell cycle arrest and apoptosis. These processes act in a concerted fashion and remain functionally linked through mechanisms not completely understood. Programmed cell death, referred to as apoptosis, is a tightly regulated phenomenon ensuring that cells that accumulate irreversible DNA damage do not replicate. Interestingly, hyperacetylation of histone proteins, which alters transcription patterns and appears linked to DNA repair, also induces apoptosis, suggesting that aspects of chromatin modification link these very distinct processes. Modulating chromatin structure in the absence of any DNA lesions also activates key DNA damage-signalling proteins, further supporting the role of higher-order chromatin structure in mediating stress responses. This review will present an overview of the epigenetic control of eukaryotic genomes by chromatin remodelling as it pertains to DNA damage and highlight the potential role of the ING PHD proteins in linking apoptosis and DNA repair to gene transcription.

Key words. Histone acetylation; HAT/HDAC; ING1; p53; PCNA; transcription; DNA damage/repair; apoptosis/senescence.

Introduction

A variety of exogenous and endogenous genotoxic agents are capable of inducing DNA damage and eliciting DNA repair, stress-induced premature senescence (SIPS) that resembles a severe cell cycle checkpoint, or apoptotic responses. It is believed that the cell's initial response is to attempt to repair damage, but if the lesion is too extensive or compromises DNA metabolism, a signalling cascade triggers alternative mechanisms so as to inhibit cellular transformation and immortalization. Therefore, it is crucial that cells are capable of recognizing the severity of damage and simultaneously activating the appropriate checkpoint responses, otherwise mutations will be introduced and faulty genomes will be propagated. Several key DNA damage sensors that bind specifically to DNA lesions such as the Mre11-Rad50-Nbs1 (MRN) complex and the BRCA-1-associated surveillance complex (BASC), are believed to activate kinases that are presumed to transduce signals generated by various types of genomic insults. However, it has recently been shown that these kinase transducers can be activated in the absence of DNA damage [1]. These stress-induced kinase proteins harbour significant sequence homology to the catalytic domains of the phosphoinositide (3) kinase [PI(3) kinase] and are therefore referred to as phosphoinositide (3) kinase-related kinases (PIKKs). Indeed, it is now clear that different forms of DNA damage and some other types of cellular stress prompt a protein phosphorylation cascade that ultimately impinges upon the transcription, replication and cell cycle machineries. Mutations that are known to increase the cell's vulnerability to specific DNA-damaging agents have helped to elucidate the mechanisms by which these proteins are activated and how their downstream targets mediate the cell's response to genomic insult (table 1). Furthermore, since genomic integrity is a vital component of all life forms, studies in a wide range of model organisms have enabled us to identify and char-

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acterize evolutionarily conserved repair protein orthologues.

The packaging of genetic material into chromatin has pronounced effects on transcriptional regulation and plays a pivotal role in DNA repair, senescence and apoptotic pathways. This type of genomic regulation is often referred to as epigenetics (literally translated to 'on genes') since it involves modifications of DNA and its associated proteins, resulting in altered gene expression without altering the DNA sequence per se. Chromatin structure can be modified by both internal stressors such as lesions to DNA and external stressors such as a non-hospitable growth environment [2, 3]. Therefore, it is likely that there is a high degree of downstream overlap in a cell's response to intracellular DNA damage as well as to extracellular stress (fig. 1).

Supporting this hypothesis is the yeast target of rapamycin (TOR) protein kinase, whose homologue in mammalian cells (mTOR) is a member of the PIKK family that responds to DNA damage [4]. In yeast, TOR has recently been shown to modulate chromatin in response to nutrient availability [2]. This finding is especially intriguing since nutrient deprivation, like DNA damage, can influence chromatin structure and initiate a signalling cascade in response to the stress. Therefore, it seems that several types of cellular stress could alter chromatin equilibrium, thereby activating similar downstream stress responses (fig. 2).

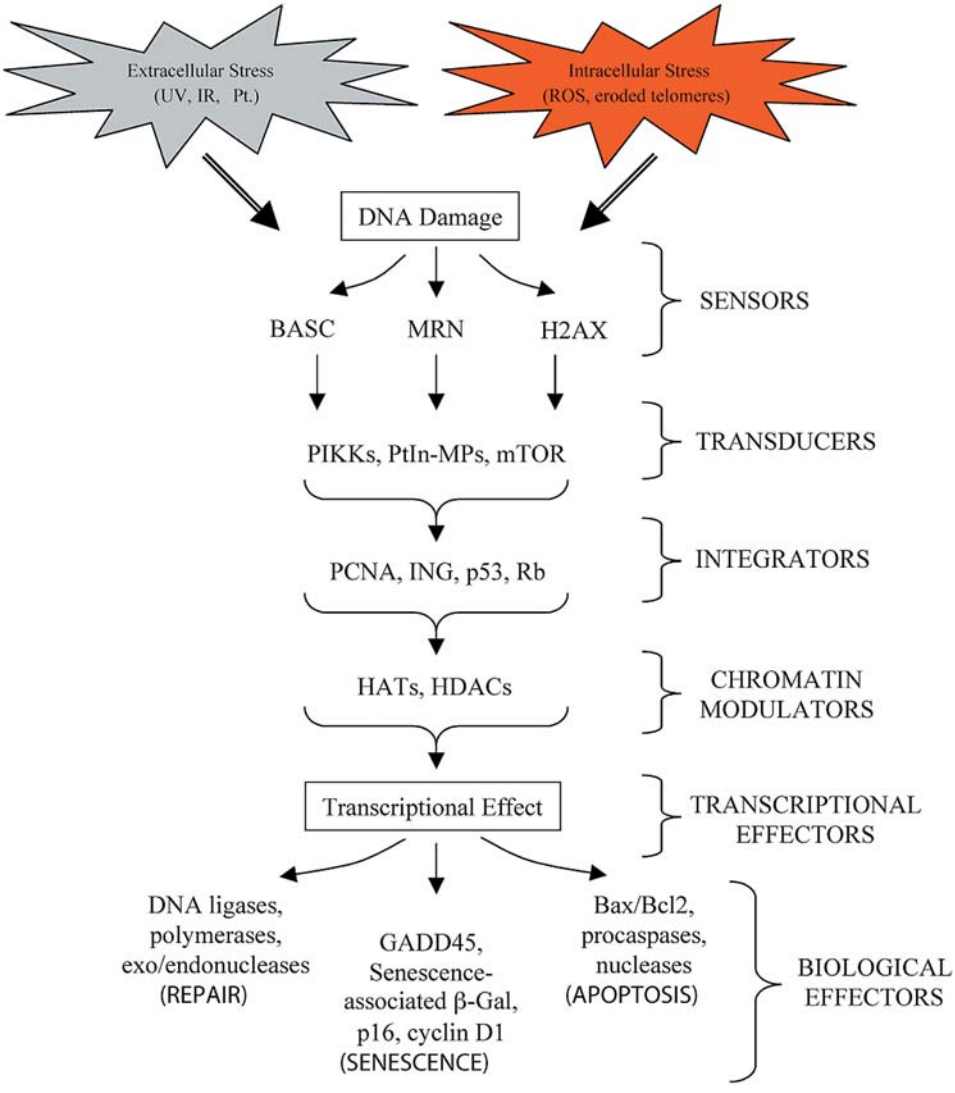

Figure 1. Cellular responses to DNA damage, telomere erosion or extracellular stress all impinge upon common regulators of transcription. Both external stresses such as UV or chemical toxins and internal stresses such as reactive oxygen species activate PIKKs. This pathway is common to all DNA damage-signalling models in that it involves sensor, transducer and effector molecules. Here we propose the addition of integrators that target chromatin-modifying proteins to particular regions of chromatin to activate or repress particular genes. The activation of ING2, and possibly other INGs by phosphatidylinositol monophosphates (PtIn-MPs) has recently been observed in response to DNA damage.

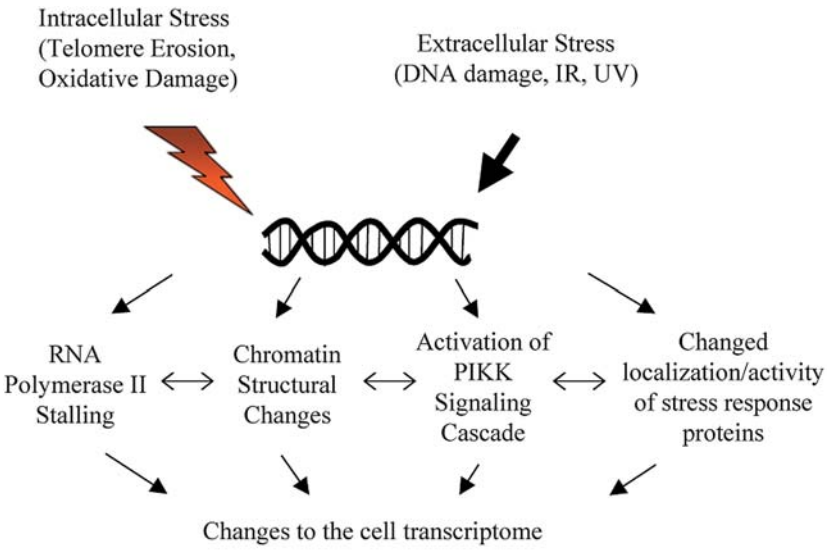

Figure 2. Several types of cellular stress could alter chromatin equilibrium, thereby activating similar downstream stress responses. Cellular stress responses impinge upon several common downstream targets that ultimately have effects on gene transcription. These targets also show a bidirectional activation possibly to reinforce the stress response pathways.

Table 1. Genomic vulnerability and accelerated aging syndromes.

Syndrome	Defective gene(s) or gene product(s)	DNA repair defect
Ataxia telangiectasia	ATM	Unable to activate cell cycle checkpoints in response to DNA double-strand breaks
Nijmegen breakage syndrome Ataxia-telangiectasia-like disease	NBS MREll	part of MRE11-RAD50-NBS1 (MRN) complex involved in initial processing of DNA double-strand breaks
Werner's syndrome	WRN helicase	WRN DNA helicase
Bloom's syndrome	BLM helicase	ablated homologous recombination repair and repair of damage at stalled replication forks
Xeroderma pigmentosum	XPA, XPB, XPC, XPD, XPF	ablated nucleotide excision repair (NER)
Trichothiodystrophy	XPB, XPD in transcription	abrogated function of DNA helicases involved
Cockayne's syndrome	CSA, CSB	unable to recognize stalled polymerase (TCR)
Fanconi's anemia	multiple 'FA genes'	abrogation of DNA damage response system
Rothmund-Thompson syndrome	RECQL4	RecQ-like DNA helicase

Chromatin structure and transcription

Chromatin in interphase cells is made up of 146 bp of DNA coiled around an octamer of histones (H2A, H2B, H3 and H4), forming a 10-nm nucleosome fiber [5, 6]. The 10-nm string of polynucleosomes can be obtained under conditions of low ionic strength; however, a 30-nm fiber consisting of an underlying coiled structure also forms under some conditions. The 30-nm fiber is the basic constituent of both interphase chromatin and mitotic chromosomes (fig. 3) [7, 8]. Chromatin structure is very dynamic and is affected by multiple modifications of chromatin-associated proteins, including, but not limited to, histones and remodelling cofactors within particular chromatic regions. Indeed, chromosomal DNA and its associated proteins undergo dramatic alterations in structure during normal cellular processes such as DNA synthesis, transcription and repair [9, 10]. Conversely, it is known that DNA damage leads to changes in gene expression [11–13], and it is now clear that mechanisms that impinge directly upon higher-order chromatin structure regulate cellular metabolic processes such as transcription, DNA replication and DNA repair. This bidirectional interaction is outlined in figure 2.

Chromatin structure is increasingly being attributed to modification of the subunits of nucleosomes, the basic histones. Histones are positively charged, low-molecular-weight DNA scaffolding proteins that are subject to numerous post-translational modifications including acety-

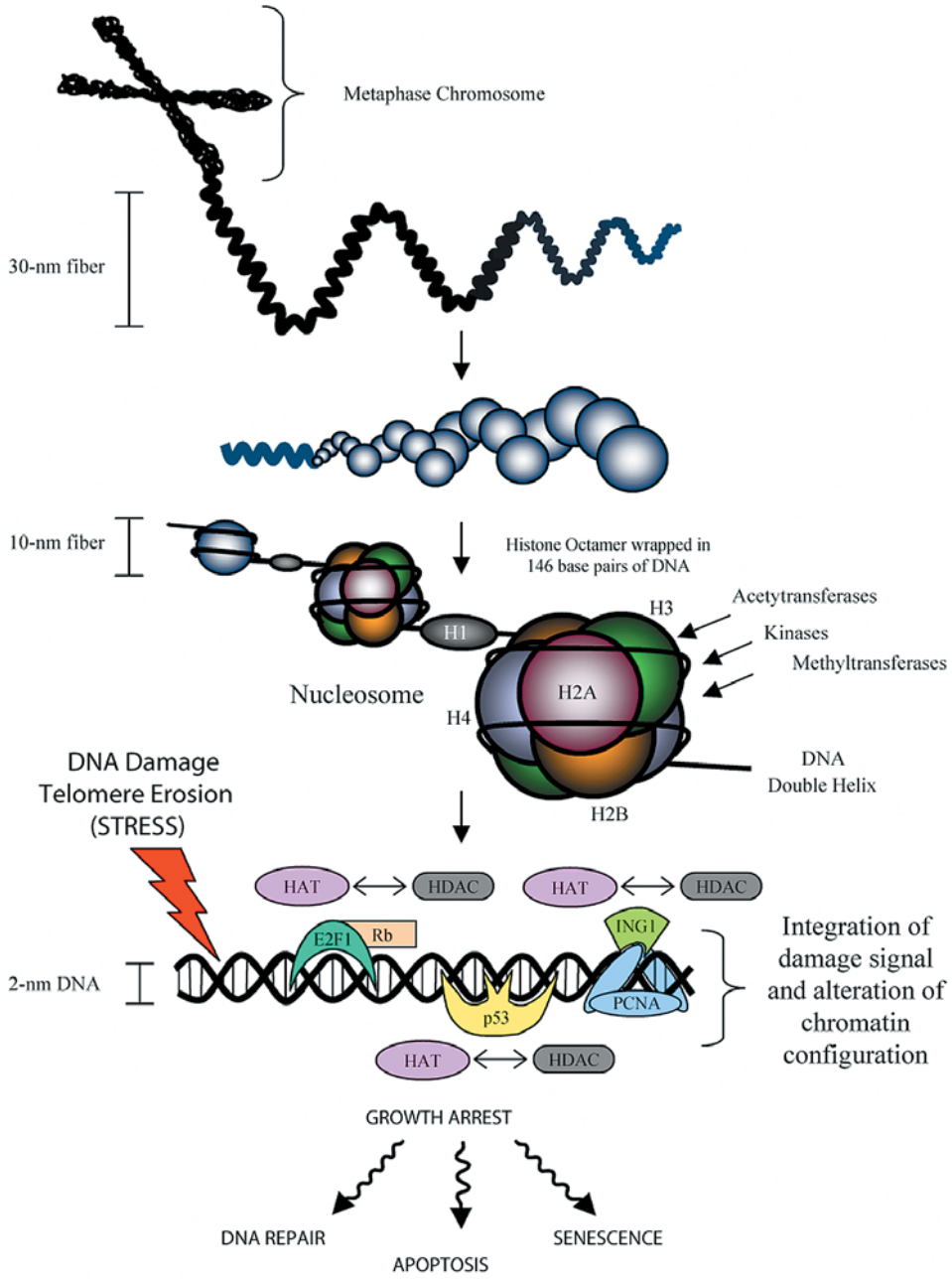

Figure 3. Chromatin modulation can result from both intracellular and extracellular stressors, ultimately inducing a common downstream signalling cascade. Recent studies have highlighted the importance of epigenetic control of the human genome. Here we propose that structural changes to chromatin such as those seen at sites of DNA damage as well as those induced by extracellular stressors can activate common key transducers of cellular stress. This signalling cascade impinges upon diverse mediators of the stress response and results in changes to the transcriptome. Ultimately, the mammalian cell's fate is dictated by how severe the stress is and culminates in either survival when the stress is repaired or removed, apoptosis or senescence when the stress is too severe, or transformation when the damage remains unchecked.

lation, methylation, phosphorylation, poly(ADP-ribosylation) and ubiquitination [14]. These modifications play diverse roles in modulating chromatin structure and have been linked to the regulation of gene transcription [15]. Histone acetylation neutralizes the charge of basic (positively charged) lysine residues within histone proteins. Consequently, there is destabilization of the binding of histones to the negatively charged DNA so that other enzymes/protein complexes are capable of unwinding the chromatin, accessing the DNA at selective sites and transcribing target genes. In other words, the dynamic modification of histones through the enzymatic actions of histone acetyltransferase (HAT) and histone deacetylase (HDAC) protein complexes modifies nucleosome struc-

ture, altering the degree of DNA relaxation and subsequently modifying the accessibility of regions of DNA to transcription factors [14].

Not surprisingly, HAT and HDAC protein complex activity must be tightly regulated in order to maintain the appropriate level of histone acetylation in a given cellular environment. To date several HAT/HDAC coactivators and corepressors have been identified. The INhibitor of Growth (ING) family of proteins are involved in chromatin remodeling, and bind to and affect the activity of both HAT and HDAC protein complexes. The first member of the ING gene family, ING1, induces histone acetylation, promotes DNA repair and interacts with proliferating cell nuclear antigen (PCNA). The ING proteins have a highly conserved plant homeodomain (PHD) zinc finger, a nuclear localization sequence (NLS) and nucleolar targeting sequences (NTS) that target the proteins to nuclear domains under certain conditions [16–18]. ING1 also has a PCNA-interacting protein (PIP) domain through which it binds PCNA in a DNA damage-inducible manner [19]. Since PCNA is an essential factor for DNA replication and repair, ING1 may act to couple these processes to chromatin remodeling. Therefore, the ING family of PHD proteins may act to help functionally link transcription to DNA repair and apoptosis.

Chromatin modifications other than acetylation also play clear roles in DNA damage repair and apoptosis. For example, phosphorylation of the histone variant H2AX on its canonical SQE motif acts to localize DNA damage repair proteins to the site of DNA damage [20, 21]. Interestingly, this has also been reported to occur in replicative senescence initiated by telomere erosion [22], suggesting that senescence may share some of the same pathways involved in the DNA damage signalling cascade initiated by external damaging agents such as ionizing radiation (IR), ultraviolet (UV) and oxygen radicals, among others. Transduction of internal and external stress signals by common pathways is illustrated in figure 1. Histone and DNA methylation also play important roles in chromatin homeostasis and gene activity [23, 24]; however, for the sake of brevity we will focus on the role of histone acetylation in these processes.

Table 2. Types of DNA damage.

DNA damage	Repair mechanisms*
Double-strand breaks (DSBs)	NHEJ, HR
Single-strand breaks (SSBs)	NHEJ, HR, nucleotide excision repair (NER), base excision repair (BER)
Thymidine dimers	NER
Mismatch	mismatch repair (MMR)
C-U deamination	BER
Covalent cross linking	NER, BER
Apurinic/apyrimidinic (AP) site (missing bases)	NER, BER

*Repair mechanisms are not an exhaustive list and do tend to show considerable overlap based on additional characteristics of DNA damage.

Upon induction of a cellular stress such as DNA damage, it is apparent that particular genes are activated or repressed and different types of DNA damage trigger different repair responses depending on the severity and type of lesion (summarized in table 2). Recently, a model by which DNA double-stranded breaks (DSBs) activated the ataxia telangiectasia-mutated (ATM) protein (a PIKK kinase) through intermolecular autophosphorylation [1] was proposed, where DNA damage induces inactive multimeric ATM to autophosphorylate, dissociate and become catalytically active. Surprisingly, chromatin structural changes in the absence of any DNA damage also appeared to activate ATM [1], supporting the idea that changes to local chromatin architecture can elicit a DNA damage repair response via a mechanism that remains to be identified. Furthermore, treatment of cells with low doses of ionizing radiation (IR) increased the amount of catalytically active monomeric ATM in the nucleus, sug-

Table 3. Key DNA damage protein motifs.

Motif*	DNA damage proteins	Role in damage	Modifications
BRCT	BRCA1, BARD1, MDC1, 53BP1, Rad9	localization of host protein	phosphorylation
PHD	ING1-5, CBP, TIP5/NoRC	chromatin modulation	phosphorylation
SQE	p53, H2AX, E2F1, SMC1, Nbs1, TRF1	activation of host protein targeted by ATM	phosphorylation
PIP	ING1, p21, GADD45, FEN1, XPG	loading dock near site of lesion	competitive binding of proteins
FAT/FATC	ATM, ATR, SMG1, DNA-PK_{cs}, mTOR (FRAP), TRRAP	protein binding, structural scaffold	none reported
PI(3)K		catalytic site of active protein kinases	phosphorylation

*BRCT, BRCA1 C-terminus; PHD, plant homeodomain; SQE, serine, glutamine, glutamic acid; PIP, PCNA interacting protein; FAT, FRAP, ATM and TRRAP; FATC, FRAP, ATM and TRRAP extreme C terminus; PI(3)K, phosphoinositide 3-kinase catalytic domain.

gesting that ATM was not activated by DNA lesions themselves via MRN or BASC complexes, but rather by modifications to the higher-order structure of chromatin.

DNA damage and the decision between senescence and apoptosis

The processes necessary to initiate and mediate DNA damage repair versus apoptotic signalling cascades are tightly regulated, and making an incorrect decision would have dire consequences to cells and organisms. Recently, it was shown that in addition to the repair-versus-apoptosis decision, low levels of DNA damage can alternatively induce a senescent-like phenotype referred to as stress-induced premature senescence (SIPS) [25–27]. Further complexity exists when we consider that different types of DNA lesions result in aberrant DNA structures and recruit various repair mechanisms, as outlined in table 2. We now know that certain proteins such as the tumour suppressors p53 and retinoblastoma (Rb) are germane to these complex cellular processes, but we still do not fully understand the context in which these and other stress response proteins act. Members of the PIKK family such as ATM and ATR (ataxia-telangiectasia mutated and Rad3 related) are believed to act as transducers of the DNA damage signal by phosphorylating downstream effector molecules, resulting in their activation [28]. It has also been shown that in response to DNA damage, the HAT and transcriptional coactivator p300, as well as ING1, which activates HATs, binds PCNA and participates in chromatin remodelling at DNA lesion sites [19, 29, 30]. This indicates that the ING1:p300 HAT protein complex associates with dynamic DNA structures, again linking DNA damage repair to chromatin modification via histone acetylation. It remains unclear whether PIKK activation and HAT complex localization to sites of DNA damage are functionally linked, but recent evidence suggests this [1].

PCNA is an essential processivity factor for DNA replication and repair. It is highly conserved evolutionarily, essential for cell survival and forms a sliding homotrimeric platform encircling DNA that can mediate the local interaction of proteins with DNA [19, 29–31]. Many proteins bind to PCNA through a small region containing a conserved motif; these include proteins involved in cell cycle regulation as well as those involved in DNA processing and chromatin modulation (table 3) [31, 32]. We and others speculate that PCNA associates with protein complexes in a DNA damage and cell growth-dependent manner, suggesting that its role in the context of DNA association is as a ‘liaison’ for the integration of various chromatin- and DNA-modifying proteins [30]. For instance, HAT protein complexes such as p300/CBP which interact with PCNA also interact with proteins such as BRCA1, which is involved with DNA repair [33], and with the ING1 protein, which binds PCNA directly and plays a role in chromatin remodelling and apoptosis [17, 19, 30] through interactions with HATs and HDACs. It is therefore possible that a DNA repair pathway, an apoptotic pathway or a senescence pathway could be triggered based on the specific multiprotein complex tethered to PCNA at any given time. This complex of proteins, therefore, could play the role of a molecular integrator of signals, as outlined in figure 1. Protein motifs that are common on proteins functioning in DNA repair pathways and that may promote complex formation are listed in table 3.

Transcription-coupled repair and RNA processing

It has been known for some time that transcriptionally active genes are repaired significantly faster than non-transcribed genes [34, 35]. This is consistent with the role of PCNA-binding partners, which include chromatin-modifying complexes, in DNA transcription, synthesis and repair. Although it is evident that chromatin structure needs to be modulated to allow transcription, DNA replication or DNA repair, the role of modular protein complexes in these processes was initially unexpected.

The transcriptional response to DNA damage may help to elucidate how chromatin modulation is linked to DNA repair and apoptosis (fig. 2). Normally, DNA damage interrupts RNA synthesis via RNA polymerase II (RNAP-II) stalling, allowing DNA damage to be repaired before transcription resumes [36, 37]. In fact, several lines of evidence indicate that a stalled polymerase is necessary to elicit transcription-coupled repair (TCR). Moreover, it ensures that DNA damage is not propagated, since the cell is temporarily put on ‘hold’ in order to accurately assess the degree of damage. It has been reported that prolonged RNAP-II stalling results in RNAP-II cleavage and apoptosis [38], suggesting a mechanism by which the cell can establish if the DNA damage is repairable or whether the insult is too severe and cell suicide must ensue. A number of models for the mechanism of transcriptional downregulation in response to DNA damage have been proposed [39]. These include RNAP-II phosphorylation, TATA-binding protein depletion and transcription/repair factor TFIIH depletion [40]. However, inactivation of RNAP-II by phosphorylation seems to be the most plausible in light of the fact that several kinase proteins that can phosphorylate RNAP-II are activated upon induction of DNA damage [41, 42].

In addition to altering transcription in response to DNA damage, recent studies suggest that preexisting messenger RNA (mRNA) is also regulated. Since genes transcribed just prior to DNA damage can potentially promote inappropriate cell growth, it is critical that this message be intercepted. This occurs by interruption of

pre-mRNA processing. Briefly, DNA repair is linked to mRNA 3′ processing [43] by virtue of the mRNA polyadenylation factor CstF (cleavage stimulation factor) interacting with the BRCA1-associated protein BARD1. The BARD1-CstF interaction represses the nuclear mRNA polyadenylation machinery, thereby inhibiting the export of newly transcribed genes. The interaction between the N-termini of BRCA1 and BARD1 mediates the effect of CstF on mRNA. Consistent with this mechanism, mouse embryonic stem cells that are BRCA1 null are defective in TCR of oxidative DNA damage [44] possibly due to an inability to process mRNA. Therefore, it appears that cells have developed mechanisms not only to abrogate de novo RNA synthesis, but also to stop the processing and export of newly transcribed genes.

Can ING proteins link transcription, DNA repair and apoptosis?

Many recent studies of DNA damage signalling have highlighted the importance of key, evolutionarily conserved protein motifs [12, 19, 28, 31, 45], some of which are listed in table 3. Many of these motifs are modified to change catalytic activity, localization or association with transcriptional coactivators or -repressors. For example, the activity of the PIKK kinases in response to DNA damage and the constellation of proteins that bind to PCNA changes markedly in response to UV and other DNA-damaging agents.

The ING family of proteins, with their evolutionarily conserved PHD domain as well as a PIP motif found in the $p33^{ING1b}$-splicing isoform of ING1, represent a family of proteins that utilize different functional domains to link different cellular processes that arise from internally generated and/or external stresses. For example, PCNA forms a homotrimeric clamp around DNA as diagrammed in figure 3 and is an essential processivity factor for DNA polymerase δ and ε, functioning in both DNA replication and nucleotide excision repair. Since PIP motifs are found in growth regulators such as $p21^{WAF1}$ and the growth arrest and DNA damage-inducible gene GADD45 and with DNA replication and repair proteins, it suggests that PCNA acts to integrate the intensity of the DNA damage signal by binding particular proteins with PIP motifs and translating the signal into distinct responses such as cell cycle arrest with subsequent DNA repair, stress-induced premature senescence, or apoptosis. Therefore, ING proteins could serve a central role in this decision-making process since they could recruit different chromatin-remodelling (HAT and HDAC) complexes to sites of repair where PCNA is bound.

Conclusion

Clearly, the links between how cellular stresses such as DNA damage, oxidative damage, heat shock and particular metabolic poisons alter DNA transcription and initiate repair, apoptosis or senescence are too numerous to mention in the context of this review. However, the aim of this report is to highlight the expanding roles of multifunctional proteins such as PCNA and ING1 in the regulation of the biological responses to DNA damage through their ability to coordinate DNA repair with higher-order chromatin structure, which subsequently impinges upon transcription regulation. The numerous functions of these proteins in the context of DNA damage and repair, apoptosis or senescence can be a consequence of protein modification and/or localization within the cell. One common feature of most DNA damage response models is that of sequential signalling of DNA damage from initial sensors of DNA damage, such as the MRN and BASC complexes, to the transducers of this signal, such as the PIKK family of protein kinases, and finally to the mediators or effectors of this signalling cascade that are ultimately responsible for generating a physiological response. As diagrammed in figures 1 and 3, we propose the addition of a signal integrator that initially blocks cell growth and, through the regulation of local chromatin structure, determines the subset of genes that are transcriptionally activated or repressed. This integrator may include tumour suppressors such as p53, Rb and ING1 that can target HAT and HDAC complexes to particular domains of chromatin. Subsequently, the genes that are regulated determine whether cells repair DNA and resume cell cycling, enter a stress-induced senescent state or undergo apoptosis.

Much like the naïve belief that individual genes were regulated entirely by cis-acting promoter elements, we are now recognizing the importance of epigenetic mechanisms in DNA damage responses and beginning to appreciate the complexity of the molecular circuitry that enables cells to shut down general transcription in response to genomic insult while concomitantly transactivating specific subsets of damage-inducible genes.

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