FORUM REVIEW ARTICLE

Post-Transcriptional Regulation of DNA Damage-Responsive Gene Expression

Bruce C. McKay

Abstract

Significance: Production of proteins requires the synthesis, maturation, and export of mRNAs before their translation in the cytoplasm. Endogenous and exogenous sources of DNA damage pose a challenge to the coordinated regulation of gene expression, because the integrity of the DNA template can be compromised by DNA lesions. Cells recognize and respond to this DNA damage through a variety of DNA damage responses (DDRs). Failure to deal with DNA damage appropriately can lead to genomic instability and cancer. **Recent Advances:** The p53 tumor suppressor plays a dominant role in DDR-dependent changes in gene expression, but this transcription factor is not solely responsible for all changes. Recent evidence indicates that RNA metabolism is integral to DDRs as well. In particular, post-transcriptional processes are emerging as important contributors to these complex responses. **Critical Issues:** Transcriptional, post-transcriptional, and translational regulation of gene expression is subject to changes in response to DNA damage. How these processes are intertwined in the unfolding of DDR is not fully understood. **Future Directions:** Many complex regulatory responses combine to determine cell fate after DNA damage. Understanding how transcriptional, post-transcriptional, and translational processes interdigitate to create a web of regulatory interactions will be one of the key challenges to fully understand DDRs. *Antioxid. Redox Signal.* 20, 640–654.

Introduction

GROWTH AND DEVELOPMENT require the coordinated regulation of tens of thousands of genes (115). Endogenous and exogenous sources of DNA damage pose a challenge to mRNA synthesis, because the template strand of transcribed genes can sustain damage that prevents normal transcription (87, 104, 150). The structure of DNA lesions and their frequency will affect their consequences on transcription elongation by RNA polymerase II (150). Minor base alteration may be readily bypassed by RNA polymerase II, leading to the potential for transcriptional mutagenesis (*i.e.*, altered mRNA sequence), while bulkier helix distorting DNA lesions may permanently inhibit the expression of damaged genes by preventing the passage of the elongating polymerase (104, 150). The arrested polymerase may deal with transcription-blocking DNA lesions in several ways, including the initiation of transcription-coupled nucleotide excision repair or activation of a DNA damage response (DDR), leading to cell cycle arrest or apoptosis (86, 88, 104). Transcription is essential for

life; so, eliciting a DDR at transcription blocking DNA lesions represents an efficient means of responding to biologically important DNA damage (86, 88, 104).

Ultraviolet Light Inhibits the Synthesis and Processing of mRNAs

The synthesis of mRNA and its translation are spatially segregated in the nucleus and cytoplasm. This necessitates complex regulatory processes to control the synthesis and maturation of nascent mRNA followed by a variety of post-transcriptional processes that are required to transport the mRNA from the nucleus to ribosomes (120). The synthesis and maturation of mRNA involves the initiation of transcription, the addition of a 5' m⁷G cap, elongation by RNA polymerase II, splicing, termination of transcription, 3' end cleavage, and polyadenylation (the addition of poly(A) tails) (146). The primary transcript is also co-transcriptionally decorated with RNA-binding proteins (RBPs) to yield functional mRNA-protein (mRNP) complexes (56, 120). All of the steps

may be subject to regulation in response to external stimuli, including DNA damage.

The ultraviolet (UV) component of sunlight is one of the most prevalent environmental carcinogens (153). DNA absorbs UV light, leading to the formation of characteristic DNA lesions: cyclobutane pyrimidine dimers and (6-4)-photoproducts, collectively referred to as UV dimers (18). These DNA lesions alter DNA structure and pose a block to elongating RNA polymerase II complexes; so, UV light leads to a dose-dependent decrease in the synthesis of nascent mRNA (Fig. 1A) (69, 101, 106, 136, 138, 149). The probability that the synthesis of a specific mRNA is blocked is a function of UV dose and the length of the gene (136). The recovery of nascent mRNA synthesis after sublethal doses (*i.e.*, 10 J/m²) of short wavelength (250 nm) ultraviolet light (UVC) typically occurs within 6 h, but this is delayed in response to higher doses (Fig. 1A). Recovery of mRNA synthesis correlates with the repair of the transcribed strand of active genes by transcription-coupled nucleotide excision repair (89, 103–106). Therefore, it is thought that UV dimers inhibit mRNA synthesis by blocking the elongating RNA polymerase until repair is complete.

UV light also leads to the inhibition of transcription at the level of initiation. This mechanism is not as clearly established, but the exposure of cells to UV light reportedly leads to decreased initiation of transcription because TATA-binding protein is sequestered from the preinitiation complex by binding DNA lesions (159). This effect can be partially overcome by microinjecting TATA-binding protein into UV-treated fibroblasts (159). UV light also leads to a shift in the proportion of the hypophosphorylated (Ilo) and hyperphosphorylated (IIa) forms of the largest subunit of RNA polymerase II (91, 105, 133). The net effect is a decrease of the Ilo form with a corresponding increase in the IIa form (91, 105, 133). It has been suggested that the depletion of the initiating Ilo form contributes to UV-induced inhibition of transcription (133). The contribution of these mechanisms to the global inhibition of transcription after UV exposure remains to be clarified, as some endogenous genes can be readily expressed

and even induced after UV exposure (154). Furthermore, the introduction of an undamaged reporter gene into UV-treated cells can lead to increased reporter gene expression compared with unirradiated cells (44, 45). Taken together, there is evidence that UV light inhibits the expression of many but not all genes at the level of transcription initiation.

UV light also affects the maturation of mRNAs after UV exposure. Poly(A) tails play important roles in regulating the stability, export, and translation of mRNAs (94). Poly(A) tails are synthesized post-transcriptionally after endonucleolytic cleavage of the primary transcript (123). Several protein factors play critical roles in 3' end processing. The cleavage and polyadenylation specificity factor (CPSF) co-transcriptionally recognizes the polyadenylation signal (PAS, typically AAUAAA) in the 3' untranslated region (3'UTR) of the nascent transcript, while the cleavage stimulatory factor (CstF) recognizes a guanidylate-uridylate (GU)-rich downstream sequence element (DSE) (94) (Fig. 2). Association of these complexes with the nascent transcript leads to the assembly of a functional cleavage/polyadenylation complex, which, in addition to CPSF and CstF, includes cleavage factors I and II (CFI and CFII), RNA polymerase II and poly(A) polymerase (PAP) (94). The 73 kDa subunit of CPSF is the endonuclease responsible for cleavage of the transcript (95) between the PAS and DSE, while PAP synthesizes the poly(A) tail (Fig. 2) (94).

The breast cancer type 1 susceptibility protein (BRCA1)-associated RING domain protein (BARD1) binds the 50 kDa subunit of CstF (CstF-50) and inhibits the 3' cleavage reaction (74). Treatment of cells with UV light leads to the formation of a CstF/BRCA1/BARD1 complex that transiently decreases the 3' end cleavage reaction and thus leads to decreased polyadenylation (71, 75, 76) (Fig. 2). The CstF/BRCA1/BARD1 complex also appears to participate in the UV-induced ubiquitination and degradation of the largest subunit of RNA polymerase II, modifications that may participate in transcription-coupled nucleotide excision and/or the recovery of mRNA synthesis after UV exposure (13, 76, 104, 105, 114, 128). Similarly, the p53 tumor suppressor also regulates

FIG. 1. The effect of ultraviolet (UV) dose and gene size on p53-dependent gene expression. (A) Schematic representation of the effect of three different doses of UV light (<15, 15–30, and >30 J/m²) on nascent mRNA synthesis (106). With increasing doses of UV light, mRNA synthesis is inhibited more strongly and is less likely to recover within the indicated time frame. (B) Schematic representation of p53-induced gene expression in the presence and absence of pre-existing UV lesions (109). In the absence of UV exposure, p53 can induce all size classes of p53 target genes (*left panel*). After cytotoxic doses of UV light (*right panel*), the expression of small genes p53-inducible genes increase more readily than average sized genes, while large p53 target genes cannot be induced efficiently (109).

FIG. 2. UV light inhibits 3' end processing reactions. 3' end processing of the spliced and capped transcripts is coupled to transcription by RNA polymerase II, but the polymerase complex is omitted from this diagram for clarity. (i) The cleavage and polyadenylation specificity factor (CPSF complex) recognizes the polyadenylation signal (PAS), while the cleavage stimulatory factor (CstF complex) recognizes the GU-rich downstream sequence element (DSE). (ii) The 73 kDa subunit of CPSF (CPSF73) is the endonuclease that cleaves the primary transcript between the PAS and DSE sequences. (iii) Poly(A) polymerase extends the poly(A) tail, while the poly(A)-specific ribonuclease (PARN) can deadenylate messages. UV light can stimulate the formation of either p53/PARN1/CstF or BRCA1/BARD1/CstF complexes that, in turn, inhibit 3' end cleavage. In addition, UV light can stimulate PARN activity in a p53-dependent manner, leading to deadenylation. BRCA1, breast cancer type 1 susceptibility protein; BARD1, BRCA1-associated RING domain protein; PAP, poly(A) polymerase; ORF, open reading frame; 3'UTR, 3' untranslated region. To see this illustration in color, the reader is referred to the web version of this article at www.liebertpub.com/ars

the recovery of mRNA synthesis (103, 105, 106, 108) and inhibits 3' end processing after UV exposure through an interaction with the CstF/BARD1 complex (118). Furthermore, p53 can stimulate the poly(A)-specific ribonuclease (PARN), in a BARD1-dependent manner (Fig. 2) (30). These combined effects help prevent the production of truncated polyadenylated mRNAs resulting from inappropriate transcriptional arrest at UV lesions and link 3' end processing to the repair of transcription-blocking DNA lesions (21).

Pre-mRNA splicing is tightly coupled to RNA polymerase II during transcription. Transcription elongation rate affects splice site selection and, thus, alternative splicing (27, 36, 132). The C-terminal domain (CTD) of the largest subunit of RNA polymerase II is important in regulating all aspects of RNA processing, including pre-mRNA splicing (16, 35, 37, 63). This CTD is made up of 52 repeats of a 7 amino-acid consensus sequence (Tyr1-Ser2-Pro3-Thr4-Ser5-Pro6-Ser7), so 5 of these 7 residues are subject to cycles of phosphorylation and dephosphorylation (16). UV light leads to increased phosphorylation of the CTD of the largest subunit of RNA polymerase II (90, 105). Increased phosphorylation of the CTD in response to UV light leads to decreased elongation rate through an unknown mechanism, leading to widespread changes in alternative splicing (96, 117). Collectively, UV light alters transcription and mRNA maturation in at least four distinct ways.

UV DDR, the Transcription Paradox, and Gene Size

The first step in DDR is the recognition of damage by sensory protein complexes (87). The structural properties of the DNA lesions and their location in the genome will dictate which sensors are required to signal the presence of DNA damage. Bulky DNA lesions, such as those induced by UV light, appear to be recognized indirectly through their effects on transcription and replication, and this can involve the 9-1-1 complex (RAD9/HUS1/RAD1) (88, 119). Serine-threonine

kinases of the phosphatidylinositol 3-kinase (PI3K) family subsequently initiate signal transduction cascades. Ataxia-telangiectasia-mutated (ATM) and RAD3-related (ATR), a PI3K family kinase, is activated by UV-induced DNA lesions (88, 169), and this protein can transduce signals directly and indirectly through checkpoint kinases 1 and 2 (Chk1 and Chk2) to numerous effector proteins, including but not limited to the p53 tumor suppressors, BRCA1 and BARD1 (71, 88, 119, 121). All these proteins are linked to transcriptional and/or post-transcriptional regulation of gene expression, so DDR leads to widespread changes in gene expression through a variety of mechanisms.

DDR-dependent changes in gene expression are dominated by the p53 tumor suppressor, a transcription factor that is frequently mutated in cancer (48, 65, 127). When activated by cellular stresses, including DNA damage, the protein is post-translationally stabilized, leading to an increase in sequence-specific DNA binding activity and a consequent increase in the rate of initiation of genes containing p53 consensus DNA binding sites (4, 93). This tumor suppressor positively regulates genes encoding proteins that are involved in cell cycle checkpoints, DNA repair, senescence, and apoptosis (4). The contribution of p53-dependent transcriptional regulation to UV-induced gene expression is well established, but the nature of UV lesions poses a challenge to these responses.

UV light induces DNA damage throughout the genome in a stochastic manner, so the probability that a gene sustains transcription-blocking DNA damage in its template strand is proportional to the size of the gene and the dose of UV light (136). This forms the conceptual basis of the UV transcription mapping assay that was extensively used in the 1970s and 1980s (136). Furthermore, host cell reactivation and the recovery of nascent RNA synthesis assays used to study the repair of transcription blocking DNA lesions rely on this fact (43, 101, 103, 106). Even mildly cytotoxic doses of UV light induce sufficient DNA damage to block gene expression with

~1 lesion per 10 kb per strand following 10 J/m² of UV light (Fig. 1A) (9, 40, 112, 152, 155–157). The median size of protein coding genes is about 25 kb in length (158), so cells exposed to 10 J/m² of UV light sustain an average of 2.5 lesions per gene (109). Therefore, UV light leads to decreased nascent mRNA followed by recovery of mRNA synthesis as the DNA template is repaired (Fig. 1A). Given the high density of DNA lesions per transcription unit, the template strand of DNA damage-responsive genes is likely to sustain DNA damage after UV exposure (107, 109). This has important implications for the unfolding of DDR transcriptional responses.

To study the consequences of UV lesions on the DDR response, a temperature-sensitive variant of murine p53 (V135A) was used to rapidly activate the p53 response in the presence or absence of pre-existing UV-induced DNA lesions. Oligonucleotide microarrays were used to monitor changes in gene expression (109). The number of p53-induced transcripts decreased as a function of UV dose, leaving primarily compact genes with significantly fewer and smaller introns to be induced at cytotoxic doses (Fig. 1B) (109). Conversely, no bias in gene size was detected among p53-repressed transcripts. The compact p53-induced genes included those encoding pro-apoptotic BH3 only proteins involved in the intrinsic mitochondrial cell death pathway, while the long genes included negative regulators of p53 and anti-apoptotic proteins such as Bcl-xL (109). Therefore, the p53 response has evolved with a gene size constraint that facilitates gene expression under conditions of transcriptional stress, and this pattern of expression favors cell death in response to cytotoxic doses of UV light, serving as a molecular dosimeter.

Despite the prominent role that p53 plays in UV-induced gene expression, not all UV-induced genes are regulated by this important transcription factor. UV light leads to increased expression of many mRNAs in p53-deficient cell lines as well. Even in the absence of p53, the same gene size relationship exists for UV-induced genes (109). Compact p53-independent UV-induced genes included AP-1 responsive immediate early genes, NFκB-regulated cytokines and histones (1, 29, 48, 55, 168). Therefore, UV-induced genes tend to be compact, regardless of the transcription factor driving expression. This has been interpreted to indicate that UV-transcriptional responses have evolved to permit specific gene expression in the face of transcription-blocking DNA damage (109).

Role of mRNA Stability in the Regulation of Gene Expression

Gene expression is regulated in large part at the level of transcription initiation; however, UV-induced inhibition of transcription poses a challenge to UV DDR. Post-transcriptional regulation of gene expression offers an alternative level of regulation that partially circumvents this issue, because cytoplasmic mRNA decay has a dramatic impact on specific mRNA levels (140). In general, mRNAs are protected from exoribonucleases by the 5' cap structure (m⁷G) and the 3' poly(A) (7, 135, 140). The first change to the message during cytoplasmic mRNA decay is de-adenylation by the PARN (Fig. 3) (77). Loss of the poly(A) tail facilitates 5' decapping such that both ends of the mRNA are accessible to exonucleolytic degradation by Xrn1 in a 5'-3' direction and the exosome complex in a 3'-5' direction. Together, these exoribonucleases are responsible for the degradation of many unstable mRNAs (140).

Decay of specific mRNAs is controlled by *cis*-acting elements in the transcript, most commonly in 3'UTRs, and transacting factors that interact directly with these elements (Fig. 3). Adenylate uridylate-rich elements (AREs) are the most common and best characterized of these *cis*-acting elements identified to date and may be present in approximately 10% of all human transcripts (2, 14). Guanidylate-uridylate-rich elements (GREs) represent another class of *cis*-acting determinants of deadenylation-dependent mRNA decay (58). Although these elements target mRNAs for degradation, they are subject to complex regulation by a variety of RBPs under different physiological conditions (49).

Over a dozen proteins have been shown to bind AREs. Some of the ARE-binding proteins are known to target specific transcripts for degradation, whereas others confer an increase in mRNA stability (140). Tristetraprolin (TTP) is a zinc finger protein that promotes the decay of ARE-containing transcripts (62). TTP can be found to be associated with the exosome (19, 144), and the addition of TTP to purified exosomes promotes the decay of ARE-containing mRNAs (23). Conversely, the embryonic lethal abnormal vision family of ARE-binding proteins, including HuR, tends to increase the stability of ARE-containing transcripts (25, 92). *In vitro*, these proteins can block degradation of deadenylated substrates (41). Changes in the stability of mRNAs can have dramatic effects on their expression and their encoded proteins.

Genome-wide analysis of mRNA turnover identified mRNAs encoding transcription factors, cell signaling proteins, and cell cycle regulators are among the most labile transcripts, while housekeeping proteins, metabolic enzymes, and structural proteins tend to be encoded by stable mRNAs (46, 97, 126, 139, 165). Furthermore, stable transcripts are typically constitutively expressed, while short-lived mRNAs are inducible (46, 97, 126, 139, 165). It is not intuitively obvious how mRNA stability is linked to inducible gene expression, but recent evidence indicates that unstable mRNAs may reach new equilibrium levels and subsequently recover faster, giving rise to a "peaked" response (59, 124).

Role of mRNA Stability in the p53 Response

The p53 response is characterized by a peaked response with most p53-induced mRNAs exhibiting half lives of 2 h or less (110). Gene ontology analysis indicated that the highly unstable yet rapidly induced p53-regulated mRNAs were associated with functions typical of the p53 response (*i.e.*, DNA repair, cell cycle arrest, apoptosis, *etc.*), while the small number of stable mRNAs did not (110). These unstable 3'UTRs were U-rich with a high density of adenylate uridylate (AU)- and GU-rich elements, consistent with rapid mRNA decay (110). Surprisingly, the unstable mRNAs were induced more rapidly than were stable transcripts. Reporter constructs containing the 3'UTRs derived from several representative p53-responsive mRNAs indicated that these 3'UTRs were able to destabilize the otherwise stable heterologous reporter mRNA (110, 111). Importantly, these 3'UTRs engendered a more rapid transcriptional response, supporting recent evidence that transcription and post-transcriptional regulation are intimately linked (111).

In *Saccharomyces cerevisiae*, the stability of mRNAs exported to the cytoplasm was greatly affected by promoter sequences (12, 34, 151). It is likely that specific promoter elements

FIG. 3. General schematic representation of the life cycle of an mRNA. The primary mRNA is transcribed by RNA polymerase II and it is co-transcriptionally 5' capped (m⁷G), spliced, and polyadenylated. The message is also co-transcriptionally decorated with numerous RBP (not shown). Specific stabilizing (green) and destabilizing (red) RBPs bind to *cis*-acting determinants of mRNA stability primarily in the 3'UTR of the mRNA. The mRNA is exported, and its fate is determined by RBP/3'UTR interactions. Destabilizing interactions direct the transcript for deadenylation and decay by the exosome or Xrn1 with Dcp1/2 (*left side*). Transcripts directed to ribosomes for translation (*right side*) may subsequently be directed for decay through changes in RBP 3'UTR binding. Interactions between miRNAs and 3'UTRs may similarly direct specific mRNAs for decay before or after initiation of translation (not shown). DDRs can affect all stages of mRNP production as well as the stability and translation of specific mRNAs and proteins (see text for details). DDRs, DNA damage responses; miRNA, microRNA; mRNP, messenger ribonucleoprotein; RBP, RNA-binding protein. To see this illustration in color, the reader is referred to the web version of this article at www.liebertpub.com/ars

affected the composition of the RNA polymerase II holoenzyme and altered the co-transcriptional assembly of the mRNP complex, leaving a lasting mark on the nascent transcript (12, 28, 50, 57, 60). A new term, *synthegradase*, refers to proteins that are associated with mRNAs throughout their life, affecting both mRNA synthesis and decay (28). Two apparent *synthegradase* complexes have been identified in

S. cerevisiae: Rbp4/7 heterodimer and Ccr4-Not complex that link various aspects of RNA metabolism from synthesis to degradation (34, 50, 60).

Our own work suggests that similar relationships between transcription and mRNA processing occur in human cells (111). The gene encoding the damage-specific DNA binding protein 2 (DDB2) is positively regulated by p53 (147). Its

transcript is unstable with a half life of ~ 2 h, and its 3'UTR can destabilize an otherwise stable reporter mRNA (111). Accelerated mRNA decay was attributed to the presence of a novel *cis*-acting element in its 3'UTR. Surprisingly, this sequence also increased expression of the heterologous reporter gene despite decreased mRNA stability (111). Furthermore, increased transcription was associated with increased nuclear export of the unstable mRNA as well as increased synthesis of the reporter protein (111). Similar sequences were identified in the 3'UTRs of several other transcripts, including the BIRC2 mRNA (encoding cellular inhibitor of apoptosis 1). A similar inverse association between mRNA decay and protein expression was observed when the BIRC2 3'UTR was inserted into a separate heterologous reporter system (111). Not all heterologous 3'UTR reporter mRNAs tested exhibited a similar inverse correlation between mRNA stability and protein expression (111). To the best of our knowledge, DDB2 and BIRC2 represent the first two examples in mammalian cells of accelerated mRNA decay positively influencing gene expression. It is clear that post-transcriptional regulation can play key roles in determining the kinetics of induction of specific transcriptionally responsive mRNAs, including p53- and hence DNA damage-responsive transcripts.

UV Light Increases the Stability of Specific Transcripts

Several years ago, the Elledge laboratory performed a proteomic analysis of ATM and ATR phosphorylated proteins and identified 700 potential targets that were phosphorylated in response to DNA damage (98). Gene ontology analysis indicated that "DNA recombination and repair" and "cell cycle" proteins were well represented, as expected. However, "RNA post-transcriptional regulation" was surprisingly and highly statistically over-represented, indicating that RNA metabolism was a prominent and unexpected component of the DDR (98). Similarly, a subsequent independent proteomic approach identified "RNA processing" and "RNA binding" as the most highly represented classes of DDR-phosphorylated proteins (6). Taken together, regulation of mRNA synthesis and processing at various stages in the mRNA lifecycle contributes to the DDR.

The steady-state level of transcripts is determined through a combination of their rate of synthesis and their rate of decay. The Gorospe laboratory compared steady-state mRNA levels with nascent RNA generated in nuclear run on assays on a genome-wide basis using cDNA microarrays (39). UV light led to increased expression of 132 transcripts, and 34 of these were not associated with increased transcription, suggesting that mRNA stability was the predominant means of increasing the abundance of one quarter of the UV-induced mRNAs (39). In general, changes in the stability of transcripts encoding functionally related proteins could be co-ordinated to yield post-transcriptional operons (46), so post-transcriptional regulation of gene expression could be an important contributor to DNA damage-responsive gene expression.

The earliest report of an increase in mRNA stability in response to DNA damage was from the Fornace lab (66). This group had previously identified many growth arrest and DNA damage-inducible (GADD) transcripts from Chinese hamster ovary cells (42) and then, subsequently determined that the stability of five of these transcripts was increased in response to UV exposure (66). They simultaneously reported

that UV irradiation led to increased expression and/or binding activity of several RBP, providing a possible mechanistic link between UV light and mRNA stability (20). The number of UV stabilized transcripts has expanded since that time (8, 51, 53, 160), and several of these UV-stabilized transcripts are also transcriptionally regulated by p53, AP-1, and NF κ B, combining multiple mechanisms of UV-induced gene expression.

The *CDKN1A* gene encoding the cyclin-dependent kinase inhibitor, p21^{WAF1/CIP1}, is a well-characterized transcriptional target of p53 and p21^{WAF1/CIP1} plays an important role in eliciting a p53-dependent G₁ cell cycle arrest (38). The *CDKN1A* mRNA is highly unstable, because its 3'UTR contains AREs (49, 51, 110, 160). AU-rich element RNA-binding protein 1 (AUF1) binds to the ARE and directs the mRNA for deadenylation-dependent decay (83). Exposure to UV light leads to decreased association of AUF1 with the 3'UTR of *CDKN1A* mRNA (83). HuR, the ubiquitously expressed member of the ELAV family, is exported from the nucleus in response to UV irradiation, where it is thought to stabilize and stimulate translation of the *CDKN1A* mRNA (8, 51, 61, 102, 160). Thus, the displacement of AUF1 derepresses *CDKN1A* mRNA, while the increased association of HuR stabilizes the transcript and facilitates translation of p21^{WAF1/CIP1} (83, 160). Very recently, the nucleoporin (Nup98) was reported to associate with the *CDKN1A* 3'UTR and stimulate p21^{WAF1/CIP1} expression in response to camptothecin treatment by increasing the stability of the transcript as well (143). Therefore, there may be multiple ways in which RBP contribute to p21^{WAF1/CIP1} expression during the DDR. Clearly, transcriptional and post-transcriptional regulation of *CDKN1A* contributes to the efficient expression of p21^{WAF1/CIP1} after DNA damage.

The *GADD45A* mRNA is also transcriptionally regulated by p53, and this transcript is further stabilized post-transcriptionally in response to UV light (66). In untreated cells, AUF1 and the TIAR RBP bind an ARE in the 3'UTR of the *GADD45A* mRNA (82). While AUF1 destabilizes the message, TIAR inhibits its translation (82). Upon UV irradiation, these proteins are phosphorylated in a p38^{MAPK}-dependent manner, displacing them and increasing mRNA stability and translation of the *GADD45 α* protein (82). Stimulation of the p38^{MAPK} pathway can also lead to the phosphorylation of 2 other RBP (PARN and hnRNPA0) that usually inhibit *GADD45 α* expression, further contributing to the derepression of *GADD45 α* expression after UV exposure (130, 131).

Importantly, not all post-transcriptionally stabilized mRNAs are linked to the p53 response. It was reported that UV light led to two waves of p53-independent UV-induced expression of c-Fos, kin17, c-jun, I κ B, and c-myc (8). The first phase was a rapid transcriptional response that occurred within minutes, did not require DNA damage *per se*, and culminated with increased NF κ B and AP-1 transcriptional activity (8, 17, 31, 125) (Fig. 4). The second response was dependent on nuclear DNA damage signaling, was delayed by several hours, and was associated with increased stability of the transcripts (8). Therefore, UV exposure can increase the stability of AP-1- and NF κ B-regulated mRNAs as well. The specific RBP or RBPs controlling the stabilization of these transcripts have yet to be ascertained.

The Ras homolog gene family member B (RhoB) mRNA is encoded by a UV responsive gene (47). UV-induced

FIG. 4. Bimodal response of c-Fos to UV light. UV light can activate growth factor receptor (GFR) signaling. Mitogen-activated protein kinases (MAPK) transduce the signal to transcription factors, including the activator protein 1 (AP-1) transcription factor, leading to increased expression from a variety of genes containing the TPA DNA response element (TRE). This rapid DNA damage-independent response leads to a transient increase in c-Fos expression within 15 min after UV exposure. UV light also leads to DNA lesions that interfere with transcription and replication. These DNA lesions lead to the activation of PI3K family kinases such as ATR. ATR, and related kinases, can phosphorylate many RBP (6, 98), leading to changes in mRNA stability. Several AP-1 regulated transcripts, including c-Fos, can be post-transcriptionally stabilized, leading to a second sustained wave of gene expression that is delayed by several hours. ATR, ataxia-telangiectasia mutated and RAD3-related; PI3K, phosphatidylinositol 3-kinase.

transcription of the *RhoB* mRNA is dependent on CCAAT-binding factor and activating transcription factor 2 (47). The 3'UTR of this mRNA contains several AREs and other U-rich sequences, so the mRNA is short lived (161). However, the half life of this mRNA increases from 1 to 3 h after UV exposure (161). This change in mRNA stability is associated with specific binding of HuR to its 3'UTR coupled with nucleocytoplasmic shuttling of HuR, increasing mRNA stability and

directing the transcript for translation (161). Therefore, RhoB expression is post-transcriptionally regulated in response to UV light, independent of p53.

These examples of UV-induced mRNA stabilization are complicated, because there was a UV-induced transcriptional component to their overall response. UV-induced transcription and UV-induced changes in mRNA stability can be uncoupled using heterologous reporter systems with promoters that are not responsive to UV light (10, 52). Tetracycline-regulated promoters represent a powerful system to study mRNA decay (10, 52, 110, 111). Cloning the 3'UTRs from the granulocyte-macrophage colony-stimulating factor (GM-CSF) and the interleukin 8 (IL-8) mRNAs downstream of the β -globin open reading frame resulted in heterologous transcripts that were far less stable than the β -globin mRNA (10, 52). In this context, the stability of these inherently unstable mRNAs increased to a great extent in response to UV exposure, indicating that these 3'UTRs are subject to post-transcriptional regulation, independent of a UV-induced transcriptional response. Collectively, post-transcriptional regulation of gene expression can occur in the absence of a UV-induced transcriptional response, but changes in mRNA stability can also be coordinated with p53-, NF κ B-, AP-1-, and ATF2-dependent transcriptional responses to modulate expression in response to UV light, providing plasticity and versatility to UV DDRs.

In addition to the direct effects of DDR kinases on the activity and subcellular localization of transcription factors and RBPs, DDR can lead to changes in the transcription of genes encoding these classes of proteins. Therefore, transcriptional changes can give rise to secondary alterations in gene expression. For example, cold inducible RNA binding protein (CIRBP) is post-transcriptionally modified, and its expression can be increased in response to many cellular stresses, including UV light (15, 164). This protein can protect specific mRNAs from degradation (ATR and *CLOCK*, for example), shuttle them to the cytoplasm, and stimulate translation of the encoded proteins (116, 166). An oligonucleotide microarray strategy was used to monitor global changes in UV-induced mRNA expression in the presence and absence of small inhibitory RNAs directed against CIRBP (15). UV light led to increased expression of five transcripts in a CIRBP-dependent manner. The three largest responders encoded inflammatory cytokines (15). The induction of these cytokines did not depend on a direct interaction of CIRBP with the 3'UTRs of these mRNAs. Instead, NF κ B activity was reduced in the absence of CIRBP, so decreased cytokine expression resulted from CIRBP-dependent effects on NF κ B-dependent transcription (15). Taken together, UV-induced gene expression can be achieved directly and indirectly through a variety of mechanisms that include both transcriptional and post-transcriptional mechanisms of gene regulation.

UV Light Can Also Lead to Accelerated Decay of Specific Transcripts

As indicated earlier, many of the UV-induced transcripts were regulated at the level of mRNA stability (39). The same study reported that destabilization was four times more prevalent than stabilization after UV exposure with 133 transcripts destabilized in response to UV exposure (39). Accelerated mRNA decay after UV exposure can result from

increased expression of RBP and/or microRNAs (miRNAs) that direct mRNAs for deadenylation-dependent decay.

Several RBP are UV inducible, and some of these can destabilize specific mRNAs. For example, TTP is an ARE binding RBP that destabilizes ARE-containing transcripts and TTP is a direct target of p53 (62, 67). In this way, p53 activation in response to DNA damage can indirectly destabilize specific mRNAs. Similarly, the B-cell translocation gene 2 (BTG2) is positively regulated by p53 (134). BTG2 interacts with the CNOT7 and CNOT8 subunits of the CCR4-NOT deadenylase complex and facilitates deadenylation of mRNAs (32, 33, 99, 100, 163). As indicated earlier, the orthologous complex in yeast contributes to the synthesis and decay of mRNAs (113), so the BTG2-CCR4-NOT complex may similarly affect various

stages in mRNA synthesis and maturation as well (70, 81). It is likely that other UV-responsive RBPs have yet to be identified. Taken together, DNA damaging agents can destabilize mRNAs through the induction of RBPs.

MiRNAs are short (22 nucleotides) evolutionarily conserved noncoding RNAs that play a critical role in post-transcriptional gene regulation (3, 84, 137, 142, 162). These short RNAs are generated by sequential processing of primary RNA polymerase II-transcribed RNAs containing large imperfect hairpins (pri-miRNA) (Fig. 5). In the first processing step, the microprocessor complex, consisting of Drosha and DiGeorge syndrome critical region 8 (DGCR8) along with a variety of possible accessory proteins, cleaves the pri-miRNA to yield ~70 nucleotide hairpin, termed the pre-miRNA (78).

FIG. 5. Schematic representation of miRNA biogenesis. Genes encoding miRNAs may be intergenic (mono- or poly-cistronic), and most are transcribed by RNA polymerase II, giving rise to polyadenylated and capped pri-miRNA (*left side*). However, some miRNAs may also be present in introns of protein coding genes (*right side*). Intergenic pri-miRNAs are processed in the nucleus by the Drosha/DGCR8 complex to yield a pre-miRNA intermediate, an imperfect hairpin of ~70 nucleotides. Processing of mirtrons may circumvent the requirement for Drosha/DGCR8. The pre-miRNA is exported to the cytoplasm in an exportin 5-dependent manner, where Dicer (another RNase III enzyme) cleaves the pre-miRNA to yield miRNA/miRNA* duplex. The guide strand gets preferentially incorporated in the miRISC, leading to mRNA decay and/or translational repression of complementary targets. The passenger strand (miRNA*) is liberated and degraded. The p53 protein can stimulate transcription of specific pri-miRNA genes as well as the processing of a subset of pri-miRNAs, as indicated. These p53 regulated miRNAs inhibit the expression of many mRNAs and proteins (see text for details). DGCR8, DiGeorge syndrome critical region 8; miRISC, miRNA-induced silencing complex; pri-miRNA, primary microRNA.

Some miRNAs circumvent this step, because they are processed from introns: the so-called mirtrons (79) (Fig. 5). Regardless of the initial step, these pre-miRNAs are exported from the nucleus to the cytoplasm in an exportin 5-dependent manner, where they are further processed to the mature double-stranded miRNA by Dicer complex (79). The “guide” strand is preferentially incorporated into the miRNA-induced silencing complex (miRISC), while the complementary “passenger” strand (often denoted by an *) is less frequently incorporated and is, thus, more likely to be released and degraded (79). These miRNAs bind to 3'UTRs of target mRNAs through short complementary seed sequences minimally encompassing nucleotides 2–7 in the 5' end of the miRNA, but the precise length of complementary regions is variable (54, 80, 141) (Fig. 5). Sequence-specific binding of miRNAs to target mRNAs can direct the transcript for deadenylation-dependent decay and/or translational inhibition (5, 137).

Considerable effort has gone into the identification of p53-regulated miRNAs, and it has been reported that p53 can regulate the expression of specific miRNAs in two ways. First, p53 can transcriptionally regulate specific pri-miRNAs, such as pri-miR-34A, leading to increased miR-34A and miR-34A* expression (22, 26, 129, 148). In addition, p53 can directly bind the microprocessor complex to stimulate the post-transcriptional processing of another subset of pri-miRNAs exemplified by the bicistronic pri-miR-143/145 without affecting its transcription rate (11, 145). miR-34A, miR-143, and miR-145 regulate many target RNAs that likely contribute to p53-related phenotypes (22, 24, 26, 64, 68, 72, 73, 129, 167). Expression of physiologically relevant levels of miR-34A, miR-143, and miR-145 inhibits cell growth and increases apoptosis, consistent with a role for these miRNAs in the p53 DDR (22, 167). The full complement of targets of p53-regulated miRNAs has not been determined but together, p53 can presumably regulate the expression of thousands of transcripts and proteins through this mechanism (85). Confirming the identity of *bonfide* targets and deciphering their contribution to DDRs remains an imposing task.

The importance of miRNAs in the UV DDR was studied in the Hoeijmakers laboratory (122). Inhibition of miRNA processing using RNA interference led to increased sensitivity of cells to UV light, suggesting that miRNAs are critical to the UV response (122). Profiling experiments led to the identification of p53-dependent and p53-independent changes in miRNA expression. The authors found that miR-16 was among the rapid UV-responsive miRNAs and that it was able to target several transcripts which were important in regulating the G₁ to S phase transition: CDC25a, cyclin E, and cyclin D1 (122). Depletion of miR-16 led to the UV-induced accumulation of cells in S phase, consistent with loss of G₁ and/or S phase checkpoint function (122). Taken together, UV-induced expression of miRNAs can inhibit the expression of mRNAs and their encoded proteins, contributing to UV DDR.

Conclusion

DNA damage poses a challenge to the co-ordinated regulation of gene expression. Many DNA lesions such as those induced by UV light pose a block to RNA polymerase II. DDRs are important to maintain genomic stability, but these

transcription-blocking DNA lesions can prevent the efficient unfolding of transcription programs in a dose-dependent manner. The DDR has evolved a variety of ways to deal with these challenges at the transcriptional and post-transcriptional level. First, UV-induced genes tend to be compact to reduce the risk of sustaining DNA lesions. Second, DNA damage-induced transcripts may be post-transcriptionally regulated as a means of modulating gene expression under conditions of global inhibition of transcription. In turn, several distinct mechanisms contribute to DNA damage-dependent changes in post-transcriptional gene regulation (Fig. 6). RBP may be post-translationally regulated in response to DNA damage, altering their subcellular localization and/or affinity for specific transcripts. Alternatively, several miRNAs and RBPs are induced in response to DNA damage, so these may alter the expression of specific proteins in response to DNA damage. Collectively, transcriptional and

FIG. 6. Interdependence of mRNA and miRNA regulation in DDRs. DNA damage leads to post-translational modifications (PTM) of many proteins, including transcription factors (TF) and RBPs. Changes in the activity of TF (like p53) can positively or negatively regulate the expression of protein (*top*) or miRNA (*bottom*) encoding genes. Changes in the binding affinity or subcellular localization of RBP can positively or negatively affect the transcription, maturation, export, and translation of mRNAs (*top*) as well as the transcription and processing of miRNAs at various stages. The functional miRNAs may either decrease target mRNA levels or inhibit the translation of specific target mRNAs in response to DNA damage (curved lines connecting *top* and *bottom*). In addition, PTM of other classes of proteins can affect other processes directly (*top*). Some of the many levels of regulation can affect the expression or activity of TF, RBP, or other proteins that, in turn, impact subsequent rounds of mRNA and miRNA transcription and/or processing. Collectively, DDR can alter the activity, expression, and localization of many proteins, directly and indirectly.

post-transcriptional regulation of gene expression is emerging as important contributors to DDR, and their complex interactions are still under investigation.

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Address correspondence to:
 Dr. Bruce C. McKay
 Department of Biology
 Institute of Biochemistry
 Carleton University
 1125 Colonel By Drive
 Ottawa
 ON K1S 5B6
 Canada

E-mail: bruce_mckay@carleton.ca

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Abbreviations Used

3'UTR = 3' untranslated region
 ARE = adenylate uridylylate-rich element
 ATM = ataxia-telangiectasia mutated
 ATR = ataxia-telangiectasia mutated and RAD3-related
 BARD1 = BRCA1-associated RING domain protein
 BRCA1 = breast cancer type 1 susceptibility protein
 BTG2 = B-cell translocation gene 2
 CFI and CFII = cleavage factors I and II
 Chk1 and Chk2 = checkpoint kinases 1 and 2
 CIRBP = cold inducible RNA binding protein
 CPSF = cleavage and polyadenylation specificity factor
 CstF = cleavage stimulatory factor
 CTD = C-terminal domain
 DDB2 = damage-specific DNA binding protein 2
 DDR = DNA damage response
 DGCR8 = DiGeorge syndrome critical region 8
 DSE = downstream sequence element
 GM-CSF = granulocyte-macrophage colony-stimulating factor
 GRE = guanidylate-uridylylate-rich element
 IL-8 = interleukin 8
 miRISC = miRNA-induced silencing complex
 miRNA = microRNA
 mRNP = messenger ribonucleoprotein
 ORF = open reading frame
 PAP = poly(A) polymerase
 PARN = poly(A)-specific ribonuclease
 PAS = polyadenylation signal
 PI3K = phosphatidylinositol 3-kinase
 pri-miRNA = primary microRNA
 RhoB = Ras homolog gene family member B
 TTP = tristetraprolin
 UV = ultraviolet
 UVC = short wavelength UV