MOLECULAR BIOLOGY

# Faulty replication can sting

**Inappropriate cellular inflammation can cause disease. It emerges that the protein SAMHD1 prevents the release of newly replicated DNA from the nucleus, blocking an undesirable pro-inflammatory response.** SEE ARTICLE P.57

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Cells need to distinguish between their own DNA and that of viruses. To solve this problem, plant, fungal and animal cells store their DNA in the nucleus, and respond to DNA in the cytoplasm by activating an inflammatory response. However, under certain abnormal circumstances, host-cell DNA can also accumulate in the cytoplasm, triggering inappropriate inflammation. On page 57 , Coquel *et al.*[1] define a role for the protein SAMHD1 in preventing this cytoplasmic host-DNA build-up. The authors' findings have implications for immune disease and cancer.

SAMHD1 is a nuclear protein that chemically inactivates nucleotides[2], preventing them from being used to build DNA. Inherited SAMHD1 mutations cause the rare inflammatory disorder Aicardi–Goutières syndrome, which involves increased production of proteins called interferons that activate the immune system. Under normal circumstances, interferons are produced only in response to infection, and help to fight off viruses[3].

Aicardi–Goutières syndrome can also be caused by mutations in the enzymes RNase H2 and TREX1, which degrade specific nucleic acids[3]. In TREX1-mutant cells, single-stranded DNA (ssDNA) fragments accumulate in the cytoplasm and activate a DNA-sensing pathway, dubbed cGAS-STING, triggering interferon production[3]. Before the current study, the cause of chronic inflammation in cells harbouring SAMHD1 mutations was unknown. Coquel *et al.* found that, as in TREX1-mutant cells, ssDNA accumulates in the cytoplasm of SAMHD1-deficient human cells. This leads to interferon production, mediated by the cGAS-STING pathway.

Why does SAMHD1 deficiency cause this defect? Dynamic structures called replication forks form at sites where double-stranded DNA is unwound, enabling each strand to be duplicated during DNA replication. The progression of forks along DNA can slow or stall if unusual DNA structures or damaged DNA block their paths[4], or if nucleotide levels become depleted (Fig. 1a). Several proteins then cooperate to circumvent or repair the damaged site and restart replication. In some cases, degradation of newly synthesized DNA at stalled forks (a process called fork resection) promotes DNA remodelling or activation of repair pathways that help to restart DNA replication. When the authors artificially induced replication-fork stalling in SAMHD1-deficient cells, cytoplasmic ssDNA levels and interferon responses increased. Moreover, the group demonstrated that the cytoplasmic ssDNA fragments were newly replicated, implying that they had been released from the stalled fork. Thus, SAMHD1 normally blocks cytoplasmic ssDNA accumulation by preventing the release of ssDNA from stalled replication forks.

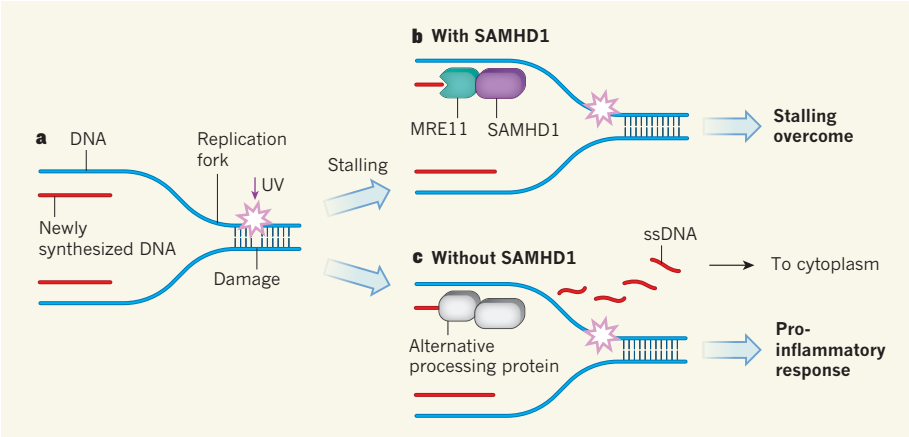


**Figure 1 | SAMHD1 at DNA-replication forks.** **a**, During DNA replication, DNA is unwound and duplicated to produce newly synthesized DNA at dynamic structures called replication forks. Forks can stall during replication if they hit unusual DNA structures (not shown) or DNA that has been damaged, for example by ultraviolet (UV) light. **b**, Coquel *et al.*[1] report that the protein SAMHD1 directs the nuclease enzyme MRE11 to degrade newly synthesized DNA — a process called fork resection, which is crucial for overcoming stalling. **c**, In SAMHD1-deficient cells, MRE11 activity is lacking, and the newly synthesized DNA at stalled forks is processed by alternative proteins, resulting in the release of single-stranded DNA (ssDNA) into the cytoplasm. The ssDNA fragments accumulate and trigger pro-inflammatory responses.

Previous work[5], confirmed by the current study, has shown that SAMHD1 regulates nucleotide levels so that replication forks can progress efficiently across the genome. But Coquel *et al.* found that SAMHD1 also has a second role in fork progression and processing — directly binding to and activating the nuclease enzyme MRE11, which degrades nascent DNA during fork resection[6] (Fig. 1b). The authors demonstrate that it is this activity of SAMHD1 that prevents newly replicated DNA from accumulating in the cytoplasm. When cells lack SAMHD1, meaning that MRE11 is either absent from stalled forks or enzymatically inactive, other enzymes aberrantly process the nascent DNA, producing fragments that move to the cytoplasm (Fig. 1c).

Several key steps in this previously undescribed SAMHD1 pathway require further investigation. For example, how does SAMHD1 bind to forks and activate MRE11? What part of the replication fork is processed by SAMHD1 and MRE11 during resection?

Of particular interest is the interplay between SAMHD1, MRE11 and other molecules that control fork resection, such as proteins encoded by the *BRCA1* and *BRCA2* genes, the loss of which promotes certain cancers. *BRCA*-deficient cells exhibit uncontrolled fork resection by MRE11, resulting in over-digested DNA[7,8], which could compromise the integrity of the genome and contribute to cancer development. However, this feature of *BRCA*-deficient cells can also make them sensitive to chemotherapy[8]. This treatment induces DNA damage and increases replication-fork stalling — during chemotherapy, *BRCA*-deficient cells might therefore be selectively killed, whereas normal cells are spared. The level of SAMHD1 in *BRCA*-deficient cells might be an indicator of patient responses to chemotherapy, with high levels increasing the activity of MRE11 and

exacerbating replication defects in tumour cells undergoing chemotherapy, and low levels indicating treatment resistance.

SAMHD1 is often mutated in leukaemias and solid tumours[9,10]. Although altered nucleotide levels might well perturb DNA replication and contribute to tumour development when SAMHD1 is mutated, Coquel and colleagues' research provides an alternative explanation. Fork-resection defects in SAMHD1-deficient cells might lead to increased problems with DNA replication — a phenomenon central to cancer development[4,6].

It remains unclear whether cGAS-STING activity, such as that induced by SAMHD1 deficiency, promotes or prevents tumour formation. On one hand, increased levels of cytoplasmic nucleic acids and cGAS-STING activation can signal potentially dangerous replication problems in abnormal cells, and thereby promote their elimination by the immune system[6]. Indeed, cGAS-STING immune signalling is suppressed in some cancers. On the other hand, persistent cGAS-STING signalling can lead to a chronic pro-inflammatory response, which can promote tumour development and spread[11,12]. Further work is required to better understand the role of these immune responses in cancer.

Coquel *et al.* also advance our understanding of the causes of immune disease by shedding light on the important question of whether the different mutations associated with Aicardi–Goutières syndrome promote disease through a common mechanism. Although cells lacking SAMHD1, TREX1 and RNase H2 all trigger interferon responses through cytoplasmic cGAS-STING signalling, there is some evidence that the activators of this pathway might be distinct. For SAMHD1 and TREX1, there are now links to ssDNA produced during DNA replication[1,3], but a role for other cytoplasmic nucleic acids is yet to be ruled out. For RNase H2, cGAS-STING is induced by DNA derived from micronuclei[13] — small, aberrant nuclei that form when chromosomes fail to segregate properly into sister cells during cell division. Although double-stranded DNA can activate cGAS-STING, ssDNA might also be present in micronuclei and thus contribute to activation of the pathway. It will be interesting to further define exactly which nucleic acids drive this syndrome.

Finally, it remains unclear how nucleic acids are released into the cytoplasm to activate the cGAS-STING pathway. One possibility is that they escape the nucleus after the surrounding nuclear envelope breaks down during cell division[13]. However, Coquel *et al.* found that cytoplasmic ssDNA accumulates rapidly in SAMHD1-deficient cells, even before division, suggesting that other pathways are involved. Understanding how the pathological build-up of nucleic acids in the cytoplasm of cells occurs might help us to identify molecular targets that have the potential to be therapeutically manipulated in immune disease. ■

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ASTRONOMY

# Helium discovered in the tail of an exoplanet

**As the exoplanet WASP-107b orbits its host star, its atmosphere escapes to form a comet-like tail. Helium atoms detected in the escaping gases give astronomers a powerful tool for investigating exoplanetary atmospheres.** SEE LETTER P.68

DRAKE DEMING

Helium is ubiquitous in the Universe. Large amounts were generated in the Big Bang[1], and nearly every star begins its life by producing helium in its core through the nuclear fusion of hydrogen. The atmospheres of giant exoplanets are expected to have an abundance of helium[2], because these planets formed from recycled gas and dust from a previous generation of stars. However, searches for helium in such atmospheres have been unsuccessful[3]. On page 68, Spake *et al.*[4] report the discovery of helium atoms in the eroding atmosphere of the giant exoplanet WASP-107b. Their work opens a new chapter in the study of exoplanetary atmospheres.

WASP-107b is of comparable size to Jupiter, but has about one-eighth the mass. The exoplanet's low mass relative to its substantial size makes it difficult for the planet to retain its atmosphere — especially in the presence of strong ultraviolet radiation from its host star. Although this star is smaller and cooler than the Sun, it is threaded with magnetic fields produced by the star. Contortions of these

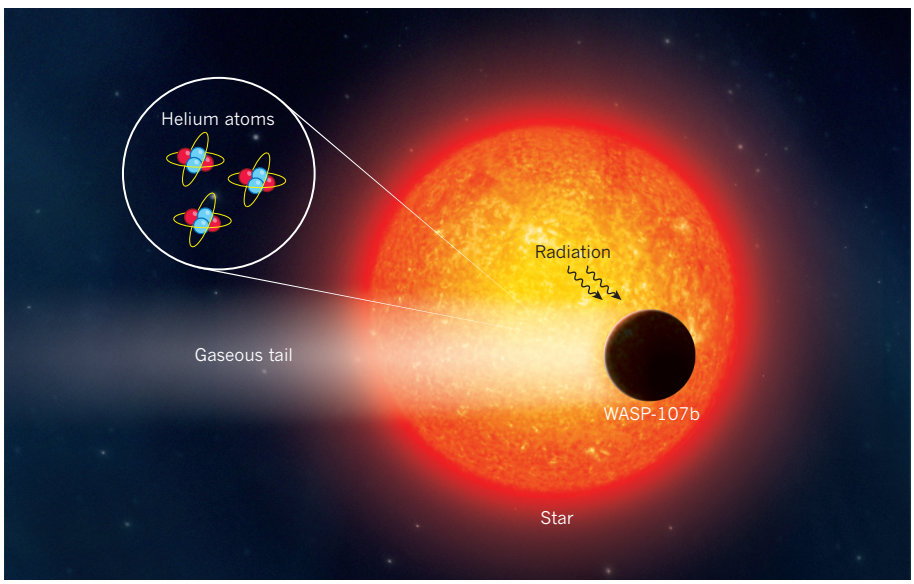


**Figure 1 | The escaping atmosphere of WASP-107b.** As the giant exoplanet WASP-107b orbits its host star, ultraviolet radiation from the star energizes the planet's atmosphere. Spake *et al.*[4] show that this causes the atmosphere to escape, and to form a gaseous tail. The authors detected helium atoms in the escaping gases. This is the first time helium has been identified in an exoplanetary atmosphere.