Review

DNA damage: RNA-binding proteins protect from near and far

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Recent work, including large-scale genetic and molecular analyses, identified RNA-binding proteins (RBPs) as major players in the prevention of genome instability. These studies show that RBPs prevent harmful RNA/DNA hybrids and are involved in the DNA damage response (DDR), from DNA repair to cell survival decisions. Indeed, specific RBPs allow the selective regulation of DDR genes at multiple post-transcriptional levels (from pre-mRNA splicing/polyadenylation to mRNA stability/translation) and are directly involved in DNA repair. These multiple activities are mediated by RBP binding to mRNAs, nascent transcripts, noncoding RNAs, and damaged DNA. Finally, because DNA damage modifies RBP localization and binding to different RNA/DNA molecules, we propose that upon DNA damage, RBPs coordinately regulate various aspects of both RNA and DNA metabolism.

The rise of RNA-binding proteins in the DNA damage response

DNA lesions are continuously generated in living cells as a result of replication errors and oxidative metabolism [1]. They also arise as a consequence of exposure to environmental agents (e.g., ultraviolet, ionizing radiation), radiation therapy, and chemotherapeutic drugs. Accumulation of DNA insults is associated with multiple diseases from neurodegenerative disorders to cancers, immune deficiencies, and infertility. It is therefore crucial for the cell to detect DNA damage, signal its presence, and effect DNA repair, cell cycle arrest, and ultimately cell fate decisions, which are together called the DNA damage response (DDR; Box 1). For simplicity, we will use the term 'DNA damage' to refer to the action of different DNA-damaging agents (Box 2).

In addition to the rapid DNA damage-dependent post-translational regulation of the activity of DDR proteins, the expression of DDR genes must be precisely regulated. This regulation involves a transcriptional program orchestrated in part by the p53 transcription factor. Abundant literature also documents that DNA damage affects post-transcriptional gene expression, including the processing of the primary transcript in the nucleus (pre-mRNA splicing and 3′-end processing also called cleavage/polyadenylation) and the control of mRNA stability, and translation in the cytoplasm. Post-transcriptional gene expression is regulated, in large, by RNA-binding proteins (RBPs), which directly bind specific RNA sequences and secondary structures in pre-mRNAs, mRNAs, or regulatory noncoding RNAs (ncRNAs; Box 3) [2,3]. Strikingly, various unbiased proteomic approaches and functional screens have identified RNA processing and/or translation factors, including RBPs, as major functional categories of gene products that are post-translationally modified by DNA damage-signaling proteins [4,5] and are required for the DDR [6,7]. In parallel with these global approaches, studies focusing on individual RBPs have begun to reveal that RBPs protect cells from DNA damage by acting from near (i.e., at the site of DNA damage) and far [i.e., bound to (pre-)mRNAs encoding DDR proteins].

RBPs allow the selective expression of DDR genes upon DNA damage

Repression of gene expression in response to DNA damage

DNA damage tends to globally repress gene expression. This is mainly achieved through a decrease in the levels of mRNAs, which occurs through several mechanisms. DNA damage leads to inhibition of transcription and also triggers a repression of pre-mRNA 3′-end processing [8,9]. The latter effect is mediated by the direct inhibitory interaction between a basic component of the 3′-end processing machinery (cleavage stimulatory factor CSTF1) and phosphorylated BARD1 (BRCA1-associated RING domain 1) within complexes that also contain the BRCA1 (breast cancer 1) DNA repair protein and the p53 tumor protein [10]. Whereas pre-mRNA splicing has not been reported to be globally inhibited by DNA damage, alternative splicing of specific pre-mRNAs is altered (discussed later). In particular, for many genes, DNA damage results in a decrease in the expression of functional gene products by switching alternative splicing towards variants harboring premature stop codons, which are subject to nonsense-mediated mRNA decay (NMD) [11,12]. Beyond inhibitory actions at the pre-mRNA level, DNA damage leads to a decrease in the stability of many

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Box 1. The DNA damage response (DDR)

The DDR relies on a highly coordinated network of factors that detect and signal the presence of different types of DNA lesions to promote their repair or tolerance, control chromatin structure, and regulate cell cycle progression, gene expression, and cell fate. Within minutes after DNA damage, a cascade of protein phosphorylation and other post-translational modifications (e.g., parylation, acetylation, ubiquitylation, sumoylation) occur to recruit and precisely regulate the activity of DDR factors in a given chromatin context. In the longer term, global gene expression is regulated to sustain the DDR and control cell fate.

DNA lesions affect either one or two DNA strands, which are repaired by different mechanisms (Figure I). Single-strand DNA damage is repaired by excision of either the base (base excision repair, BER) or the nucleotide (nucleotide excision repair, NER, and mismatch repair, MMR). During transcription, DNA lesions located on a transcribed strand are repaired faster than lesions located on the nontranscribed strand owing to transcription-coupled repair (TCR). TCR involves some components of the NER machinery and TCR factors such as CSA and CSB (Cockayne syndrome). The repair of damage affecting both DNA strands, such as double-strand DNA breaks, is supported by homologous recombination (HR) and by non-homologous end joining (NHEJ). Inter-strand crosslinks (ICLs) are repaired by the concomitant action of HR and the Fanconi anemia (FA) pathway.

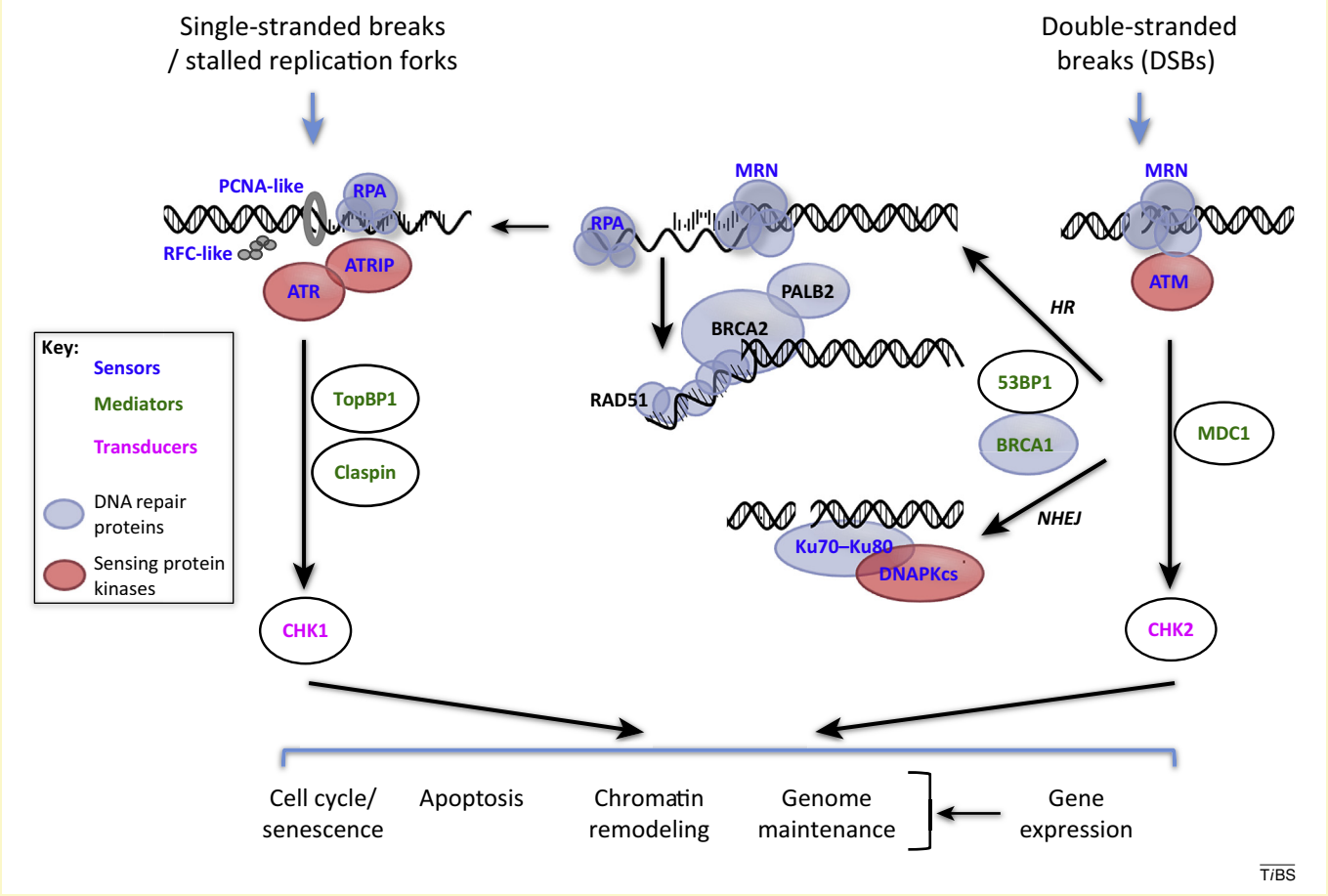

Figure I. Scheme of the DNA damage response (DDR) to double-strand DNA breaks, single-strand DNA breaks, and stalled replication forks. DNA damage is sensed and signaled by sensors (blue text), mediators (green text), and transducers (purple text). Sensors recognize the DNA damage and are thought to detect either double-strand break or single-stranded break DNA exposed during the repair of DNA damage. Sensors include the MRN (MRE11/RAD50/NBS1) complex, the Ku70–Ku80 heterodimer, the RFC-like (replication factor C) complex, and the PCNA-like (proliferating cell nuclear antigen) complex. These contribute to the activation of three main sensing protein kinases (red icon): ATM (ataxia telangiectasia mutated), ATR (ATM and Rad3 related), and DNAPKcs (DNA-dependent protein kinase catalytic subunit). Sensor kinases locally phosphorylate several targets to amplify the signal and together with mediators {such as TopBP1 [topoisomerase (DNA) II binding protein 1], MDC1 (mediator of DNA-damage checkpoint 1), Claspin, 53BP1 (tumor protein p53 binding protein 1), and BRCA1 (breast cancer 1)} activate transducers, including notably the checkpoint kinases CHK1 and CHK2. This DDR protein kinase cascade regulates the activity of a plethora of effectors involved in cell cycle arrest, DNA repair, chromatin remodeling, gene expression, and cell death. Blue icons represent proteins with DNA repair function: MRN complex and RPA (replication protein A) have an early function in signaling DNA damage and repair; RAD51, BRCA2 (breast cancer 2), and PALB2 (partner and localize of BRCA2) are involved in HR (homologous recombination); Ku70–Ku80 is involved in NHEJ (non-homologous end joining); and BRCA1 is involved in both repair pathways.

mRNAs [13] and to an inhibition of the activity of general translation factors involved in initiation [14] and elongation [15]. The DNA damage-induced decrease in mRNA stability and translation is more widespread than transcriptional repression [13,16] and can be strengthened by RBPs in a gene selective manner through two mechanisms. First, human antigen R (HuR), an RBP that promotes mRNA stability and translation, is dissociated from many mRNAs in response to DNA damage (see Table S1 in the supplementary material online) [17]. Second, RBPs such as the KH-type splicing regulatory protein (KSRP) enhance the maturation of a large subset of miRNAs that would in turn inhibit the stability and/or translation of their target mRNAs in response to DNA damage [18].