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Mini Review

Structure and functions of cellular redox sensor HSCARG/NMRAL1, a linkage among redox status, innate immunity, DNA damage response, and cancer

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ABSTRACT

NmrA-like proteins are NAD(P) (H) interacting molecules whose structures are similar to that of short-chain dehydrogenases. In this review, we focus on an NADP(H) sensor, HSCARG (also named NMRAL1), which is a NmrA-like protein that is widely present in mammals, and provide a comprehensive overview of the current knowledge of its structure and physiological functions. HSCARG selectively binds to the reduced form of type II coenzyme NADPH via its Rossmann fold domain. In response to reduction of intracellular NADPH concentration, HSCARG transforms from homodimer to monomer and exhibits enhanced interactions with its binding partners. In the cytoplasm, HSCARG negatively regulates innate immunity through impairing the activities of NF-κB and RLR pathways. Besides, HSCARG regulates redox homeostasis via suppression of ROS and NO generation. Intensive and persistent oxidative stress leads to translocation of HSCARG from the cytoplasm to the nucleus, where it regulates the DNA damage response. Taken together, HSCARG functions as a linkage between cellular redox status and other signaling pathways and fine-tunes cellular response to redox changes.

1. Introduction

Nitrogen metabolite repressor (NmrA) is a transcription repressor which is involved in regulation of nitrogen metabolism in *Aspergillus nidulans*. *A. nidulans* uses a wide array of small-molecule compounds as its source of nitrogen, including ammonium, nitrate, glutamate, and arginine. When *A. nidulans* cells are able to simultaneously intake sufficient amount of these compounds from environment, ammonium and glutamate are preferentially utilized. During the above phenomenon known as nitrogen metabolite repression, NmrA is highly expressed to inhibit the transcription of enzymes participating in nitrate or arginine catabolism [1,2]. The structure of NmrA, resembling that of the short-chain dehydrogenase/reductase (SDR) superfamily, consists of an N-terminal Rossmann fold and a C-terminal domain [3]. Proteins comprising Rossmann fold are able to bind intracellular coenzymes NAD(H) and NADP(H). However, NmrA is incapable of catalyzing dehydrogenation reactions because the crucial tyrosine enzymatic site within the Rossmann fold is mutated to methionine. Interestingly, NmrA binds to NAD^+ and $NADP^+$ with much higher affinities in comparison with their reduced form, suggesting a potential role of NmrA in redox sensing. Specifically, in the complex of NmrA with coenzymes, residue Tyr-276 is very close to the nicotinamide in space. Therefore, an additional hydrogen atom present at the C4-position in the reduced nicotinamide leads to steric clashes with the hydroxyl group on the side chain of Tyr-276 [4]. So far, the regulatory effects of NAD^+ and $NADP^+$ on NmrA in nitrogen metabolite repression have remained incompletely elucidated.

Since the structure of NmrA was resolved, researchers have discovered several NmrA-like proteins which are able to bind coenzymes NAD(H) or NADP(H) but lack the function of dehydrogenation, including PadA from *Dictyostelium discoideum*, QOR2 from *Escherichia coli*, PcNMRAL1 from *Phytophthora capsica* [5–7]. While NmrA and the majority of NmrA-like proteins are identified in bacteria or fungi, HSCARG, which is also known as NMRAL1, is widely present in higher animals.

2. Structural features of HSCARG

The *HSCARG* gene is located in chromosome 16 and consists of 5 exons in both *Homo sapiens* and *Mus musculus*. The crystal structure of human HSCARG protein was revealed via X-ray diffraction in 2007 [8,9], after which the interaction proteins of HSCARG and its regulatory

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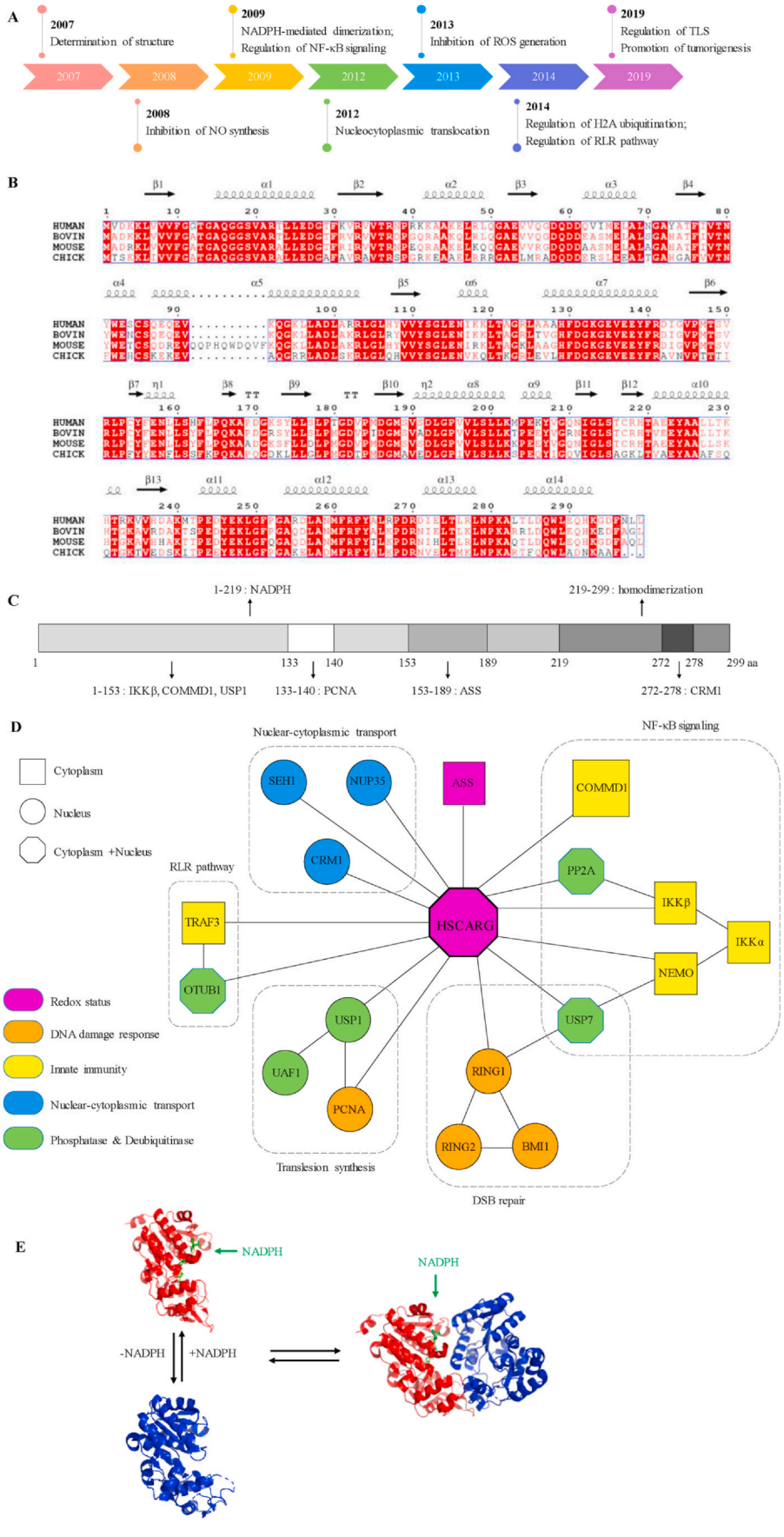

Fig. 1. HSCARG structural features. (A) timeline of HSCARG studies; (B) amino acid sequence alignment of HSCARG among mammals. Identical and similar sequences are shown in red background and blue box, respectively. Arrows and helices indicate the secondary structures of HSCARG; (C) a schematic diagram of HSCARG protein showing the domains and sequence motifs that contribute to its interactions with intracellular binding partners; (D) Interaction network of all identified protein–protein interactions between HSCARG and its binding partners. The shape of node indicates the subcellular localization of the factor. The color of node indicates the function of the factor or the signaling pathway the factor participates in. (E) NADPH-mediated regulation of HSCARG dimerization. Upon binding to NADPH, HSCARG undergoes conformational alterations that further promotes its homodimerization. Within the HSCARG dimer, one subunit (red molecule) is associated with NADPH while another (blue molecule) is free of coenzyme. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

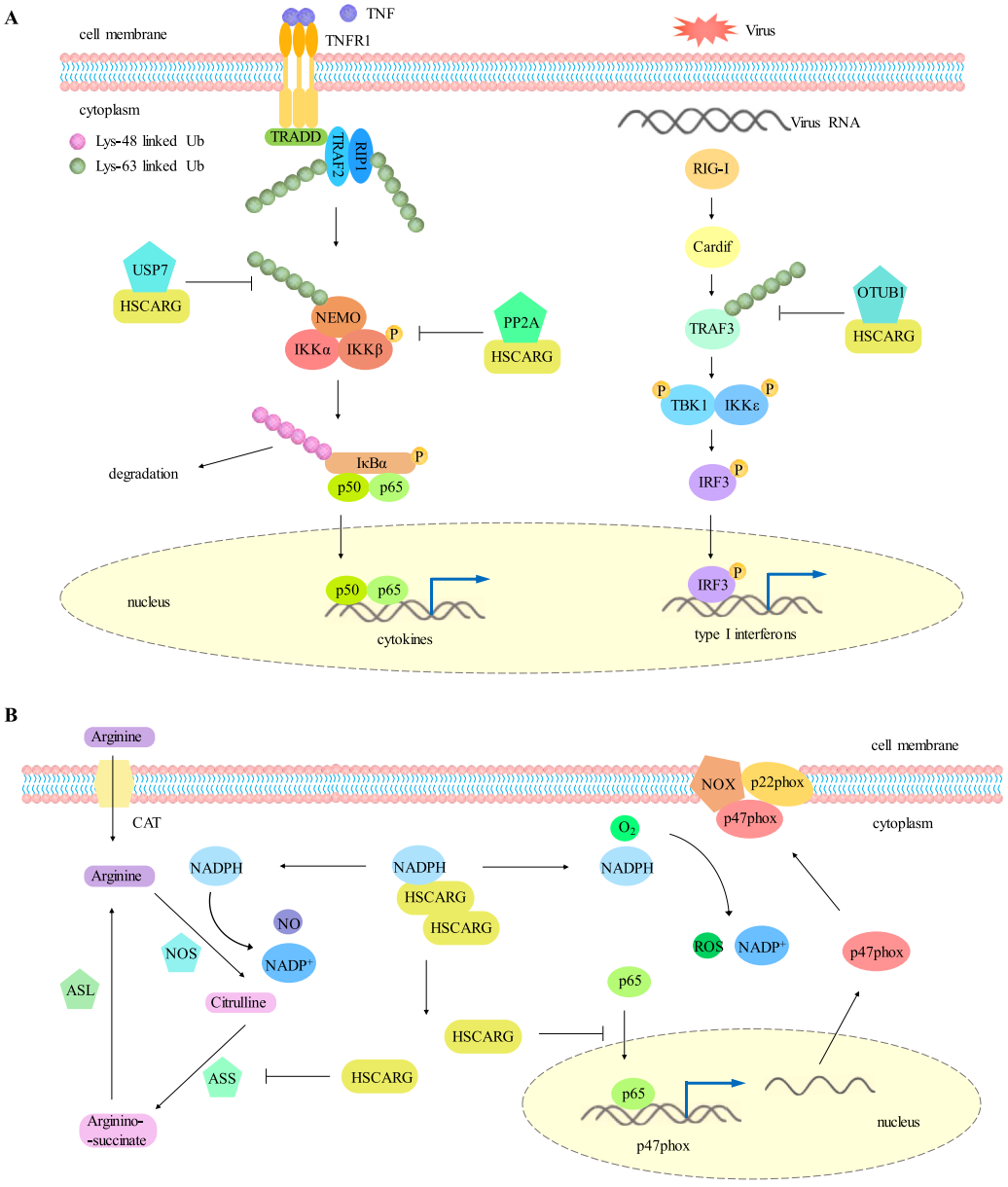

Fig. 2. Functions of HSCARG in the cytoplasm. (A) HSCARG blocks signal transduction in innate immunity. In canonical NF-κB signaling, HSCARG cooperates with USP7 and PP2A to inhibit the K63-polyubiquitination of NEMO and phosphorylation of IKKβ, thereby decreasing the activity of IKK complex, repressing the degradation of IκBα, and restraining NF-κB in the cytoplasm. In RLR pathway, HSCARG stimulates the deubiquitination of TRAF3 by OTUB1, which further attenuates the phosphorylation of IKKε and IRF3, and finally decreases the production of type I interferons; (B) HSCARG is involved in intracellular NADPH homeostasis. Decrease in NADPH concentration leads to disaggregation of HSCARG dimer into monomers, and thus activates its functions. HSCARG reduces overproduction of NO and ROS via suppressing the activity of ASS and blocking the transcription of p47phox, respectively.

functions and mechanisms were clarified (Fig. 1A, C, D). The amino acid sequence of HSCARG protein has a high similarity among species (Fig. 1B). Human HSCARG can be essentially divided into an N-terminal Rossmann fold consisting of residues 1–219 and a C-terminal domain consisting of residues 220–299 (Fig. 1C). The central parallel β-sheet of the Rossmann fold domain is composed of β-strands 1–6 interconnected by α-helixes 1–7 (Fig. 1B).

Although the overall topology of HSCARG is nearly identical to that of NmrA, HSCARG binds to the reduced form of NADPH (but not NADH) with a much higher affinity. Correspondingly, there is no residue similar to NmrA Thr-276 in the C-terminal region of HSCARG. A total of 20 hydrogen bonds are formed between NADPH and the Rossmann fold of HSCARG, making the association extremely tight *in vitro*. 6 of the 20 hydrogen bonds are formed between residues Thr-13, Arg-37, and Lys-41 and the extra 2′-phosphate on the AMP moiety, which accounts for selective binding of HSCARG to the type II coenzyme NADPH [9]. Indeed, there is normally high selectivity for one type of coenzyme in the case of SDRs, and NADP-specific SDRs commonly contain a pair of conserved basic residues, which are similar to Arg-37 and Lys-41 in HSCARG, that provide the discrimination by interacting with the 2′-phosphate [10].

3. Dimerization of HSCARG

HSCARG exists in three different forms *in vivo*: (i) NADPH-bound monomers; (ii) NADPH-unbound monomers; (iii) asymmetrical dimers with one subunit binding to NADPH (molecule I) and the other unoccupied (molecule II). Redox status fine-tuned concentration of NADPH regulates the equilibrium among these three forms (Fig. 1E). The major conformational alterations of HSCARG upon NADPH binding

are reorientation of residue Tyr-81 to form hydrogen bonds with the NMP moiety and rotation of residue Gly-123, which changes the secondary structure of residues 127–143 to a complete α-helix [9]. As SDR family proteins commonly undergo oligomerization, the NADPH-bound HSCARG can associate with a second molecule of HSCARG which is free of coenzyme [11]. The formation of asymmetrical HSCARG dimer which exhibits unique surface characteristics further stabilizes the interaction between molecule I and NADPH and prevents binding of molecule II to coenzyme. Mutation of either residue R37 or Y81A to alanine abrogates the binding of HSCARG to NADPH. As a result, mutants R37A and Y81A only exist as monomers *in vivo*, while their overall structures are similar to the NADPH-bound molecule I of the wild-type HSCARG dimer. In contrast, mutant K41S retains the capability of homodimerization because serine, unlike alanine, is able to form similar hydrogen bond with NADPH as lysine [12]. In comparison to the wild-type protein, mutants R37A and Y81A, but not mutant K41S, exhibit enhanced interactions with their binding partners, indicating that formation of asymmetrical dimers inactivates the regulatory functions of HSCARG [13,14].

4. Subcellular localization of HSCARG

Under normal redox status, HSCARG is predominantly located in the cytoplasm surrounding the nucleus and associates with intermediate filaments [9]. Enrichment of HSCARG in the cytoplasm is mediated by a leucine-rich nuclear export signal (NES) at residues 272–278 that induces nuclear export of HSCARG in a CRM1-dependent manner. Loss of C-terminal residues 272–299 or point mutations within NES sequester HSCARG to the nucleus [15]. Besides, redistribution of HSCARG is observed in response to decreased intracellular ratio of NADPH/$NADP^+$, which could be realized by targeting NADPH-producing enzymes. Three categories of enzymes are able to reduce NADPH from its oxidized form, which are glucose-6-phosphate dehydrogenase (G6PD) in the pentose phosphate pathway, isocitrate dehydrogenase (IDH) in the tricarboxylic acid cycle, and malic enzyme in the pyruvate cycling pathway [16]. Activities of G6PD and IDH are inhibited by endogenous steroid dehydroepiandrosterone (DHEA) and signaling molecule nitric oxide (NO), respectively [17,18]. Therefore, treatment with DHEA or SNAP, a commonly used NO donor, and overexpression of argininosuccinate synthetase (ASS), a rate-limiting enzyme in NO regeneration, lead to dissociation of HSCARG from intermediate filaments and translocation of HSCARG from the cytoplasm to the nucleus [14,19].

5. Functions of HSCARG in innate immunity

HSCARG is a negative regulator of innate immunity. In response to infection with RNA viruses, RIG-I-like receptors recognize cytosolic viral RNA and trigger type I interferon production through a Cardif-TRAF3-TBK1/IKKε-IRF3 axis [20,21]. K63-polyubiquitination of TRAF3 stimulates the above signal transduction process by enhancing the interaction between TRAF3 and IKKε, while HSCARG cooperates with deubiquitinase OTUB1 to remove the ubiquitin chain from TRAF3 (Fig. 2A). Accordingly, overexpression of HSCARG impairs the recruitment of IKKε, decreases the phosphorylation and nuclear translocation of IRF3, and thereby downregulates the level of IFN-β after viral infection [22].

Besides the RLR pathway, HSCARG suppresses cytokine-induced nuclear factor-κB (NF-κB) activation. NF-κB is a heterodimer composed of subunits p50 and p65 [23]. In resting cells, interaction between NF-κB and IκB proteins sequesters p65 and p50 in the cytoplasm, thereby inhibiting the transcription activity of both factors. In the canonical NF-κB signaling pathway, receptors on the cell membrane recognize cytokines such as tumor necrosis factors (TNF) or interleukin 1 (IL-1) and transduce signals to the IκB kinase (IKK) complex through ubiquitination reaction cascade. Activated IKK complex then phosphorylates IκB, which subsequently leads to ubiquitination and proteasome-mediated degradation of IκB, and thus permits nuclear translocation of p50 and p65 to execute their transcription regulatory functions [24,25]. While mounting reports have confirmed the suppressive effects of HSCARG on TNF and IL-1-induced NF-κB activation, different underlying mechanisms were proposed. On the one hand, HSCARG impairs the activity of the IKK complex. The IKK complex consists of three subunits, namely IKKα, IKKβ and NEMO (IKKγ). HSCARG interacts with both IKKβ and NEMO, but not IKKα. Post-translational modifications of IKK subunits, including phosphorylation of IKKβ and K63-polyubiquitination of NEMO, have been reported to enhance the activity of IKK complex. HSCARG stimulates the formation of IKKβ-PP2A and NEMO-USP7 complexes, and thereby facilitates the dephosphorylation of IKKβ by PP2A and deubiquitination of NEMO by USP7 [26–28] (Fig. 2A). On the other hand, HSCARG interacts with COMMD1, a copper metabolism regulator which is also involved in negative regulation of NF-κB pathway through stabilizing IκBα and promoting degradation of p65 [29,30]. Specifically, under normal physiological conditions, cytosolically located HSCARG accelerates the K48-polyubiquitination and subsequent degradation of COMMD1. In response to redox changes resulted from DHEA or SNAP treatment, nuclear translocation of HSCARG relieves its inhibitory effect on COMMD1 [31]. Experiments with the same reporting system showed that repression of HSCARG on the transcription activity of NF-κB was significantly attenuated in IKKβ knockdown cells, but not in COMMD1-depleted cells, indicating that HSCARG primarily functions through the former mechanism. HSCARG binds to both IKK subunits and COMMD1 via residues 1–153, which constitutes the central core of the Rossmann fold. Notwithstanding, HSCARG truncation 154–299 is still able to suppress NF-κB activation, although with decreased efficiency in comparison to the full-length protein [27,31]. This suggests that the C-terminal domain of HSCARG is involved in modulation of NF-κB activation via an alternative mechanism which is independent of the IKK complex or COMMD1.

Knockdown of G6PD enhances the susceptibility of human lung carcinoma cells to coronavirus infection through a HSCARG-mediated mechanism. It was observed that in G6PD-depleted A549 cells, transcription of NF-κB downstream antiviral genes, including TNF-α and MX1, is impaired upon infection with HCoV-229E, which consequently promotes viral replication. The effect could be rescued through knockdown of HSCARG [32]. It is worth mentioning that deficiencies in G6PD lead to decreased intracellular ratio of NADPH/$NADP^+$ and depolymerization of inactive HSCARG dimer into monomers. Therefore, the foregoing observation is a vivid example how redox changes active the function of HSCARG in NF-κB regulation.

6. Functions of HSCARG in redox homeostasis

As a consequence of inhibition of NF-κB activation, HSCARG impairs the recruitment of p65 to the promotor of p47phox and reduces the transcription of p47phox, a subunit of NADPH oxidase. NADPH oxidase catalyzes the transfer of electron from NADPH to oxygen, which generates $NADP^+$ and reactive oxygen species (ROS) [33]. Moderate concentration of ROS is essential for microbial killing, while excessive production of intracellular ROS through NADPH oxidase leads to overconsumption of NADPH and accumulation of oxidative damages. Upregulation of HSCARG decreases the endogenous protein level of p47phox, downregulates the catalytic activity of NADPH oxidase, and thus prevents overproduction of ROS [34] (Fig. 2B).

Another important molecule that influences cellular redox status is NO. Production of NO in the cytoplasm is catalyzed by nitric oxide synthase (NOS) at the consumption of arginine and NADPH. Arginine is the sole precursor of NO in cells; hence synthesis of NO is rate-limited by availability of arginine. Besides being transported from extracellular fluid, intracellular arginine can be recycled from citrulline, the co-product of NOS, through successive actions of argininosuccinate synthetase and argininosuccinate lyase [19]. As shown in Fig. 1C and Fig. 2B, HSCARG interacts directly with ASS via residues 153–189 and

attenuates the activity of ASS and production of NO [14].

As mentioned above, in response to decreased NADPH, disaggregation of HSCARG dimer into monomers activates its regulatory functions. Accordingly, enhancement of interaction between HSCARG and ASS was observed in DHEA-treated cells, proving that the ability of HSCARG to impair arginine recycling and NO synthesis is activated after dissociation with NADPH [14]. The conclusion was reinforced by the fact that HSCARG NADPH-unbound mutants R37A and Y81A, which exists only as monomer, exhibit increased interaction with ASS and more efficient inhibitory effects on p47phox protein level in comparison to the wild-type protein [12,13]. Considering both NADPH oxidase-catalyzed ROS production and NOS-catalyzed NO production are couple with oxidation of NADPH into $NADP^+$, one can speculate that HSCARG might regulate NADPH homeostasis via feedback inhibition of NADPH-consuming pathways and promote cell resistance against oxidative stress. Further studies are necessary to clarify the real functional effects of HSCARG on intracellular NADPH level.

7. Functions of HSCARG in DNA damage response

In the nucleus, HSCARG retains its interaction with deubiquitinase USP7. HSCARG cooperates with and depends on USP7 to inhibit the ubiquitination of core components of polycomb repressive complex 1 (PRC1). PRC1 is an E3 ligase complex that catalyzes mono-ubiquitination of histone H2A at Lys-119, while the self-ubiquitination of PRC1 is crucial for its catalytic activity [35,36]. Ubiquitination of H2A plays a vital role in the DNA damage response to double-strand break (DSB) through providing docking sites for DSB downstream repair proteins such as RAP80 and 53BP1 [37]. In response to ionizing radiation (IR), HSCARG suppresses PRC1-mediated H2A ubiquitination in a USP7-dependent manner (Fig. 3). Deletion of HSCARG increases the persistence of H2A ubiquitination in IR-treated cells, which further leads to retention of RAP80 at DNA lesion sites [38].

HSCARG also regulates the translesion synthesis (TLS) pathway that targets ultraviolet (UV) radiation-induced lesions during DNA replication. UV radiation leads to autocleavage and subsequent degradation of USP1, and thereby abolishes the deubiquitination effects of USP1 on its substrate PCNA [39]. Mono-ubiquitination of PCNA at Lys-164 then recruits polymerase eta (POLH) to bypass the UV-damaged sites [40]. HSCARG directly interacts with PCNA via its PCNA-interacting protein (PIP)-box at residues 133–140, which is highly conserved among species (Fig. 1B, C). Moreover, HSCARG stimulates the deubiquitination of PCNA by enhancing the interaction between USP1 and PCNA (Fig. 3). Overexpression of HSCARG partly rescues UV-induced decrease of chromatin-associated USP1 level. As a result, upregulation of HSCARG or nuclear enrichment of HSCARG caused by high dosage of SNAP treatment block the accumulation of POLH at replication stalling sites in response to UV radiation, which leads to collapse of replication forks and generation of DSBs [13].

8. HSCARG and cancer

The role of HSCARG in NF-κB signaling, ROS generation and DNA damage response implies its biological relevance to cancer. On the one hand, overproduction of ROS contributes to genomic instability via introduction of oxidative DNA damages and constitutive activation of NF-κB promotes cell proliferation while prevents apoptosis [41,42]. Therefore, the inhibitory effects of HSCARG on ROS and NF-κB in the cytoplasm ought to suppress cancer development. On the other hand, enrichment of HSCARG in the nucleus leads to deficiencies in TLS and DSB repair, which elevates genome mutation rate. Thus it can be seen that subcellular localization of HSCARG counterbalances its oncogenic and tumor suppressive functions. Indeed, bioinformatics analysis reveals that HSCARG is highly expressed in various types of cancer. Consistently, deletion of HSCARG in female polyomavirus middle T antigen (PyMT) transgenic mice delays the genesis of breast carcinoma. Interestingly, in newly developed tumors from PyMT mice, the upregulated HSCARG protein accumulate in the nucleus, which is most likely due to oxidative stress in the microenvironment [13]. This observation reinforces the conclusion that negative regulation of DNA damage response in the nucleus is, at least in part, responsible for the oncogenic effects of HSCARG (Fig. 3).

9. Frontiers

As summarized here, HSCARG participates in regulation of cellular redox homeostasis, innate immunity, and the DNA damage response; the functions of HSCARG are deeply associated with post-translational modifications of key components in these pathways. HSCARG interacts directly with deubiquitinases OTUB1, USP1, and USP7 and stimulates their deubiquitination effects on substrates. These observations indicate that inhibition of substrate ubiquitination via recruitment of deubiquitinases is a regular functional mode of HSCARG. Further studies should focus on identification of other HSCARG binding partners, especially among deubiquitinase family members, to reveal the potential functions of HSCARG in other pathways.

As a NmrA-like protein, HSCARG is unable to the catalyze metabolic reactions independently due to mutation of the crucial tyrosine enzymatic site within the Rossmann fold into histidine (His-129). It is natural to assume that HSCARG is derived from duplication and mutation of SDR family members. Usually, genes with loss-of-function mutations are subjected to negative selection during evolution. However, HSCARG is widely conserved in higher species in spite of its incapability of dehydrogenation. This suggests that HSCARG must play a positive role in

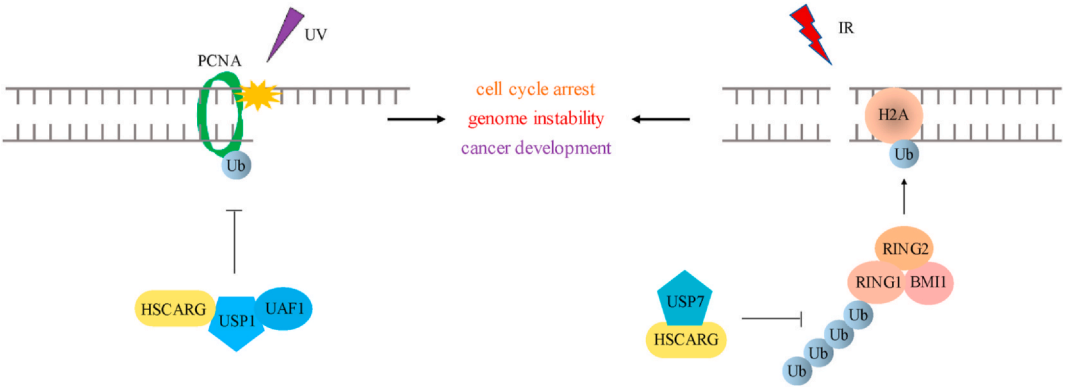

Fig. 3. HSCARG negatively regulates DNA damage response in the nucleus. HSCARG facilitates the deubiquitination of RING1 by USP7, and thus attenuates the PRC1 complex-catalyzed ubiquitination of H2A in response to IR. Besides, HSCARG abrogates the ubiquitination of PCNA dependently on the USP1/UAF1 complex under UV-induced replication stress.

other aspects. Under normal physiological conditions, the functions of HSCARG are silenced due to NADPH-promoted homodimerization. Oxidative stress-caused reduction in NADPH concentration plays a dual role on HSCARG. On the one hand, upon dissociation from NADPH, HSCARG transforms from functionally inactive homodimer to active monomer. Indeed, it was observed that treatment of cells with moderate amount of SNAP (50 μM) and DHEA (100 μM) activated the interaction between HSCARG and ASS and elevated the inhibitory effect of HSCARG on ROS production [13,14]. On the other hand, over-enrichment of HSCARG in the nucleus under violent and persistent oxidative stress attenuates its functions in the cytoplasm. For example, an excess of SNAP (500 μM) and diethylmaleate (2 mM) impaired the interaction between HSCARG and ASS and attenuated the suppression of HSCARG on NF-κB activity [14,15]. The current observations on behaviors of HSCARG in response to redox change are predominantly based on cell-based assays. Therefore, further researches should focus on the phenotype differences between HSCARG wild-type and knockout mice fed or injected with drugs that cause oxidative stress. Taken together, HSCARG functions as a linkage between cellular redox status and other signaling pathways and fine-tunes cellular response to redox changes.

Declaration of competing interest

The authors declare that they have no competing interests.

Abbreviations

53BP1	p53 binding protein 1
AMP	adenosine monophosphate
ASL	argininosuccinate lyase
BMI1	B lymphoma Mo-MLV insertion region 1 homolog
Cardif	caspase recruitment domain adaptor inducing IFN-β
CAT	cationic amino acid transporter
COMMD1	copper metabolism gene MURR1 domain containing protein 1
CRM1	chromosome region maintenance 1
HCoV	human coronavirus
IFN	interferon
IRF3	interferon regulatory factor 3
MX1	myxovirus resistance 1
NAD(P) (H)	(reduced) nicotinamide adenine dinucleotide (phosphate)
NEMO	NF-kappaB essential modulator
NMP	nucleoside monophosphate
NOX	NADPH oxidase
OTUB1	ovarian tumor protease domain-containing ubiquitin aldehyde-binding protein 1
PCNA	proliferating cell nuclear antigen
PP2A	protein phosphatase 2A
RAP80	receptor associated protein 80
RIG-I	retinoic acid inducible gene I
RING1/2	really interesting new gene 1/2
RIP1	receptor-interacting protein 1
RLR	RIG-I like receptor
SNAP	S-nitroso-N-acetylpenicillamine
TBK1	TANK binding kinase 1
TNFR1	tumor necrosis factor receptor 1
TRADD	TNFR1-associated death domain protein
TRAF2/3	tumor necrosis factor receptor associated factor 2/3
Ub	ubiquitin
USP	ubiquitin specific protease

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