Trends in Genetics

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Spotlight

SAMHD1 Sheds Moonlight on DNA Double-Strand Break Repair

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SAMHD1 (sterile α motif and histidine (H) aspartate (D) domain-containing protein 1) is known for its antiviral activity of hydrolysing deoxynucleotides required for virus replication. Daddacha *et al*. identify a hydrolase-independent, moonlighting function of SAMHD1 that facilitates homologous recombination of DNA double-strand breaks (DSBs) by promoting recruitment of C-terminal binding protein interacting protein (CTIP), a DNA-end resection factor, to damaged DNA. These findings could benefit anticancer treatment.

DNA damage arises frequently (>10 000 lesions per cell per day) through endogenous and exogenous sources, such as cell metabolism, sunlight radiation, and tobacco smoke chemicals. Cells have developed elaborate ways, collectively termed the DNA-damage response (DDR), which sense and repair DNA lesions, and activate cell cycle checkpoints to allow time for repair. Improperly repaired damage can lead to cell death, genome instability, and cancer. Moreover, hereditary DNA-repair defects are associated with cancer predisposition, immunodeficiency, neurodegeneration, infertility, and premature ageing, highlighting the importance of DDR processes to human health [1].

Depending on the source, DNA damage can come in different 'flavours', triggering specific cellular responses. DSBs are highly cytotoxic lesions mostly repaired through two major pathways: one, termed nonhomologous end-joining (NHEJ), can be error prone, acts throughout the cell cycle and involves direct religation of broken DNA ends. The other, homologous recombination (HR), templates off homologous sequences (usually the sister chromatid), leading to accurate repair, while being restricted to S/G2 cell cycle phases. HR is initiated by a nucleolytic process called DNA-end resection (or simply resection), that removes nucleotides from 5′ DSB ends. Resection relies on recruitment of CTIP (also known as RBBP8) to DSBs to activate the MRE11–RAD50–NBS1 (MRN) DNA nuclease complex. Resection is subsequently extended by other nucleases in conjunction with helicases. The resulting 3′ single-stranded DNA (ssDNA) overhangs are coated by the ssDNA-binding protein RPA, which is then replaced by the RAD51 recombinase to form nucleoprotein filaments that mediate strand invasion, followed by final HR steps (Figure 1A) [1–3].

In a recent issue in *Cell Reports*, Daddacha *et al*. link a novel player to resection; a protein called SAMHD1 [4]. SAMHD1 is known for its antiviral activity of catalysing the triphosphohydrolysis of deoxynucleotides (dNTPs), thereby depleting cellular dNTPs required for viral processes such as reverse transcription. As a consequence, SAMHD1 renders various cell types refractory to infection by viruses like HIV-1. A potential nuclease activity of SAMHD1 remains controversial, having been assigned to copurifying contaminants [5]. Mutations in *SAMHD1* are associated with Aicardi–Goutieres syndrome; an autosomal recessive congenital neurological disorder [5]. SAMHD1 is mutated and/or downregulated in several cancers, suggestive of a tumour suppressor role.

Apart from impacting on dNTP levels, Daddachi *et al*. wondered if SAMHD1 could play a more direct role in genome maintenance pathways. Indeed, through a series of biochemical and cell biological studies, the authors identify a moonlighting function of SAMHD1 independent of its dNTPase activity. Through siRNA-mediated depletion, CRISPR-Cas9-induced knockout or proteasomal degradation of SAMHD1 in several cancer and nontransformed cell lines, the authors firmly establish that SAMHD1 protects cells from a range of DSB-inducing agents such as ionising radiation (Figure 1B) [4]. But what could the molecular basis of this phenotype be?

Daddacha *et al*. show that SAMHD1 accumulates at DNA damage sites (Figure 1C), where it colocalises with nascent DNA and DDR factors including RAD51 [4]. Suggestive of a direct role in DSB repair, the authors conducted cellular GFP-based DSB repair reporter assays, elucidating that SAMHD1 is specifically required for HR (Figure 1B). Using immunofluorescence assays they assessed recruitment dependencies of known HR factors on SAMHD1. The approach allowed them to pinpoint SAMHD1 function to resection, placing it upstream of CTIP recruitment and downstream of MRN accrual (Figure 1A, B) [4]. Importantly, the authors established that the role of SAMHD1 in resection is independent of its potential nuclease activity. Instead, coimmunoprecipitation experiments suggest a scaffolding function mediated through IR-induced interaction between SAMHD1 and CTIP (Figure 1C). Using mutant versions of SAMHD1 lacking key parts of the protein, the authors revealed an evolutionary conserved C-terminal region in SAMHD1 essential for CTIP interaction [4]. Daddacha *et al*. then focused on a K484T mutation in this region, naturally occurring in a gastric cancer patient. Consistent with being a *bona fide* separation-of-function mutation, K484T-containing SAMHD1 is deficient in HR, while retaining its dNTPase activity [4].

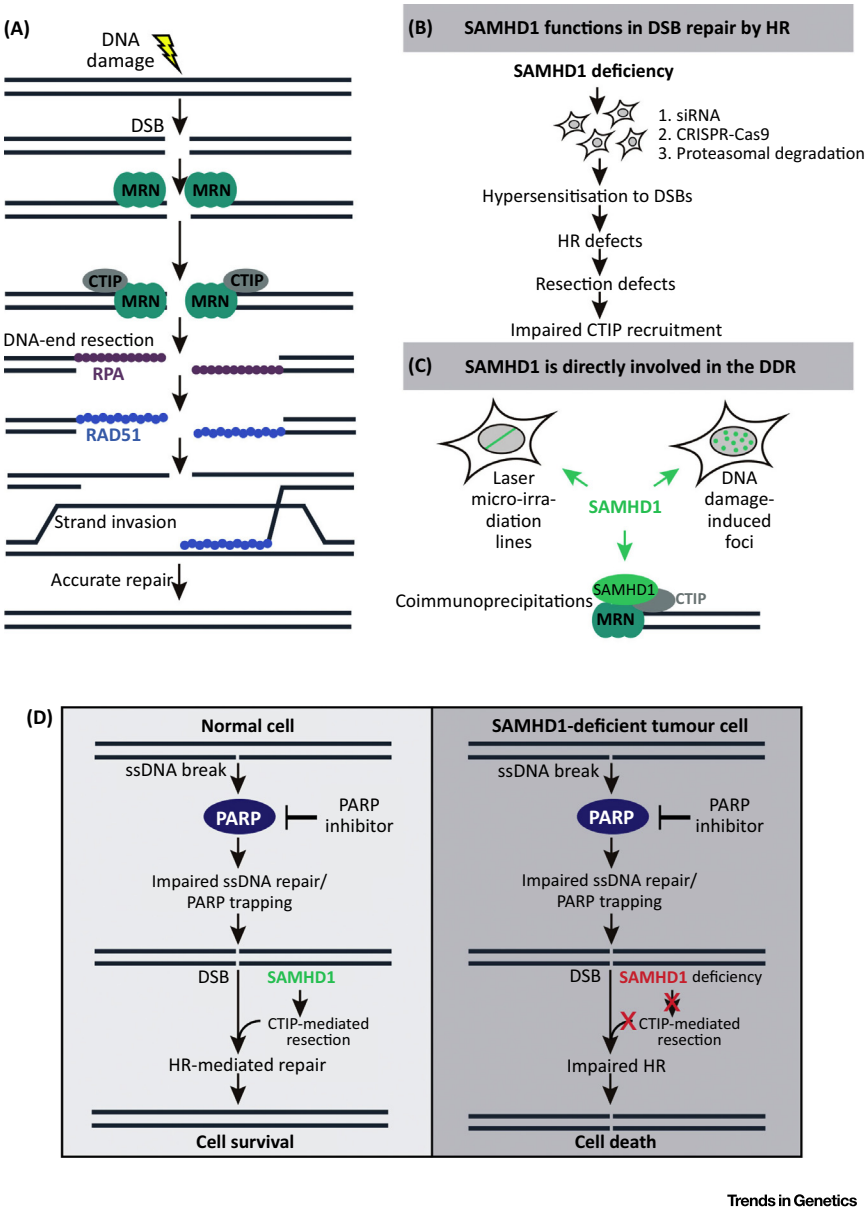

Figure 1. SAMHD1 Implications in the DRR and Cancer. (A) Simplified DSB repair model by HR. (B) Summary of SAMHD1 depletion/deletion methods and their main effects in response to DNA damage-inducing agents. (C) Selected experimental pipelines indicating a direct role for SAMHD1 in the DDR. (D) Suggested mode-of-action of PARP inhibitors. Note that treatment with PARP inhibitors leads to transformation of ssDNA breaks to DSBs. Abbreviations: CTIP, C-terminal binding protein interacting protein; DDR, DNA damage response; DSB, double-strand break; HR, homologous recombination; MRN, MRE11–RAD50–NBS1 complex; PARP, poly(ADP-ribose) polymerase; RPA, replication protein A; SAMHD1, sterile α motif and histidine (H) aspartate (D) domain-containing protein 1; ssDNA, single-stranded DNA.

SAMHD1 has recently been implicated as a biomarker for cytarabine response in acute myeloid leukaemia [6]. Excitingly, Daddacha *et al*.'s work extends the potential of SAMHD1 for patient stratification, suggesting that SAMHD1-deficient, and thus HR-defective, cancer patients could respond well to poly(ADP-ribose) polymerase (PARP) inhibitors via synthetic lethality mechanisms. The concept is based on the fact that inhibition of PARP-mediated ssDNA repair is lethal in HR-defective cells (Figure 1D). Indeed, the authors showed that SAMHD1 abrogation hypersensitises cells to PARP inhibition [4]. Notably, PARP inhibitors have recently been implemented in the clinic [7]. Daddacha *et al*.'s study could therefore have a wide impact, particularly in the cancer field.

The authors' findings provide rich grounds for future studies. It will for instance be intriguing to assess how SAMHD1 itself is recruited to DNA damage sites. Could it be through its nucleic-acid-binding region [4,5]? Moreover, SAMHD1 functions as a triphosphohydrolase only in a tetrameric conformation, whereas ssDNA binding of SAMHD1 prevents this configuration. Could the soluble and DNA-damage-bound SAMHD1 pools exist in distinct structural conformations, thereby consolidating its different functionalities [4]? Similarly to CTIP, SAMHD1 is cell cycle regulated through cyclin-dependent-kinase-mediated phosphorylation [5,8]; a feature that could help limit HR activity to S/G2 cell cycle phases. Moreover, it remains to be investigated which molecular determinants of CTIP mediate SAMHD1 binding. In this regard, it will be interesting to assess if IR-induced modifications on CTIP, such as UBE2D–RNF138-dependent ubiquitylation [9], could account for the IR inducibility of the interaction. Generally, numerous features, such as post-translational modifications, protein–protein interactions, DNA binding, tetramerisation, and prolyl isomerisation, have been implicated in regulating CTIP ([2,3,10], etc.). A major challenge will be to understand how these different processes interconnect to optimise resection and protect stable genomes.

Daddacha *et al*. provide us with a glimpse into the future of modern cell biology. In an era characterised by an ever-growing number of publicly available disease genomes, mechanistic studies exploiting such genome sequences will undoubtedly have an impact on how we can

prevent, diagnose, and treat diseases in a more targeted and personalised manner in the future.

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