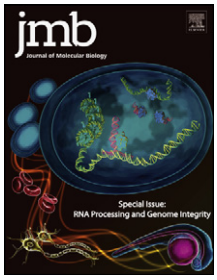

DNA-Damage Response RNA-Binding Proteins (DDRBPs): Perspectives from a New Class of Proteins and Their RNA Targets

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Abstract

Upon DNA damage, cells trigger an early DNA-damage response (DDR) involving DNA repair and cell cycle checkpoints, and late responses involving gene expression regulation that determine cell fate. Screens for genes involved in the DDR have found many RNA-binding proteins (RBPs), while screens for novel RBPs have identified DDR proteins. An increasing number of RBPs are involved in early and/or late DDR. We propose to call this new class of actors of the DDR, which contain an RNA-binding activity, DNA-damage response RNA-binding proteins (DDRBPs). We then discuss how DDRBPs contribute not only to gene expression regulation in the late DDR but also to early DDR signaling, DNA repair, and chromatin modifications at DNA-damage sites through interactions with both long and short noncoding RNAs.
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A wide variety of both extrinsic (e.g., radiations, chemicals, and chemotherapeutic drugs) and intrinsic factors (e.g., replication errors and reactive oxidative species) frequently induce DNA lesions, including modified bases, mismatches, adducts, intra- and inter-strand crosslinks, and single- and double-strand breaks (DSBs). Depending on the type of DNA damage and the phase of the cell cycle, cells trigger a DNA-damage response (DDR) that involves various pathways of DNA repair and cell cycle checkpoints activation. The "core" or early DDR (within minutes after damage) relies on the interaction of damaged DNA with sensor proteins (e.g., the Ku70/Ku80 heterodimer) and the activation of sensor protein kinases [e.g., DNA-dependent protein kinase (DNA-PK), ataxia telangiectasia mutated (ATM), and ATM and Rad3 related (ATR)], which, together with mediators [e.g., tumor protein p53 binding protein 1 (53BP1) and breast cancer 1 (BRCA1)], lead to the activation of transducer protein kinases (e.g., checkpoint kinases CHK1 and CHK2). In addition to protein phosphorylation, these early events include other post-translational modifications (e.g., poly-ADP-ribosylation). In turn, transducers activate or inhibit various effectors involved in cell cycle, apoptosis, genome maintenance, chromatin remodeling, and gene expression (for review, see Refs. [1,2]). In particular, specific transcription programs orchestrated by effector transcription factors (e.g., tumor protein p53) mediate late DDR responses that determine cell fate, such as cell death, definitive cell cycle arrest (senescence) or adapted growth (resistance).

Canonical RBPs involved in the DDR constitute DDRBPs

Several proteomics and functional genomics screens for gene products that are post-translationally modified by DNA-damage-signaling proteins or are required for the DDR have been conducted. One of the most prominent, functional gene categories enriched in these screens is "RNA-processing and translation" and includes many RNA-binding proteins (RBPs) [3–5]. A growing number of RBPs, through their ability to bind *cis*-acting elements in RNAs, are described as post-transcriptional regulators of gene expression

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(from pre-mRNA processing—splicing and polyadenylation—in the nucleus to mRNA export, stability, and translation in the cytoplasm). RBPs can also contribute to transcriptional regulation, owing to their interactions with noncoding RNAs (ncRNAs; see below). The enrichment of RBPs among proteins involved in the DDR may therefore reflect their now well-established role in the specific regulation of expression of genes involved in the DDR (reviewed in Refs. [1,6,7]).

In addition, many RBPs have a more direct role in genome stability and DDR signaling. First, some RBPs have been reported to control the formation of R loops (RNA:DNA hybrids), which can induce DNA damage upon collision with replication forks [8]. In post-mitotic cells, R loops can also mediate ATM activation by transcription-blocking lesions, due to chromatin displacement of the splicing machinery [9]. Second, an increasing number of well-known RBPs are found at sites of DNA damage, interact with DNA-damage sensors, mediators, and DNA repair proteins, and control their activity [5,10–21] (reviewed in Ref. [1]).

Altogether, an increasing number of RBPs are involved in the DDR, and these proteins therefore constitute a new class of actors of the DDR that contain an RNA-binding activity and that we propose to call DNA-damage response RNA-binding proteins (DDRBPs). It should be noted that unlike their functions in gene expression regulation, it is not always clear whether RBP functions at DNA-damage sites depend on interactions with RNA since some RNA-binding domains can also bind single- or double-stranded DNA, proteins or poly(ADP-ribose). However, as we discuss below, there is increasing evidence that RNA is involved at sites of DNA damage, and RNA-binding activities have also been found among canonical DDR proteins, thus increasing this new class of DDRBPs.

More DDRBPs: canonical DDR proteins interacting with RNA

It has been a long-standing observation that the Ku70–Ku80 heterodimer, a key sensor of DSBs and a regulatory subunit of DNA-PK, directly interacts with RNAs in both yeast and human [22–28]. Recently, the catalytic subunit of DNA-PK (DNA-PKcs; also called PRKDC or XRCC7) has also been found to interact with RNA [27]. BRCA1 and 53BP1, two DDR mediators involved in DSB repair, have been reported to associate with RNA [29,30], although direct RNA binding has yet to be formally confirmed.

In recent years, large-scale screens for RBPs have extended the list of core DDR proteins that interact with RNA. Specifically, so-called RNA interactome capture experiments allow the determining of the repertoire of proteins that directly bind to mRNAs. UV crosslink of living cells induces the covalent binding of RBPs to RNAs. Polyadenylated mRNAs are purified and bound proteins are identified by mass spectrometry. Initial screens identified several core DDR proteins, including BRCA1, Ku70, and Ku80 [31–33]. More recently, a refined screen focusing on nuclear RBPs identified 22 proteins with Gene Onotology annotation related to the DDR, which, together with their interacting proteins, form a network that is highly enriched in DSB components, DDR signaling, and p53 interactors [34]. Key DDR proteins identified in this screen include mediator of DNA-damage checkpoint 1 (MDC1) and replication timing regulatory factor 1, the main effector of 53BP1-mediated DSB repair pathway choice. In the future, the list of DDR proteins that can bind RNA directly is likely to expand, for example, through the application of RBP identification screens to cells exposed to DNA-damaging agents [35]. It will also be important to refine this list through validation assays, using techniques that allow the showing of direct protein binding to endogenous RNA, such as CLIP (UV crosslinking and immunoprecipitation).

In conclusion, a growing number of core DDR proteins, including sensors of DNA damage, have been found to bind RNA, thus adding to the list of DDRBPs. This finding brings about the question of what endogenous RNAs may be bound by these DDRBP proteins and of whether RNA binding plays a role in the core DDR.

(Pre-)mRNA targets and activities of DDRBPs

Many DDRBPs bind to (pre-)mRNAs to directly regulate the expression of specific DDR genes (or isoforms) at (post-)transcriptional levels in response to DNA damage (reviewed in Refs. [1,6,7]). In this context, it is worth to highlight that this paradigm not only applies to DDRBPs that were historically considered as canonical RBPs but also to canonical DDR proteins. For example, BRCA1 has been found in complexes containing RNA processing factors to promote splicing/stability of transcripts encoding DDR proteins in response to DNA damage [36]. In addition, the Ku70–Ku80 heterodimer has been recently shown to repress p53 mRNA translation through its direct binding to the p53 5′-untranslated region [28]. In response to DNA damage, this interaction is inhibited, thereby favoring p53 protein synthesis. The data suggest a model, where Ku acetylation, in response to DNA damage, induces a binding switch of its dual RNA/DNA-binding domain from p53 mRNA to damaged DNA [28]. Conversely, in response to DNA damage, phosphorylation of the human homolog of murine double minute-2 protein (MDM2, a key regulator of p53) by the sensor protein kinase ATM inhibits its binding to p53 protein (to

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