throughout the field of medicine. Time will tell whether this design strategy truly sticks.

Sophia J. Bailey and **Eric A. Appel** are in the Department of Materials Science & Engineering, Stanford University, Stanford, California 94305, USA. **E.A.A.** is also in the Department of Bioengineering, and at the Chem-H Institute and the Woods Institute for the Environment, Stanford University; and in the Department of Pediatrics – Endocrinology, Stanford University School of Medicine.
e-mail: eappel@stanford.edu

1. Shi, J. *et al. Nature Chem. Eng.* https://doi.org/10.1038/s44286-023-00008-y (2024).
2. Armstrong, J. P. K. *et al. Sci. Transl. Med.* **12**, eaaz2253 (2020).
3. Yang, Q. *et al. Nature Mater.* **20**, 1559–1570 (2021).
4. Deng, J. *et al. Nature Mater.* **20**, 229–236 (2021).
5. Yuk, H., Wu, J. & Zhao, X. *Nature Rev. Mater.* **7**, 935–952 (2022).
6. Fang, Y. *et al. Matter* **2**, 948–964 (2020).
7. Li, J. & Mooney, D. J. *Nature Rev. Mater.* **1**, 16071 (2016).
8. Patterson, J., Martino, M. M. & Hubbell, J. A. *Mater. Today* **13**, 14–22 (2010).
9. Gomes, B. S., Simões, B. & Mendes, P. M. *Nature Rev. Chem.* **2**, 0120 (2018).

The authors declare no competing interests.
This article was published online on 11 January 2024.

Cell biology

DNA sensing and repair team up against cancer

Silvia Monticelli & Petr Cejka

DNA in the cytoplasm can be a sign of abnormalities such as viral infections or cancer. A protein with a role in DNA-damage response was unexpectedly found to activate defences against the threats indicated by cytoplasmic DNA. **See p.585**

Cellular DNA is usually found in the nucleus. It is rare to find DNA outside the nucleus, in the cytoplasm, and it can be a harbinger of viral infections or cancer. Among the cellular sensors of cytoplasmic DNA, a protein termed cGAS orchestrates defence pathways against threats posed by foreign or damaged DNA. On page 585, Cho *et al.*[1] reveal a previously unknown partnership that helps to activate cGAS and protect from cancer.

The cGAS pathway is part of a powerful defence signalling cascade that is triggered by cytoplasmic DNA and that probably evolved in response to viral infection. After infection, the presence of viral nucleic acids in the cytoplasm provides an opportunity for early detection of the unwanted intruder. In a sequence-independent, and hence highly versatile, manner, cGAS can bind to viral DNA, which triggers the enzymatic activity of cGAS, resulting in the synthesis of the molecule cGAMP from nucleotides.

cGAMP binds to and activates the protein STING, triggering an antiviral response program through the production of defence molecules such as interferon proteins and other inflammatory molecules called cytokines. However, excessive activation of this cGAS–STING pathway can be harmful and is associated with inflammatory, autoimmune and degenerative disorders[2]. Understanding how the pathway is regulated and how it distinguishes between cellular and foreign DNA is therefore relevant to its protective and disease-causing outcomes.

Initially, cGAS was thought to function mainly from its cytoplasmic location. However, it has become clear that the protein is also present in the nucleus[3]. The activation of nuclear cGAS by genomic self DNA is prevented by several mechanisms, including those that rely on the presence of the DNA-binding protein BAF (ref. 4), and interactions with the histones H2A and H2B (refs 5–9). Histones are the protein components of nucleosomes, which help to package long genomic DNA into the tight 3D space in the nucleus.

The mechanisms that lead to the release of cGAS from nucleosomes have not been clear. Now, Cho and colleagues have identified a human protein that helps to release inactivated cGAS from nucleosomes (Fig. 1). Once it has been released, cGAS can move into the cytoplasm, where it becomes activated on contact with DNA. The protein that aids cGAS release from nucleosomes is MRE11, a component of a three-protein complex termed MRE11–RAD50–NBN (MRN), which has a well-established role in the response to DNA double-strand breaks[10].

MRE11 is a nuclease, a type of enzyme that has DNA-cleaving abilities, and the MRN complex has DNA-tethering functions that it uses during the process of repairing DNA breaks. When bound to the ends of broken DNA, MRN is also essential for the activation of an enzyme called ATM (which is a kinase – an enzyme that can attach phosphate groups to proteins in a process called phosphorylation). ATM phosphorylates various protein targets to drive responses to DNA breaks, including the activation of proteins involved in DNA repair and in regulation of the cell cycle[10]. Cho and colleagues demonstrate that MRE11's role in the release of cGAS from nucleosomal DNA is independent of its nuclease and ATM-activation roles but is dependent on having an intact MRN complex.

The authors present *in vitro* experiments showing that MRN binds to nucleosomes and can help to liberate cGAS. Treating cells with a drug that causes DNA breaks notably

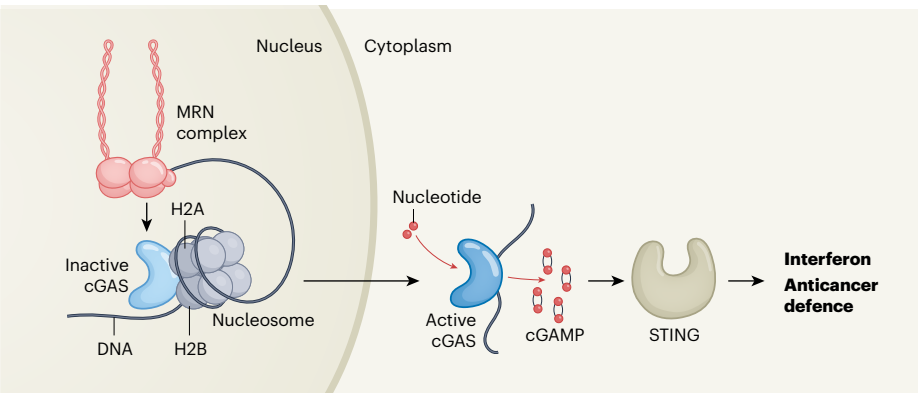

Figure 1 | The activation of a pathway that defends against foreign or abnormal cytoplasmic DNA. The presence of DNA in the cytoplasm can be a sign of problems, such as the high levels of DNA damage associated with cancer. When the protein cGAS, which is usually trapped in the nucleus[3], senses DNA in the cytoplasm, it becomes activated and uses nucleotides to generate the molecule cGAMP. cGAMP then activates the protein STING, which aids production of interferon proteins to promote anticancer defences. Cho *et al.*[1] shed light on how cGAS is activated. The activation depends on a complex called MRE11–RAD50–NBN (MRN) and, in particular, one of its constituent proteins, called MRE11, which is involved in recognizing DNA damage[10]. When MRE11 is present as part of this intact complex, it can free cGAS from interaction with the histone proteins (H2A and H2B) that bind to nuclear DNA in a structure called a nucleosome, thereby enabling cGAS to enter the cytoplasm.

enhanced the release of cGAS, but only when the MRN complex was intact. Therefore, MRN complex can displace cGAS from nucleosomes in response to DNA damage. As a universal sensor of DNA breaks, the MRN complex is an ideal candidate for this function.

It remains to be established whether DNA-break recognition by MRN is required to activate the complex for cGAS release. Also unclear is how cGAS moves into the cytoplasm and whether there are factors that aid that movement. Another unknown is whether factors prevent cGAS from rebinding to nucleosomes, given that nucleosomes vastly outnumber MRN complexes. Cho and colleagues' study will open doors for subsequent research to fill these crucial gaps in our knowledge.

What are the biological consequences of cGAS release from nucleosomes by MRN? First, it is necessary to consider that cGAS is part of an organism's defence against cancer[11]. In addition to its protective function against viral DNA, cGAS can also be activated by cytoplasmic self DNA[2], which might be present in some cancer cells. DNA alterations (mutations and genomic changes that lead to instability) are one of the hallmarks of cancer.

Cancer cells, particularly those with mutations in genes encoding DNA-repair factors such as the *BRCA1* or *BRCA2* genes can have high levels of DNA damage. As a result, broken DNA in the nucleus might trigger MRN activation and cGAS release. The DNA fragments might then escape to the cytoplasm and trigger the cGAS–STING pathway. In the absence of DNA damage in healthy cells, the activation of these mechanisms would be extremely rare.

Consistent with this model for the anticancer role of the pathway identified, Cho *et al.* observed that in a breast cancer model in mice, MRE11 promoted the activation of the cGAS–STING pathway, ultimately leading to a slowdown in cellular proliferation and, more broadly, to a process called senescence and to a type of cell death termed necroptosis. However, in the absence of functioning MRE11, tumour cells continued to proliferate and cancer development was enhanced. MRE11 can therefore help to protect against cancer through cGAS–STING activation. This newly discovered link with cGAS adds to the established anticancer roles of MRN through its activity in DNA repair and ATM activation[10]. Discovering the relationships between these processes and understanding their contribution to our health will certainly be a subject of exciting research in the future.

"This newly discovered link with cGAS adds to the established anticancer roles of MRN through its activity in DNA repair."

Silvia Monticelli and **Petr Cejka** are at the Institute for Research in Biomedicine, Università della Svizzera italiana, 6500 Bellinzona, Switzerland.
e-mails: silvia.monticelli@irb.usi.ch; petr.cejka@irb.usi.ch

1. Cho, M.-G. *et al. Nature* **625**, 585–592 (2024).
2. Decout, A., Katz, J. D., Venkatraman, S. & Ablasser, A. *Nature Rev. Immunol.* **21**, 548–569 (2021).
3. Volkman, H. E., Cambier, S., Gray, E. E. & Stetson, D. B. *eLife* **8**, e47491 (2019).
4. Guey, B. *et al. Science* **369**, 823–828 (2020).
5. Michalski, S. *et al. Nature* **587**, 678–682 (2020).
6. Boyer, J. A. *et al. Science* **370**, 450–454 (2020).
7. Cao, D., Han, X., Fan, X., Xu, R.-M. & Zhang, X. *Cell Res.* **30**, 1088–1097 (2020).
8. Kujirai, T. *et al. Science* **370**, 455–458 (2020).
9. Pathare, G. R. *et al. Nature* **587**, 668–672 (2020).
10. Reginato, G. & Cejka, P. *DNA Repair* **91–92**, 102869 (2020).
11. Samson, N. & Ablasser, A. *Nature Cancer* **3**, 1452–1463 (2022).

The authors declare no competing interests.
This article was published online on 10 January 2024.